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Regional variation in the incidence of pseudo-exfoliation in the Andhra Pradesh Eye Disease Study (APEDS)

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BACKGROUND: To report the 15-year incidence rate of pseudo-exfoliation (PXF), PXF glaucoma and regional variation among rural participants in the Andhra Pradesh Eye Disease Study (APEDS) III.

METHODS: This population-based longitudinal study was carried out at three rural study sites. Individuals of all ages who participated at baseline with a mean 15-year follow-up visit were included. Detailed Comprehensive ophthalmic examination was performed on all participants. The main outcome measure was development of PXF during the follow-up period in participants who were phakic in one or both eyes without PXF at baseline.

RESULTS: Among 5395 participants, 5108 (94.6%) met the inclusion criteria. There were 93 (1.82%; 95% confidence interval (CI), 1.47–2.22) cases of incident PXF. Their median baseline age (1st, 3rd quartiles) was 51 (44, 59) years and the male: female ratio was 1.3:1. There was no case of incident PXF in participants aged <30 years at baseline. The incidence rate per 100 person years (95% CI) among all ages and those aged ≥30 years at baseline was 1.73 (1.64–1.82) and 3.73 (3.53–3.93), respectively. PXF material was located on iris as well as anterior surface of lens and it was often bilateral. Participants living in two study sites and increasing age were associated with the incidence of PXF. The 15-year incidence of PXF glaucoma (95% CI) in participants ≥30 years of age at baseline was 0.33% (0.14–0.66).

CONCLUSION: There is significant regional variation in incidence of PXF in south India which warrants further investigation.

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INTRODUCTION

Pseudo-exfoliation (PXF) is an age-related disorder of the extracellular matrix. The condition is often unilateral at the time of initial diagnosis but becomes bilateral in the majority over time. It is characterized by progressive accumulation of fibrillar extracellular amyloid-like deposits in several intraocular and extraocular tissues. The exfoliation material is a highly glycosylated proteinaceous complex, which is extremely resistant to degradation [1]. In the eye, the material deposits on the lens zonules, anterior lens capsule, pupillary margin, corneal endothelium and trabecular meshwork via the circulating aqueous humor [2]. The condition can lead to pseudo-exfoliation glaucoma (PXFG) that is the most common cause of secondary open angle glaucoma globally [3]. The mechanism of increased intraocular pressure (IOP) is thought to be due to greater resistance to the outflow of aqueous humor as a result of passive deposition of exfoliation material within the meshwork and inner wall of the Schlemm's canal, as well as local production [2]. PXFG runs a more aggressive clinical course than primary open angle glaucoma [3].

The prevalence of PXF increases with advancing age [2]. However, the prevalence of the condition shows large ethnic and geographic variation. Scandinavian, Mediterranean and several African countries are much more affected than other parts of the world, such as the USA, Australia and Asian countries [2, 4]. While there may be true population differences, heterogeneity in the study sample, differences in diagnostic criteria and clinician-dependent factors may account for some of the variability. Moreover, there is scarcity of data on the incidence of PXF and associated risk factors [5–9], which limits comparison between geographic locations.

The Andhra Pradesh Eye Disease Study (APEDS) was a large population-based cohort study undertaken in southern India. The baseline study i.e., APEDS I (1996–2000) was designed to determine the prevalence of eye diseases and their risk factors, the magnitude of blindness and low vision and their effect on quality of life, and barriers to accessing eye care services [10]. The study had urban and rural sites. APEDS II (2009–2010) was a feasibility study in which participants examined in APEDS I were traced to estimate migration

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and mortality rates, and to identify participants willing to be re-examined [11]. In APEDS III (2012–2016), rural participants (the urban site could not be identified because of change in landscape and new infrastructure development in the region) were re-examined 15 years (range 13–17 years) after APEDS I, with the objective of estimating the incidence and progression of visual loss from the major eye diseases [11]. In this publication, we report the incidence of PXF and risk factors at baseline associated with its development.

