Pseudoexfoliation in Southern India: The Andhra Pradesh Eye Disease Study

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Purpose. To report the prevalence of pseudoexfoliation (PXF) and its associations with ocular diseases in a south Indian population.

Methods. This was a population-based, cross-sectional epidemiologic study in the south Indian state of Andhra Pradesh (AP). A total of 10,293 subjects of all ages from one urban and three rural areas representative of the population of AP were interviewed and underwent a comprehensive ophthalmic evaluation. PXF was diagnosed on slit lamp biomicroscopy by the presence of white dandruff-like material in the pupillary margin, on the trabecular meshwork, and/or on the anterior lens capsule of one or both eyes.

Results. The age-gender-area–adjusted overall prevalence of PXF was 0.69% (95% CI: 0.53–0.86). The prevalence of PXF increased with increasing age: 3.01% (95% CI: 2.45–3.80), in those 40 years of age or older, and 6.28% (95% CI: 4.80–7.76), in those 60 years of age or older. The prevalence of PXF was significantly higher among people whose occupation involved outdoor activities (adjusted odds ratio [OR], 2.14; 95% CI: 1.10–4.16). After adjustment for age, the prevalence of PXF was significantly higher in those with nuclear cataract (adjusted OR, 2.00; 95% CI: 1.13–3.54). PXF was significantly associated with blindness (adjusted OR, 2.19; 95% CI: 1.16–4.13). Fifteen (20.5%; 95% CI: 11.20–29.80) of those with PXF were blind, with age-adjusted relative risk (RR) = 4.25 (95% CI: 4.01–4.51). Unilateral blindness (41.2%; 95% CI: 29.81–52.39) and visual impairment (45.21%; 95% CI: 34.29–57.13) were also more common with PXF. Four subjects (5.5%; 95% CI: 0.27–10.2) of those with PXF had glaucoma. The prevalence of PXF in those with glaucoma was 4.2%; (95% CI: 0.17–8.23). In general linear models, the estimated mean ± SE of IOP with glaucoma and PXF was 24.14 ± 1.41 mm Hg and was 18.94 ± 0.26 mm Hg with glaucoma in the absence of PXF; the difference was statistically significant ($P < 0.0001$).

Conclusions. The association of PXF with blindness and aging has public health implications for India. This is especially so considering the burden of cataract with aging and the association of PXF with cataract as well as complications of cataract surgery. The diagnosis of PXF may also be important in the management of glaucoma in this population. (*Invest Ophthalmol Vis Sci.* 2005;46:1170–1176) DOI:10.1167/iovs.04-1062

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Pseudoexfoliation (PXF) is an age-related disorder characterized by the accumulation of a fibrillar extracellular material in ocular tissues and is often associated with glaucoma.[1] The prevalence of PXF world-wide ranges from 0.5% in those aged <60 years to 15% in those aged ≥60 years.[2] The prevalence of PXF based on hospital reports from India varies between 1.87% and 13.5%.[3] Population-based studies from south India have recently reported the prevalence of PXF to be between 3.8% and 6.0% among persons aged ≥40 years.[4,5] The wide range of prevalence may reflect a true phenomenon or maybe be related to the differences in methodology, including examination techniques and definitions used to diagnose PXF. Although a genetic factor has been postulated, the reasons for true differences in prevalence between populations remain unknown.[6] In previous studies, a strong occupational association has been found with the occurrence of PXF.[7,8]

The prevalence of glaucoma in south India has been reported to be between 1.6% and 4.7%.[9–11] The prevalence of glaucoma among subjects with PXF reported by recent population-based surveys from south India were 7.5% and 13%, respectively.[4,5] PXF is associated with poor dilatation and is a risk factor for zonular dialysis and vitreous loss during cataract surgery.[4] PXF is therefore important from the perspective of both glaucoma and cataract management.[12,13]

The Andhra Pradesh Eye Disease Study (APEDS) is a large population based cross-sectional epidemiologic study conducted between 1996 and 2000 that provided information about the prevalence of ocular disease in the state of Andhra Pradesh (AP) in southern India.[10,14–17] In the current study, we determined the prevalence of PXF and its associations with ocular disease in AP in southern India.

Materials and Methods

The design of the APEDS is described in detail elsewhere.[14–16,18] We obtained approval of the Ethics Committee of the Institute before study was conducted during the 5-year period from 1996 to 2000, in compliance with the tenets of the Declaration of Helsinki.[18] The aspects of study design relevant to this article are summarized in the following text.

Population Sampling

Briefly, we used a multistage sampling procedure to select a study sample of 10,000 persons comprising 5,000 persons each, younger and older than 30 years. We selected one urban and three rural areas from different parts of Andhra Pradesh (AP) that approximately reflected the urban–rural and socioeconomic distribution of the population of the state. The four areas selected were Hyderabad (urban), West Godavari district (semirural), and Adilabad and Mahabubnagar districts (poor, rural). We randomly chose 24 clusters (including one cluster representing the homeless), using stratified random cluster sampling from Hyderabad to reflect the urban population of the study, and 70 rural clusters to identify the rural population of the study.

Examination

Comprehensive ocular exams were performed for all eligible subjects after an interview to collect demographic details and personal risk behavior, dietary history, and utilization of eye care services. Ocular

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examinations were conducted in a clinic specially set up for the study by two ophthalmologists and optometrists trained for the study.[18] Written informed consent was obtained from the participants before any examination. The optometrists measured distance and near visual acuity, both presenting (with current refractive correction if any) and best corrected after refraction, with logarithm of minimum angle of resolution (logMAR) charts,[19] and performed an external eye examination, assessment of pupillary reaction, and anterior segment examination with a slit lamp biomicroscope. The optometrist also measured intraocular pressure (IOP) with a Goldmann applanation tonometer or a Perkins applanation tonometer if the IOP of a subject could not be measured using the Goldmann applanation tonometer. After examination by the optometrist, the subject was further examined by the ophthalmologist, who verified all abnormal findings noted by the optometrist. The ophthalmologist performed gonioscopy on all participants with an two-mirror lens (NMRK; Ocular Instruments Inc., Bellevue, WA), and the angle was graded according to the classification of Scheie.[20] If the pigmented posterior trabecular meshwork was not visible in three fourths or more of the angle circumference in the primary position without manipulation in the presence of low illumination, the angle was considered occludable; otherwise, it was considered open. If the patient could not cooperate for gonioscopy, the van Herick technique was used to grade the peripheral anterior chamber depth with the slit lamp[21]; if the peripheral chamber was less than one fourth of corneal thickness, the angle was considered occludable, otherwise it was considered open. All patients had their pupils dilated unless contraindicated because of the risk of angle closure. After dilatation, the lens was examined with the slit lamp for the presence of PXF and for lens opacities. The lens was graded clinically at the slit lamp against photographic standards for nuclear opalescence, according to the Lens Opacities Classification System III (LOCS III),[22] and for cortical and posterior subcapsular lens opacities, according to the Wilmer classification.[23] Stereoscopic examination of the optic disc and peripapillary area was performed at the slit lamp using a 78-D lens. The vertical cup-to-disc ratio was assessed in units of 0.05 by the ophthalmologist. The following disc features evoked suspicion of glaucomatous damage: vertical cup-to-disc ratio 0.65 or more in either eye; asymmetry in cup-to-disc ratio of >0.2 between the two eyes; neuroretinal rim <0.2 in any quadrant in either eye; notch in the disc in either eye; disc hemorrhage in either eye; and nerve fiber layer defect. We assessed the agreement of examining ophthalmologists in this study for two parameters in 80 eyes: gonioscopy and optic disc evaluation with a 78-D lens. The agreement for grading the angle as open or occludable was high (κ statistic, 0.85), as was the agreement in determining the vertical cup-to-disc ratio (intraclass correlation, 0.97). Fundus examination was also performed with the indirect ophthalmoscope with a 20-D lens. Standard classifications were used to grade age-related macular degeneration and diabetic retinopathy.[24,25]

Visual Fields

Automated visual fields were performed with the Humphrey visual field analyzer (Carl Zeiss Meditec, Dublin, CA)[26] using the threshold central 24-2 strategy (stimulus size III) in those participants assessed to have suspected glaucoma based on the following criteria: any of the disc features listed earlier for suspected glaucomatous disc damage, IOP 22 mm Hg or more in either eye, and an IOP difference of 6 mm Hg or more between the two eyes. If the visual field was abnormal or unreliable, it was repeated on another day. Visual fields were considered unreliable if fixation losses were >20%, if false-positive responses were greater than 33%, and/or if false-negative responses were greater than 33%. Visual field defects were considered to be the result of glaucoma if they were consistent with optic disc damage and met at least two of the following three criteria: (1) abnormal glaucoma hemifield test, (2) $P < 5\%$ for corrected pattern SD, (3) a cluster of three non–edge-points with $P < 5\%$, including at least one point with a $P < 1\%$ on the pattern deviation plot.[27] The sensitivity and specificity of each of these criteria to detect glaucomatous visual field loss has been reported to be reasonable.[28] We chose to combine at least two of these criteria to define glaucomatous visual field loss to reduce the chance of false positives.

Examination at Home

Participants who were physically debilitated and unable to come to the clinic were examined at home with portable equipment, including a hand-held slit lamp and a Perkins applanation tonometer. This examination was similar to the one at the clinic, except that gonioscopy, examination with a 78-D lens, indirect ophthalmoscopy, and automated visual field perimetry were not performed.

Definitions

We diagnosed PXF on biomicroscopy if there was white dandrufflike material in the pupillary margin (undilated examination), on the anterior lens capsule (dilated examination), and/or on the trabecular meshwork (on gonioscopy).

For the present analysis, we defined nuclear cataract as nuclear opalescence of grade 3.0 or higher, according to LOCS III.[4] Cortical cataract was considered to be present if at least one eye had a Wilmer grade >2.[18] Posterior subcapsular cataract was considered present if at least one eye had a Wilmer >1.[18] Blindness was defined as presenting distance visual acuity <6/60 or central visual field loss of <10° in the better eye. Visual impairment was defined as presenting distance visual acuity <6/18 in the better eye or central visual field loss <20° in the better eye.