MATERIALS AND METHODS

The study adhered to the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board of the Hyderabad Eye Research Foundation, L V Prasad Eye Institute, Hyderabad, India and the London School of Hygiene and Tropical Medicine, London. Written informed consent was obtained from all participants, and from legal guardians for minors (<18 years of age).

Details of methodology of the three phases of Andhra Pradesh Eye Disease Study (APEDS I to III) have already been published [10, 11]. In brief, APEDS I examined 7771 participants from three rural and 2552 participants from one urban cluster in Andhra Pradesh state (before the state was divided) in southern India between 1996 to 2000 [11]. In the feasibility study (APEDS II, 2009–2010), 5447 (70.1%) participants in the rural areas were traced in Thoodukurthy (Mahbubnagar district), Mudhole (Adilabad district) and Tanuku (West Godavari district). Between 2012 and 2016 (APEDS III) these three rural areas were visited and 5395 (69.4% of the original rural cohort) were re-examined using the same methodology as in APEDS I [11]. Relevant details of the design and methodology of APEDS III are summarized below.

At baseline (APEDS I) and follow-up (APEDS III), socio-demographic and data on risk factors were collected from participants in their place of residence [10, 11]. A comprehensive eye examination was performed on all participants at study sites set up in each district. The study team was trained on the procedures. There were four clinical investigators in the study but only one was present at any given time. All clinical investigators underwent interobserver agreement assessment with the principal investigator (PI, an experienced glaucoma specialist) for lens grading, gonioscopy and optic disc evaluation before joining the study. Agreement between the PI and other investigators in the classification of the anterior chamber angle into occludable or open was high (kappa coefficient range 0.78–0.85). The vertical cup-to-disc ratio (CDR) was assessed subjectively in units of 0.05, with a kappa coefficient ranging between 0.69 and 0.81 [12].

Visual acuity (VA) was tested in each eye separately and then binocularly. Participants with a presenting distance or near VA of logMAR >0.0 underwent streak retinoscopy followed by subjective refraction, performed by a trained optometrist/vision technician. The IOP was measured using Goldmann applanation tonometer (Carl Zeiss Meditec, Inc) before and after pupillary dilatation. One more reading was taken if the initial reading was >21 mm Hg. Gonioscopy was performed in a dark room with a short and narrow light beam (1–2 mm) to avoid pupillary constriction. In APEDS I, an NMR-K 2-mirror lens (Ocular Instruments, Bellevue, WA) was used, whereas in APEDS III, an NMR-K 2-mirror lens was used followed by a Sussman 4 mirror lens (Volk, OH, USA). The angle was considered occludable if the pigmented posterior trabecular meshwork was not visible in 180° of the angle circumference in the primary position without manipulation under dim illumination. Eyes with an occludable angle underwent laser iridotomy prior to pupil dilation. Evaluation of the optic disc and peripapillary area were performed by slit-lamp biomicroscopy using a 78-D (Volk, OH, USA) lens. Indirect ophthalmoscopy was performed to examine the entire fundus using a 20-D (Volk, OH, USA) lens. The presence of PXF material was specifically sought on the pupil margin and on the anterior surface of the lens, before and after pupil dilation, respectively. Participants who were unable to visit the study site were examined at home using similar methods [11].

Automated visual fields with the Humphrey Visual Field analyzer (Humphrey Instruments Inc., San Leandro, CA) were attempted using the threshold central 24-2 strategy (stimulus size III) for all participants with or suspected to have glaucoma [11]. Visual fields were also assessed if the IOP was ≥22 mm Hg in either eye, or if the inter-eye IOP difference was ≥6 mm Hg. If the visual field was abnormal or unreliable, the test was repeated. The criteria used to determine a glaucomatous visual field defect included a field defect that correlated with optic disc damage and met ≥2 of Anderson's three criteria.