We have published details of the diagnosis of the subtypes of glaucoma.[10,17] To summarize, primary open-angle glaucoma was defined as glaucomatous optic disc damage with visual field loss in the presence of an open angle. Primary angle-closure glaucoma was defined as IOP of ≥22 mm Hg or glaucomatous optic disc damage with visual field loss in the presence of an occludable angle. We defined age-related macular degeneration (AMD) based on the international ARM classification.[24]

Statistical Analysis

The prevalence of PXF and other estimates in our sample were adjusted for the estimated age and sex distribution of the population in India for the year 2000[29] (http://www.census.gov). The 95% confidence intervals were calculated by assuming a Poisson distribution for prevalence <1% and normal approximation of binomial distribution for prevalence of >1%.[30] The association between PXF, demographic factors and other ocular diseases was assessed on computer with bivariate analysis, using either the χ^2 or Fisher exact test and by multiple logistic regression analysis (SPSS, ver. 12.0 for Windows; SPSS, Chicago, IL) for statistical analysis. A random-effects repeated model of generalized estimating equations modeling (GEE) was used to test the association of PXF with blindness and glaucoma defined at eye level considering subjects as random factors and adjusting the standard errors after computing the within-subject correlation of the eyes. Odds ratios (OR) were determined from the GEE model parameters, and 95% confidence intervals (CIs) are given. We used the general linear models (GLM; univariate ANOVA) to compare the mean difference of IOP between groups after adjusting for age. We also used the repeated-measures ANOVA to compare the IOP differences between groups. Another computer program (STATA ver. 8.0; Stata Corp., College Station, TX) was used to do these analyses. A two-tailed $P < 0.05$ was considered to be statistically significant for this analysis.

Results

The study had a high response rate with 10,293 (87.3%) of the 11,786 sampled subjects participating in the study. The response rate varied between 85.4% in the urban area (Hyderabad) and 84.6%, 91.6%, and 87.7% in the rural areas of West Godavari, Adilabad, and Mahabubnagar districts, respectively. Of the study subjects, 5439 (52.8%) of subjects were female,

TABLE 1. Associations of Age, Sex, Occupation, Socioeconomic Status and Place of Residence with the Prevalence of PXF in the Study Population

Characteristic	Total Population (n = 10,293)	Unilateral PXF n (%)	Bilateral PXF n (%)	PXF n (%)	P
Age					
0–15	2861	—	—	—	<0.0001*
16–29	1845	—	1 (0.1)	1 (0.1)	
30–39	1863	1 (0.1)	—	1 (0.1)	
40–49	1424	2 (0.1)	1 (0.1)	3 (0.2)	
50–59	1047	6 (0.6)	3 (0.3)	9 (0.9)	
60–69	900	18 (2.0)	13 (1.4)	31 (3.4)	
70+	353	7 (2.0)	21 (5.9)	28 (7.9)	
Sex					
Male	4854	16 (0.3)	24 (0.5)	40 (0.8)	0.197†
Female	5439	18 (0.3)	15 (0.3)	33 (0.6)	
Occupation§					
Indoor activity	5077	9 (0.2)	9 (0.2)	18 (0.4)	<0.0001†
Outdoor activity	4370	25 (0.6)	30 (0.7)	55 (1.3)	
Socioeconomic status‡					
Extreme lower	1354	5 (0.3)	5 (0.4)	10 (0.7)	0.678*
Lower	5212	18 (0.4)	22 (0.4)	40 (0.8)	
Middle	3172	10 (0.3)	10 (0.3)	20 (0.6)	
Upper	362	1 (0.3)	—	1 (0.3)	
Place of residence					
Urban	2522	6 (0.2)	5 (0.2)	11 (0.4)	0.081†
Rural	7771	28 (0.4)	34 (0.4)	62 (0.8)	

* χ^2 test.

† Fisher exact test.

‡ Socioeconomic status defined according to monthly per capita income in Indian rupees: ≤200 extreme lower; 201–500 lower; 501–2000 middle, and >2000 upper. Data on socioeconomic status were not available for 193 subjects. Data on education were not available for 811 subjects.

§ Data on occupation were not available for 846 subjects. All the subjects who were laborers (skilled and unskilled), fishermen, armed services/police, salespersons, and owners of cultivated land were considered to be in the outdoor activity group. Professionals, executives, managers, businesspersons, teachers, serviceworkers, homemakers, students/trainees, unemployed, and others were considered to be in the indoor activity group.

4303 (41.8%) subjects were illiterate, and 4370 (42.5%) subjects were engaged in outdoor occupational activities.

Prevalence of PXF

We found PXF present in one or both eyes of 73 (0.71%) of 10,293 participants of all ages, an overall age-gender-area–adjusted prevalence of 0.69 (95% CI: 0.53–0.86). The median age for participants with PXF was 66 years (mean ± SD, 64.9 ± 9.8; range, 26–84). The prevalence of PXF showed a significant age-related increase (χ^2 test; $P < 0.0001$; Table 1). The age-gender-area–adjusted prevalence of PXF in those ≥40 years of age was 3.01 (95% CI: 2.45–3.80); it was 6.29 (95% CI: 4.80–7.76) in those ≥60 years of age (Table 2). We calculated the age-specific standardized rates of PXF by using the U.S. population as a standard. The age-standardized rates of PXF were compared across various population-based studies (Table 3). The adjusted odds of prevalence of PXF increased significantly with each decade of increasing age. After adjustment for other demographic variables, PXF was not significantly associated with gender in this population (Table 4). The prevalence of PXF was significantly higher ($P < 0.0001$) among those engaged in predominantly outdoor occupational activities (n = 55, 1.3%), compared with those engaged in predominantly indoor occupational activities (n = 18, 0.4%). After adjusting for demographic factors, subjects with occupational outdoor activities had significantly higher ORs of prevalence of PXF (adjusted OR, 2.14; 95% CI: 1.10–4.16). The ORs of the prevalence of PXF also increased with decreasing socioeconomic status, but the increase was not statistically significant (Table 4).

PXF was present in 112 eyes of 73 persons—in only one eye in 34 (46.6%) and in both eyes in 39 (53.4%). It was present in the pupillary margins of 65 (58.0%) eyes and on the lens of 71 (63.4%), only on the lens surface in 48 (42.9%), only on the pupillary margins in 38 (33.9%), and in both locations combined in 26 (23.2%). We detected PXF on the trabecular meshwork (TM) of one (0.9%) eye with the combination of the

TABLE 2. Adjusted Prevalence Estimates of PXF by Age and Gender

	Adjusted Prevalence	95% CI
Over all (all ages)*	0.69	0.53–0.86
Age*		
<60 years	0.12	0.05–0.19
≥40 years	3.01	2.45–3.80
≥60 years	6.28	4.80–7.76
Gender†		
Over all (All ages)		
Male	0.49	0.29–0.69
Female	0.40	0.24–0.57
<60 years		
Male	0.12	0.02–0.22
Female	0.11	0.02–0.21
≥40 years		
Male	1.91	1.15–2.43
Female	1.60	1.05–2.15
≥60 years		
Male	5.66	3.84–7.47
Female	4.25	2.68–5.83

* Adjusted for age-area-gender.

† Age-area–adjusted prevalence.

TABLE 3. Comparison of Age-Specific Standardized Rates of PXF between Population-Based Studies in the ≥40-Year Age Group

Study Population	Age-Standardized Rates of PXF* (%)
Current Study (APEDS)	3.02
ACES[4]	7.6
Chennai Study[5]	4.9
Framingham Eye Study[31]†	1.9
Visual Impairment study[38]	0.98
Blue Mountains Eye Study[34]	2.3
Central Iran[41]†	9.4

* Age-standardization was done by considering the U.S. age-specific population as a standard.[29]

† Age-specific standardized PXF rates calculated for the Framingham Eye Study and for Central Iran were based on ≥52- and ≥50-year-old populations, respectively.

presence of PXF on the pupillary margin. Among the 112 eyes with PXF, 1 (0.89%) eye was pseudophakic, 12 (10.71%) were aphakic, and 1 aphakic eye had deposition of PXF material on the TM. One (1.4%) subject with PXF had a cataract-surgery–related complication in the affected eye.

Fifteen (20.5%; 95% CI: 11.2–29.8) subjects with PXF were blind (presenting distance visual acuity <6/60 in the better eye and/or central visual field loss of <10° in the better eye). The prevalence of blindness was significantly higher in subjects with PXF (age-adjusted OR, 2.19; 95% CI: 1.16–4.13). Eighteen (24.65%) subjects with PXF (95% CI: 14.81–34.59) were visually impaired (presenting distance visual acuity <6/18–6/60 in the better eye and/or central visual field loss <20° in the better eye). Three (4.1%) subjects with PXF were blind due to glaucoma. Other causes of blindness included cataract in seven (46.7%) persons, corneal diseases in two (13.3%), retinal diseases in two (13.3%), and refractive error in one (6.7%). Thirty (41.09%; 95% CI: 29.81–52.39) subjects with PXF were blind in the affected eye, and 33 (45.21%; 95% CI: 34.29–57.13) were visually impaired (presenting distance visual acuity <6/18–6/60 in the affected eye). When GEE was applied, blindness was significantly associated with PXF (adjusted OR, 2.97; 95% CI: 1.46–6.11; $P = 0.003$). However, the association of glaucoma with PXF was not statistically significant (adjusted OR, 2.04; 95% CI: 0.25–16.78; $P = 0.510$; Table 5).

Associations of PXF with Other Eye Diseases

Bivariate analysis showed an association between PXF and primary open-angle and closed-angle glaucoma; the presence of any cataract including nuclear, cortical, and posterior subcapsular cataract; and age-related macular degeneration (AMD; Table 6). After adjusting for age in the multivariable logistic regression model, the prevalence of PXF was found to be significantly more common in those with any type of cataract (adjusted OR, 2.86; 95% CI: 1.35–6.07; $P < 0.0001$). On further exploration of the association with the types of cataract, we found that PXF was significantly associated only with nuclear cataracts (adjusted OR, 2.00; 95% CI: 1.13–3.54; $P < 0.0001$). PXF was associated with open-angle and closed-angle glaucoma in bivariate analysis but the associations were not statistically significant after adjusting for age in a multivariate model (Table 6).