The rural cohort was re-examined in three phases between 2012 and 2016 after a mean of 15 years (range 13–17 years) to determine the incidence of eye diseases. The study locations were visited as follows: 2012/2013, Thoodukurthy village, Mahbubnagar district; 2013/2014, Mudhole village, Adilabad district; and 2015/2016 Tanuku village, West Godavari district.

Definition of glaucoma

The definition of glaucoma was based on the International Society of Geographical and Epidemiological Ophthalmology (ISGEO) classification [13], using normative data from the Chennai Glaucoma Study (CGS), south India for the 99.5th and 97.5th percentile cutoffs for IOP and CDRs [14]. The rationale for using CGS data, the cutoff and the three levels of evidence to make the diagnosis of glaucoma in survey settings have been explained earlier [15].

The incidence of PXF was defined as the development of PXF during follow up among participants who were phakic in one or both eyes and who did not have PXF in APEDS I. Hyperopia and myopia were defined as spherical equivalent ±0.50 D or greater in a phakic eye. Hypertension (HTN) was considered to be present if a participant had a history of high blood pressure diagnosed by a physician and/or was on anti-hypertensive medication at the time of examination and/or was found to have blood pressure of ≥140/90 mm Hg. Data on systemic HTN were obtained from participants aged over 15 years of age at baseline. Diabetes mellitus (DM) was considered to be present if there was a history of DM and/or diabetic retinopathy was detected on clinical examination.

Statistical analysis

Shapiro–Wilk test was used to check normality of data distribution. Data are presented as means (standard deviation) and medians (1st, 3rd quartile), as appropriate. Participants were classified into five groups using their age at baseline (APEDS I) as 0–29 years, 30–39 years, 40–49 years, 50–59 years and 60 years and above. The association of PXF with study site location, and baseline risk factors viz. age, sex, outdoor work, body

Table 1. Incidence of pseudo-exfoliation by age at baseline and gender.

Age group (years)	Male		Female		Total		Incidence rate/100 person years (95% CI)
	At risk	*n* (%) (95% CI)	At risk	*n* (%) (95% CI)	At risk	*n* (%) (95% CI)	
0–29	1346	0	1389	0	2735	0	0
30–39	494	3 (0.6) (0.12, 1.76)	635	4 (0.62) (0.17, 1.6)	1129	7 (0.62) (0.24, 1.27)	0.59 (0.48, 0.72)
40–49	324	19 (5.86) (3.56, 9)	388	13 (3.35) (1.79, 5.66)	712	32 (4.49) (3.09, 6.28)	4.39 (4.01, 4.8)
50–59	173	18 (10.4) (6.28, 15.94)	190	15 (7.89) (4.48, 12.68)	363	33 (9.09) (6.34, 12.53)	8.55 (7.82, 9.34)
≥60	77	13 (16.88) (9.3, 27.13)	92	8 (8.69) (3.82, 16.41)	169	21 (12.42) (7.85, 18.36)	11.96 (10.71, 13.3)
Total	2414	53 (2.19) (1.64, 2.86)	2694	40 (1.48) (1.06, 2.01)	5108	93 (1.82) (1.47, 2.22)	1.73 (1.64, 1.82)

CI confidence interval.

Table 2. Comparison of participants with or without incident pseudo-exfoliation.