Four (5.5%) subjects with PXF had glaucoma (95% CI: 0.27–10.2). When GLMs were applied, the estimated mean ± SE of IOP with glaucoma and PXF was 24.14 ± 1.41. The mean ± SE of IOP for glaucoma in the absence of PXF was 18.94 ± 0.26; the difference was statistically significant ($P < 0.0001$). The interaction effect of PXF and glaucoma for the difference of mean IOP was significant ($P = 0.001$). After the main effects of any glaucoma and PXF were split, the presence of glaucoma was significantly associated with the difference of IOP across all levels of PXF ($P < 0.0001$).

DISCUSSION

PXF is associated with cataract and glaucoma and is the most common identifiable form of secondary open-angle glaucoma worldwide. Our results suggest that blindness was significantly

TABLE 4. Association of Age, Sex, Occupation, Socioeconomic Status, and Place of Residence with the Prevalence of PXF in a Multivariate Logistic Regression Analysis

Characteristic	Total Population (n = 10,293)	PXF n (%)	Adjusted OR (95% CI)	P
Age				
≤30	4706	1 (0.0)	1.00	
30–40	1863	1 (0.1)	1.66 (0.10–26.73)	0.720
40–50	1424	3 (0.2)	6.84 (0.71–66.23)	0.097
50–60	1047	9 (0.9)	26.97 (3.38–215.00)	0.002
60–70	900	31 (3.4)	107.59 (14.54–795.92)	<0.0001
70+	353	28 (7.9)	257.95 (34.58–1924.07)	<0.0001
Sex				
Male	4657	40 (0.7)	1.04 (0.63–1.70)	0.891
Female	5233	33 (0.6)	1.00	
Occupation				
Indoor activity	5077	18 (0.4)	1.00	
Outdoor activity	4370	55 (1.3)	2.14 (1.10–4.16)	0.021
Socioeconomic status				
Extreme lower	1354	10 (0.7)	2.10 (0.26–17.15)	0.489
Lower	5212	40 (0.8)	1.92 (0.25–14.58)	0.527
Middle	3172	20 (0.6)	1.49 (0.19–11.48)	0.690
Upper	362	1 (0.3)	1.00	
Place of residence				
Urban	2522	11 (0.4)	1.00	
Rural	7771	62 (0.8)	1.01 (0.46–2.19)	0.984

See footnotes in Table 1 for explanations of Occupation and Socioeconomic Status categories.

TABLE 5 Odds Ratios and Probabilities of the GEE Model to Assess the Association of PXF with Blindness and Glaucoma

Eyes (*n*)	PXF OR (95% CI)	*P*
Blind (*n* = 1103)	2.97 (1.46–6.11)	0.003
Any glaucoma (*n* = 163)	2.04 (0.25–16.78)	0.510

more common in subjects with PXF than in those without PXF (adjusted OR, 2.19; 95% CI: 1.16–4.13). We also found that 20.5% of those with PXF were blind, similar to data reported in the Aravind Comprehensive Eye Study (ACES) from a different part of southern India (25.7%).[4] If we use the World Health Organization (WHO) definition of blindness (visual acuity < 3/60 and visual field loss of <10° in the better eye) the prevalence of blindness among persons with PXF is 15.1% (95% CI: 6.9–23.3).

Previous studies have shown a marked age-related increase in the prevalence of PXF; typically <1% in persons younger than 60 years and increasing to 6.28% among subjects 60 years of age or older.[4,5,31–38] Although the reason for this age-related increase is unknown, it has been speculated that the changes in gene expression that occur with age may be responsible.[39] Our prevalence estimates for those 40 years of age or older are similar to those in the recent report from Chennai[5] (3.08%; 95% CI: 3.50–4.05), but less than that reported from Madurai[4] (6.0%; 95% CI: 5.3–6.6), both in southern India. This may be attributable to differences in the definitions and methodology or could even be caused by true population differences. As none of the studies seem to have looked for the earliest changes (brown stage or precapsular stage),[13] the true prevalence of PXF is more likely to be higher than the estimates reported by studies from south India. The age-specific standardized PXF rate (direct standardization using the population estimates for the U.S. for the year 2000 as the standard) in our study population for those 40 years of age or older was similar to the age-standardized rates of PXF in the Chennai study[5] and Blue Mountains Eye Study[34] and higher than the rates in the Framingham Eye Study,[31] and Visual Impairment Study[38] (Table 3). However, the age-specific standardized PXF rates in other population-based studies— one from southern India[4] and another from central Iran[41]—were high in comparison to those in our study (Table 3). Differences in prevalence of PXF across populations have to be interpreted with caution considering the difficulties and lack of standardization in diagnosis and the potential for subclinical or early cases to be missed.

There are conflicting reports of gender differences in the prevalence of PXF.[4,31–34,40,42,43] We found the prevalence of PXF among men to be marginally higher than in women, but the difference was not statistically significant. We also found a strong association between PXF and occupation. The fact that people exposed to outdoor activity as part of their occupation had a significantly higher prevalence of PXF (adjusted OR, 2.14; 95% CI: 1.10–4.16) compared with those whose occupation was restricted to indoor activity provides some support to the theory of an association between environmental factors (possibly solar radiation) and PXF.[7,8] The majority of India's population (almost 58%) depends heavily on the agricultural sector for employment and income and would be exposed to outdoor activities in a routine way that may constitute a significant risk factor for the occurrence of PXF in this population.

TABLE 6. Bivariate and Multivariable Logistic Regression Analyses for Associations with PXF

Characteristic	Total Population (*n* = 10,293)	PXF *n* (%)	Crude OR (95% CI)	*P*	Adjusted OR (95% CI)*	*P*
Blind						
Yes	275	15 (5.5)	9.91 (5.54–17.71)	<0.0001	2.19 (1.16–4.13)	0.015
No	10,018	58 (0.6)	1.00		1.00	
Any Cataract†						
Yes	1,554	61 (3.9)	29.71 (15.96–55.31)	<0.0001	2.86 (1.35–6.07)	0.006
No	8,739	12 (0.1)	1.00		1.00	
Nuclear cataract‡						
Yes	909	44 (4.8)	18.59 (11.33–30.54)	<0.0001	2.00 (1.13–3.54)	0.017
No	9,166	25 (0.3)	1.00		1.00	
Cortical Cataract‡						
Yes	541	17 (3.1)	6.26 (3.58–10.94)	<0.0001	1.02 (0.56–1.87)	0.937
No	9,498	49 (0.5)	1.00		1.00	
PS Cataract‡						
Yes	571	18 (3.2)	6.34 (3.69–11.07)	<0.0001	1.00 (0.53–1.71)	0.877
No	9,482	48 (0.5)	1.00		1.00	
Any glaucoma§						
Yes	95	4 (4.2)	6.45 (2.31–18.05)	<0.0001	1.89 (0.65–5.02)	0.241
No	10,198	69 (0.7)	1.00		1.00	
POAG						
Yes	48	2 (5.3)	6.23 (1.48–26.15)	0.012	1.42 (0.32–6.42)	0.646
No	10,243	71 (0.7)	1.00		1.00	
PACG						
Yes	47	2 (6.1)	6.37 (1.52–26.75)	0.011	2.63 (0.56–12.36)	0.219
No	9,856	71 (0.7)	1.00		1.00	
AMD‖						
Yes	75	3 (4.0)	6.03 (1.86–19.62)	0.003	1.60 (0.47–5.48)	0.456
No	10,215	70 (0.7)	1.00		1.00	

* Age-adjusted estimates.

† Significant nuclear, cortical, or posterior subcapsular cataract and/or a history of prior cataract surgery and/or total cataract.

‡ The data are missing on lens opacities, due to the presence of prior cataract surgery (pseudophakia or aphakia), total cataract, or the presence of phthisis bulbi, or the pupil was not dilated because of the risk of angle closure.

§ Primary open-angle glaucoma (POAG) and/or primary angle-closure glaucoma (PACG).

‖ AMD, age-related macular degeneration (includes both dry and wet forms).

The lack of a statistically significant association between decreasing socioeconomic status and PXF also seems to support the possibility of an environmental factor that may possibly be related to solar radiation. Our study, however, was not designed to explore this possibility further.

We found a difference ($P = 0.002$; repeated-measures ANOVA) in mean IOP of 1.06 mm Hg (data not shown) between eyes with PXF and eyes without PXF in our study population, almost similar to the earlier reports from Chennai[5] (1.29 mm Hg) and Australia[38] (1.02 mm Hg). Other studies have reported as much as a 5-mm Hg difference in mean IOP between these two groups.[44] GLM analysis revealed that the difference in mean IOP after adjustment for age was greater in people with the presence of both PXF and glaucoma. The lack of any statistically significant association between PXF and glaucoma (open angle or angle closure) could be related to the small sample size of persons with glaucoma and PXF in the study population. Slit lamp biomicroscopic examination (especially dilated), and gonioscopic evaluation of the angles is necessary to identify the presence of PXF, especially on the lens or TM. Many Indian ophthalmologists still primarily rely on IOP measurements for primary testing of glaucoma.[4] Routine slit lamp and dilated examinations must become preferred practice if PXF is to be detected.

The increasing prevalence of PXF and cataract with age and the association of PXF with the most common type of cataract (nuclear cataract) have public health implications for India. Improved healthcare results in a definite demographic shift toward aging in India that may result in a higher burden of both PXF and cataract. Eyes with PXF have a greater frequency of complications such as zonular dialysis, capsular rupture, and vitreous loss at the time of cataract extraction. The surgical procedure is more difficult because the pupil may not dilate well. It has also been shown that PXF patients have an increased risk of acute increase in IOP after cataract surgery.[45] Postoperative complications of posterior capsular opacification, capsule contraction syndrome, intraocular lens decentration, and inflammation are also greater in eyes with PXF. A preoperative diagnosis of PXF and appropriate precautions during surgery may help to reduce the frequency of complications. If the risk of complications is increased in the earlier stages of PXF (brown and precapsular), the magnitude of the problem is likely to be even higher.[13] Associations between AMD and PXF have been reported previously.[46] We did not have enough cases ($n = 3$) to study the association of PXF with AMD.