Variable	Participants ($n = 5108$)	Without PXF ($n = 5015$) (98.18%)	With PXF ($n =$)93 (1.82%)	p value
Study center, *n* (%)				
West Godavari	1512 (29.6)	1500 (29.9)	12 (12.9)	
Adilabad	1923 (37.6)	1890 (37.6)	33 (35.4)	
M. Nagar	1673 (32.7)	1625 (32.4)	48 (51.6)	**<0.01**
Age group (years), *n* (%)				
0–29	2735 (53.5)	2735 (54.5)	0	
30–39	1129 (22.1)	1122 (22.3)	7 (7.5)	
40–49	712 (13.9)	680 (13.5)	32 (34.4)	
50–59	363 (7.1)	330 (6.5)	33 (35.4)	
60 and above	169 (3.3)	148 (2.9)	21 (22.5)	**<0.01**
Male sex, *n* (%)	2414 (47.2)	2361 (47)	53 (56.9)	0.05
Outdoor work, *n* (%)[a]	2620 (71.6)	2550 (71.5)	70 (75.2)	0.43
BMI, *n* (%)[b]				
18.5–24.99	1631 (34.5)	1588 (34.3)	43 (46.2)	
<18.5	2847 (60.3)	2806 (60.6)	41 (44)	
25–29.9	192 (4)	184 (3.9)	8 (8.6)	
≥30	50 (1)	49 (1)	1 (1)	**<0.01**
Hypertension, *n* (%)[c]	881 (25.7)	861 (25.9)	20 (21.5)	0.33
Diabetes mellitus, *n* (%)	16 (0.3)	14 (0.2)	2 (2.1)	**<0.01**
Smoking status, *n* (%)				
Never smoker	4187 (81.9)	4134 (82.4)	53 (56.9)	
Past smoker	132 (2.5)	125 (2.4)	7 (7.5)	
Current smoker	789 (15.4)	756 (15)	33 (35.4)	**<0.01**
Alcohol consumption, *n* (%)				
Never alcohol	3908 (76.5)	3868 (77.1)	40 (43)	
Past alcohol	123 (2.4)	115 (2.2)	8 (8.6)	
Current alcohol	1077 (21)	1032 (20.5)	45 (48.3)	**<0.01**
IOP in mm Hg				
[randomly selected eye; median (1st, 3rd quartiles]	14 (14, 16)	14 (14, 16)	16 (14, 17)	**<0.01**
Education level (years), *n* (%)[d]				
None	2239 (48.3)	2177 (47.9)	62 (66.6)	
Primary	1343 (28.9)	1323 (29.1)	20 (21.5)	
Secondary	845 (18.2)	837 (18.4)	8 (8.6)	
Higher	208 (4.4)	205 (4.5)	3 (3.2)	**<0.01**

Statistically significant p values are bold.
PXF pseudo-exfoliation, *M. Nagar* Mahabubnagar, *BMI* body mass index, *IOP* intraocular pressure.
[a]Data recorded for those over 15 years of age at baseline, i.e., APEDS I. Missing data: 74.
[b]Missing data: 388.
[c]Data recorded for those over 15 years of age at baseline, i.e., APEDS I. Missing data: 60.
[d]Missing data 473.

mass index, systemic HTN, DM, smoking, alcohol intake and education level were evaluated first using univariable analysis, followed by multivariable analysis using logistic regression. The choice of risk factors was guided by published literature and our clinical insight. The variables which achieved statistical significance in the univariable analysis or were considered clinically important were included into the multivariable analysis. Model selection was performed using the Akaike information criterion. The goodness of fit for logistic regression model was checked using the Hosmer–Lemeshow test, and multi-collinearity was checked by calculating the variance inflation factor. Statistical analyses were performed using Stata 12.1 (StataCorp, College Station, TX). A two-sided p value of <0.05 was considered statistically significant.

RESULTS

In APEDS I, 7771 participants aged 0–95 years were examined in the three rural clusters. In APEDS III, 5395 (69.4%) of these participants were re-examined. The examination was performed at home in 417 (7.7%) participants using similar methods [11]. Visual field assessments were advised in 734 (13.6%) participants and were performed in 579 participants in APEDS III. Reasons for non-participation and a comparison between participants and non-participants in APEDS III has been published [16]. Among participants, 52.9% were female and 49% had not received any formal education. The majority of participants did not have diabetes or HTN, and did not smoke or consume alcohol [16].

Incidence and risk factors for PXF

At baseline (APEDS I), there were 11 cases of PXF, and in another 93 participants data on the presence or absence of PXF was not recorded. In APEDS III, the status of PXF was not recorded in 14 participants, 167 participants were pseudophakic in both eyes and two others had bilateral aphakia and were excluded. Thus, after excluding 287 participants, data from 5108 participants were analyzed (Supplementary Fig. 1).

Table 3. Logistic regression to assess the association between pseudo-exfoliation and risk factors.

Variable	Sub-variable	Univariate regression		Multivariate regression	
		Odds ratio (95% CI)	*p* value	Odds ratio (95% CI)	*p* value
Study site	West Godavari	1.0		1.0	
	Adilabad	2.18 (1.12, 4.24)	**0.02**	2.67 (1.31, 5.44)	**<0.01**
	M. Nagar	3.69 (1.95, 6.97)	**<0.01**	2.42 (1.17, 5.0)	**0.01**
Age (years) per 1-year increase		1.11 (1.09, 1.13)	<0.01	1.1 (1.08, 1.12)	**<0.01**
Male sex		1.48 (0.98, 2.25)	0.05	1.37 (0.7, 2.69)	0.35
Outdoor work		1.21 (0.75, 1.95)	0.43		
Body mass index	18.5–24.99	1.0		1.0	
	<18.5	0.53 (0.35, 0.83)	<0.01	0.94 (0.59, 1.51)	0.81
	25–29.9	1.60 (0.74, 3.46)	0.22	1.73 (0.75, 3.96)	0.19
	≥30	0.75 (0.1, 5.58)	0.78	1.23 (0.15, 9.67)	0.83
Hypertension		0.78 (0.47, 1.29)	0.34		
Diabetes mellitus		7.85 (1.75, 35.04)	<0.01	2.66 (0.51, 13.76)	0.24
Smoking status	Never	1.0		1.0	
	Past	4.36 (1.94, 9.79)	<0.01	0.99 (0.36, 2.69)	0.99
	Current	3.4 (2.18, 5.29)	<0.01	1.02 (0.52, 2.01)	0.94
Alcohol intake	None	1.0		1.0	
	Past	6.72 (3.07, 14.69)	<0.01	1.56 (0.63, 3.87)	0.33
	Current	4.21 (2.73, 6.49)	<0.01	1.55 (0.9, 2.69)	0.11
Education level	None	1.0			
	Primary	0.65 (0.17, 2.48)	0.53		
	Secondary	1.03 (0.3, 3.5)	0.95		
	Higher	1.94 (0.6, 6.25)	0.26		

Statistically significant *p* values are bold.

Overall, there were 93 (1.82%, [95% confidence interval (CI) 1.47–2.22) cases of incident PXF (Table 1), giving an incidence rate of 1.73 (CI 1.64–1.82)/100 person years. There was no case of incident PXF in participants aged <30 years at baseline. Therefore, the crude 15-year incidence and incidence rate of PXF in participants aged ≥30 years were 3.91% (95% CI, 3.17, 4.77) and 3.73 (95% CI, 3.53–3.93) per 100 person years, respectively. The median baseline age of participants who developed PXF was 51 (44, 59, range 37–76) years. The male: female distribution was 53 (56.9%): 40 (43%). About half of the cases, 48 (51.6%) were detected in Mahbubnagar district, 33 (35.4%) in Adilabad district and the remaining 12 (12.9%) were detected at West Godavari district.

Among the 93 participants with incident PXF, 69 were bilaterally phakic and the rest ($n = 24$) were unilaterally phakic. Among the former, the condition was unilateral in 29 (42%) and bilateral in 40 (57.9%). Findings in affected right ($n = 61$) and left ($n = 72$) eyes were similar with respect to the location of the PXF material: iris and lens (66.9%), iris only (24.8%) and lens only (8.3%).

Participants with incident PXF differed from those without incident PXF in terms of district of residence, age, BMI, presence of DM, smoking and alcoholism, level of IOP and level of education (Table 2).