Our estimates of PXF may be an underestimate, since patients examined at home (approximately 2% of the total population studied) did not undergo standard slit lamp biomicroscopy and gonioscopy, and the diagnosis of PXF could have been missed. In addition, the presence of PXF material only on the lens in 42.9% of persons with PXF may mean that a proportion of the persons who had undergone bilateral cataract operations may have had PXF that we could not have diagnosed. The prevalence of glaucoma may be an underestimate in this study, because visual field tests were performed only on those subjects with suspicious discs or elevated IOP and were not performed on the 2% who had examinations only at their homes. A major strength of the study is that a standardized protocol was used, and a high participation rate was obtained (87.3%) in all the selected areas.[16] Another strength is the random selection of study subjects, which means that the sample can be considered representative of the entire population of AP. The proportions of refusals were equally distributed among all categories of age and gender and were similar to those who participated in the study (data not shown).

In summary, subjects with PXF had a significantly higher prevalence of blindness than did those without PXF. We also found a strong association of PXF with age and any type of cataract—in particular, nuclear cataract. India has a large cataract burden and has an aggressive cataract surgical program. Detection of PXF syndrome preoperatively may reduce or at least allow us to be prepared for the management of complications of surgery associated with this condition. The high prevalence of PXF in this older population mandates a complete clinical examination including slit lamp biomicroscopy and dilated examination to detect early PXF and other disease.

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References

1. Ritch R, Schlotzer-Schrehardt U. Exfoliation syndrome. *Surv Ophthalmol*. 2001;45:265–315.
2. Schumacher S, Schrehardt US, Martus P, Lang W, Naumann GOH. Pseudoexfoliation syndrome and aneurysms of the abdominal aorta. *Lancet*. 2001;357:359–360.
3. Thomas R, Paul P, Muliyil J. Glaucoma care update: glaucoma in India. *J Glaucoma*. 2003;12:81–87.
4. Krishnadas R, Nirmalan PK, Ramakrishnan R, et al. Pseudoexfoliation in a rural population of southern India: the Aravind Comprehensive Eye Survey. *Am J Ophthalmol*. 2003;135:830–837.
5. Arvind H, Raju P, Pual PG, et al. Pseudoexfoliation in south India. *Br J Ophthalmol*. 2003;87:1321–1323.
6. Allingham RR, Loftsdottir M, Gottfredsdottir MS, et al. Pseudoexfoliation syndrome in Icelandic families. *Br J Ophthalmol*. 2001; 85:702–707.
7. Taylor HR. Pseudoexfoliation, an environmental disease? *Trans Ophthalmol Soc UK*. 1979;99:302–307.
8. Taylor HR. The environment and the lens. *Br J Ophthalmol*. 1980;64:303–310.
9. Jacob A, Thomas R, Koshi SP, Braganza A, Muliyil J. Prevalence of primary glaucoma in an urban south Indian population. *Indian J Ophthalmol*. 1998;46:81–86.
10. Dandona L, Dandona R, Srinivas M, et al. Open-angle glaucoma in an urban population in southern India; The Andhra Pradesh Eye Disease Study. *Ophthalmology*. 2000;107:1702–1709.
11. Ramakrishnan R, Nirmalan PK, Krishnadas R, et al. Glaucoma in a rural population of southern India: the Aravind comprehensive eye survey. *Ophthalmology*. 2003;110:1484–1490.
12. Jehan FS, Mamalis N, Crandall AS. Spontaneous late dislocation of intraocular lens within the capsular bag in pseudoexfoliation patients. *Ophthalmology*. 2001;108:1727–1731.
13. Conway RM, Schrehardt US, Kuchle M, Naumann GOH. Pseudoexfoliation syndrome: pathological manifestations of relevance to intraocular surgery. *Clin Exp Ophthalmol*. 2004;32:199–210.
14. Dandona L, Dandona R, Naduvilath TJ, et al. Is current eye-care policy focus almost exclusively on cataract adequate to deal with blindness in India? *Lancet*. 1998;351:1312–1316.
15. Dandona L, Dandona R, Naduvilath TJ, et al. Burden of moderate visual impairment in an urban population in southern India. *Ophthalmology*. 1999;106:497–504.
16. Dandona L, Dandona R, Srinivas M, et al. Blindness in the Indian State of Andhra Pradesh. *Invest Ophthalmol Vis Sci*. 2001;42:908–916.
17. Dandona L, Dandona R, Mandal P, et al. Angle-closure Glaucoma in an urban population in southern India; The Andhra Pradesh Eye Disease Study. *Ophthalmology*. 2000;107:1710–1716.
18. Dandona R, Dandona L, Naduvilath TJ, et al. Design of a population-based study of visual impairment in India: the Andhra Pradesh Eye Disease Study. *Indian J Ophthalmol*. 1997;45:251–257.

19. Ferris FL, Kassoff A, Bresnick GH, Bailey I. New visual acuity charts for clinical research. *Am J Ophthalmol*. 1982;94:91–96.
20. Scheie HG. Width and pigmentation of the angle of the anterior chamber: a system of grading by gonioscopy. *Arch Ophthalmol*. 1957;58:510–512.
21. Van Herick W, Shaffer RN, Schwartz A. Estimation of width of angle of anterior chamber: incidence and significance of the narrow angle. *Am J Ophthalmol*. 1969;68:626–629.
22. Chylack LT, Wolfe JK, Singer DM, et al. The Lens Opacities Classification System III. *Arch Ophthalmol*. 1993;111:831–836.
23. Taylor HR, West SK. A simple system for the clinical grading of lens opacities. *Lens Research*. 1988;5:175–181.
24. Bird AC, Bressler NM, Bressler SB, et al. An international classification and grading system for age-related maculopathy and age-related macular degeneration. the International ARM Epidemiological Study Group. *Surv Ophthalmol*. 1995;39:367–374.
25. Olk RJ, Lee CM. *Diabetic Retinopathy: Practical Management.* Philadelphia: JB Lippincott;, 1993;3–20.
26. Humphrey Instruments, Inc. Humphrey Field Analyzer II User's Guide. San Leandro, CA: Humphrey Instruments Inc.; 1994.
27. Anderson DR. *Automated Static Perimetry.* St. Louis: Mosby Year Book, 1992;123.
28. Katz J, Sommer A, Gaasterland DE, Anderson DR. Comparison of analytic algorithms for detecting glaucomatous visual field loss. *Arch Ophthalmol*. 1991;109:1684–1689.
29. International Database available at http://www.census.gov/ Washington, DC: U.S. Census Bureau, September, 2004
30. Rosner B. *Fundamentals of Biostatistics.* 2nd ed. Boston. PWS Publishers; 1986;84–92,404–8.
31. Hiller R, Sperduto RD, Krueger DE. Pseudoexfoliation, intraocular pressure, and senile lens changes in a population-based survey. *Arch Ophthalmol*. 1982;100:1080–1082.
32. Ringvold A, Blika S, Elsas T, et al. The middle-Norway eye-screening study. *Acta Ophthalmol*. 1988;66:652–658.
33. Summanen P, Jonjum AM. Exfoliation syndrome among Saudis. *Acta Ophthalmol* 1988;(suppl)184:107–111.
34. Mitchell P, Wang JJ, Hourihan F. The relationship between glaucoma and pseudoexfoliation: The Blue Mountains Eye Study. *Arch Ophthalmol*. 1999;117:1319–1324.
35. Tarkkanen AH. Exfoliation syndrome. *Trans Ophthalmol Soc UK*. 1986;105:233–236.
36. Shimizn K. Prevalence of exfoliation syndrome in the Japanese. *Acta Ophthalmol*. 1988;(suppl)184:112–115.
37. Cashwell LF, Shields MB. Exfoliation syndrome: prevalence in a south eastern United States population. *Arch Ophthalmol*. 1988; 106:335–336.
38. McCarthy CA, Taylor HR. Pseudoexfoliation syndrome in Australian adults. *Am J Ophthalmol*. 2000;129:629–633.
39. Karger RA, Jeng SM, Johnson DH, Hodge DO, Good MS. Estimated incidence of pseudoexfoliation syndrome and pseudoexfoliation glaucoma in Olmsted Country, Minnesota. *J Glaucoma*. 2003;12: 193–197.
40. Mitchell P, Wang JJ, Smith W. Association of pseudoexfoliation syndrome with increased vascular risk. *Am J Ophthalmol*. 1997; 124:685–687.
41. Nouri-Mahdavi K, Nosrat N, Sahebghalam R, et al. Pseudoexfoliation syndrome in central Iran: a population-based survey. *Acta Ophthalmol Scand*. 1999;77:581–584.
42. Ekstrom C. Prevalence of pseudoexfoliation in a population 65–75 years of age. *Acta Ophthalmol*. 1987;(suppl)65:9–10.
43. Kozobolis VP, Papazanaki M, Vlachonikolis IG, Pallikaris IG, Tsambarlakis. Epidemiology of pseudoexfoliation in the island of Crete (Greece); *Acta Ophthalmol Scand*. 1997;75:726–729.
44. Davanger M, Ringvold A, Bilka S. Pseudoexfoliation, IOP and glaucoma. *Acta Ophthalmol* (*Copenh*). 1991;69:569–573.
45. Savage JA, Tohmas JV, Belcher CD, Simmons RJ. Extracapsular cataract extraction and posterior chamber intraocular lens implantation in glaucomatous eyes. *Ophthalmology*. 1995;92:1506–1516.
46. Kozobolis VP, Detorakis ET, Tsilimbaris MK, et al. Correlation between age-related macular degeneration and pseudoexfoliation syndrome in the population of Crete (Greece). *Arch Ophthalmol*. 1999;117:664–669.