In the univariable regression model, the following variables were statistically associated with the incidence of PXF: Adilabad and Mahbubnagar districts, older age, lower BMI, presence of DM, smoking, and consumption of alcohol (Table 3). However, only study sites (Adilabad and Mahbubnagar district) and older age retained significance in the multivariable regression model. Gender, outdoor work, presence of systemic HTN and education level were not associated with incident PXF. The Hosmer–Lemeshow test indicated a good fit of the regression model ($p = 1.00$).

Incidence and risk factors for PXF glaucoma

Eight participants (0.15%, 95% CI: 0.06–0.3) had incident PXF glaucoma in one or both eyes; the diagnosis was based on level 1 ISGEO evidence (four participants) and level 2 evidence (four participants). The 15-year incidence of PXF glaucoma in participants aged ≥30 years was 0.33% (95% CI: 0.14–0.66). In another 12 (0.23%) participants, the presence or absence of glaucoma could not be determined due to non-visualization of the optic disc as well as their inability to perform automated perimetry due to poor VA. None of these 12 participants had IOP > 99.5th percentile. In addition, one (0.01%) participant each had ocular hypertension secondary to PXF, optic disc hemorrhage and suspicion of glaucomatous optic neuropathy. Overall, 13 (0.25%) participants had >180 degrees of occludable angles, with or without synechiae formation in one eye or both eyes; three had incident PXF glaucoma and remaining ten had incident PXF.

DISCUSSION

In this study, the crude 15-year incidence of PXF was 1.82% (95% CI, 1.47–2.22) across all ages. There were no cases in the youngest age group, and the crude incidence in participants aged over 30 years at baseline was 3.91% (95% CI, 3.17, 4.77). A higher incidence of PXF was identified in two of the rural cluster sites and in older participants but none of the other risk factors showed a statistically significant difference.

In our study, among 69 bilaterally phakic participants with incident PXF, the PXF material was unilateral in 29 (42%). In contrast, incident PXF was unilateral in 73% of participants in the US [5] study and in 61% in the Greek [9] study. The mean age of the participants who developed PXF was higher in both these studies than in our study. However, the possibility of subclinical

Table 4. Comparison among three study sites.

Variable	West Godavari	Adilabad	M. Nagar	*p* value[a]	*p* value[b]	*p* value[c]
Participants with incident PXF, *n* (%)	12 (0.7)	33 (1.7)	48 (2.8)	**<0.01**	0.12	**<0.01**
Mean age (SD)	27.6 (16)	24.5 (16.4)	28.6 (17.7)	**<0.01**	**<0.01**	0.19
Male sex, *n* (%)	704 (46.5)	930 (48.3)	780 (46.6)	0.47		
Outdoor work, *n* (%)[d]	590 (53.8)	1044 (78.6)	986 (79.8)	**<0.01**	**<0.01**	**<0.01**
BMI, *n* (%)[e] (Age ≥12 years at baseline)						
18.5–24.99	569 (35.1)	456 (28.1)	594 (36.6)			
<18.5	631 (24.3)	1128 (43.5)	829 (32)			
25–29.9	110 (57.5)	27 (14.1)	54 (28.2)			
≥30	24 (57.1)	14 (33.3)	4 (9.5)	**<0.01**	**0.01**	0.06
Hypertension, *n* (%)[f]						
(Age >15 years at baseline)	339 (32.6)	300 (24.5)	242 (20.8)	**<0.01**	**<0.01**	**<0.01**
Smoking status, *n* (%)						
Never smoker	1196 (28.5)	1641 (39.1)	1350 (32.2)			
Past smoker	52 (39.3)	36 (27.2)	44 (33.3)			
Current smoker	264 (33.4)	246 (31.1)	279 (35.3)	**<0.01**	**<0.01**	0.73
Alcohol consumption, *n* (%)						
Never alcohol	1361 (34.8)	1650 (42.2)	897 (22.9)			
Past alcohol	34 (27.6)	32 (26)	57 (46.3)			
Current alcohol	117 (10.8)	241 (22.3)	719 (66.7)	**<0.01**	**<0.01**	**<0.01**
Education level, *n* (%)[g]						
None	493 (22)	941 (42)	805 (35.9)			
Primary	554 (41.2)	456 (33.9)	333 (24.8)			
Secondary	294 (34.7)	242 (28.6)	309 (36.5)			
Higher	56 (26.9)	69 (33.1)	83 (39.9)	**<0.01**	**<0.01**	**<0.01**
House visits, *n* (%)	156 (10.3)	85 (4.4)	176 (10.5)	**<0.01**	**<0.01**	0.99
Participants who underwent bilateral cataract surgery between 2 examination points, *n* (%)	78 (4.9)	53 (2.6)	38 (2.2)	**<0.01**	**<0.01**	**<0.01**

Statistically significant *p* values are bold.
M. Nagar Mahabubnagar, *PXF* pseudo-exfoliation, *SD* standard deviation, *BMI* body mass index.
[a]Overall.
[b]Between West Godavari and Adilabad.
[c]Between West Godavari and M. Nagar.
[d]Data recorded for those over 15 years of age at baseline, i.e., APEDS I. Missing data: 74.
[e]Missing data: 388.
[f]Data recorded for those over 15 years of age at baseline, i.e., APEDS I. Missing data: 60.
[g]Missing data 473.

PXF may explain the difference in the distribution of incident PXF between studies [17, 18].

The exfoliative material was visible most commonly on the iris as well as the anterior surface of the lens in phakic eyes. We found the PXF material on the lens surface in ~60% of cases, similar to the study from Greece [9]. Anterior lens surface was also the commonest location of PXF in the other Indian study [7].

It is recognized that the incidence of PXF increases with increasing age [5, 7, 8]. Our study supports this observation. There was no incident case in individuals below the age of 30 years at baseline. The incidence of PXF (Supplementary Fig. 2) as well as the incidence rate per 100 person years (Table 1) showed a steady increase with increasing age. The number of older participants was small, which could be due to mortality; cataract surgery or out-migration. However, PXF has not been shown to affect all-cause mortality in population-based studies [19, 20].

In our study, the incidence of PXF did not differ by sex, unlike most earlier studies which had a higher odds of incident PXF in females [5, 6, 8, 9]. The high rate of cataract surgery in females (56.5% versus 43.4% in males) might have contributed to our observation. The Chennai Eye Disease Incidence Study also did not find relation between sex and incident PXF [7].

Our study showed regional variation in the incidence of PXF (Table 4). Tanuku (West Godavari district) had the lowest incidence of PXF. Participants in Tanuku differed in several respects to those in other districts, as they were more likely to have undergone cataract surgery, and to work indoors. They were also better educated, had higher BMIs and were more likely to have systemic HTN. These findings point to less UV exposure, which may explain the lower incidence of PXF. Although PXF is more difficult to detect clinically after cataract surgery [21, 22], PXF was detected in 3/169 (1.8%) participants with bilateral pseudophakia or aphakia, which is not different from the overall sample. However, as PXF is a risk factor for cataract, a higher proportion in operated eyes might be expected. Ascertainment bias, may therefore, contribute to the lower incidence. Different study teams worked in the different study sites, but all underwent rigorous training, and interobserver agreement findings for a number of parameters had high kappa values [12]. We do not therefore consider that measurement error contributed to the findings. In the Chennai Eye Disease Incidence Study, the incidence of PXF was lower among urban participants than rural dwellers and the authors attributed the lower incidence in urban areas to lesser UV exposure [7]. Another study from US also suggested UV exposure as a risk factor for incident PXF [23]. The prevalence of PXF has also been shown to vary significantly across neighboring population samples [24, 25].

Table 5. Comparison with previous incidence studies.

Study	Country	Age at baseline	Sample size at baseline	Sample size at follow up	Study duration (years)	Overall incidence		Annual incidence (95% CI)
						Percentage (95% CI)	Per 1000-person years (95% CI)	
Karger et al. [5]	USA	All ages	73,602	Not stated	16		–	0.025 (0.022, 0.028)
Arnarsson et al. [6]	Iceland	50–79	1045	511	12	8.0 (5.6, 10.4)	–	0.66 (0.27, 1.4)
Vijaya et al. [7]	India	≥40	7774	4228	6	2.0 (1.6, 2.5)	–	0.33 (0.18, 0.55)
Ekström et al. [8]	Sweden	65–74	1908	1065	9.9	16.8 (14.6, 19.1)	14.8 (11.5–18.1)	1.69 (1.0, 2.65)
Topouzis et al. [9]	Greece	>60	2554	1092	12	19.6 (17.1, 22.2)	–	1.6 (0.92, 2.59)
Present study	India	All ages	7771	5395	15	1.82 (1.47–2.22)	17.3 (16.4–18.2)	0.12 (0.04, 0.25)
Present study	India	≥40	2790	1470	15	6.91 (5.56, 8.46)	6.61 (6.26, 6.98)	0.46 (0.17, 1.04)

The prevalence of PXF shows large variation between countries, being low in Inuit populations and high in Nordic and several African populations [2]. Assuming a linear incidence of PXF, the annual incidence in our study was 0.12% per year in all age groups, and 0.46% per year in individuals aged 40 years and above. Our incidence data are similar to the Chennai Eye Disease Incidence Study, which was also undertaken in a south Indian population [7], and the Reykjavik Study in Iceland (Table 5) [6], but higher than in USA [5] and considerably lower than in Sweden [8] and Greece [9]. The incidence of PXF in the Reykjavik Study is lower than anticipated, as Iceland is a Nordic country. Possible explanations are that in the Reykjavik Study, participants aged >80 years and those who were pseudophakic in one or both eyes were excluded [6]. Age differences are also likely to explain differences in the studies in Sweden and Greece, where older age groups were studied [8, 9], whereas the USA study included participants of all ages and did not disaggregate data by age group [5]. In addition, in the US study, pupil dilation was not performed on all participants and multiple investigators were involved, which could have introduced ascertainment and reporting bias [5]. Other factors related to the detection of PXF may also contribute to the variability in incidence. For example, whether pupils were maximally dilated, which is required to detect subtle signs of PXF. The differences in study design and the age groups studied limit interpretation in terms of genetic predisposition and the influence of environmental factors. We recommend that future studies are standardized with respect to the age groups studied, inclusion of participants who have undergone cataract surgery, and the method of detection of PXF material, and that data are disaggregated by age group.

The major strengths of our study include the population-based design, long-term longitudinal follow up with well-defined variables, adherence to standard protocols and completeness of data collection. We actively looked for the PXF material. Our incidence of PXF is comparable to the Chennai Eye Disease Incidence Study [7] which studied the same ethnic population. We investigated several ocular, systemic and lifestyle variables as potential risk factors for incident PXF, which have only been explored in the Reykjavik [6], Chennai [7] and Greece [9] studies.

We did not study the association between ocular biometric parameters and the incidence of PXF. In the early stages of the APEDS, we did not perform ocular biometry, which was added later. In the risk factor analysis, all the factors were fixed at baseline, whereas in real life these factors can vary over time. The number of participants with diabetes was low in our study as we relied on self-reporting of diabetes, and blood sugar testing was performed only on participants with retinopathy presumed to be due to diabetes but with a negative history of diabetes. This limited our ability to explore diabetes as a risk factor for PXF. We could only re-examine about 70% of the original rural cohort, and the main reason for loss to follow-up was mortality[16].

In conclusion, this long-term population-based study reports the incidence rate of PXF and PXF glaucoma. The results show that older people and those living in two study sites were at a higher risk. Studies on the incidence of PXF are limited and ours might be a valuable addition to the literature. We recommend that a standardized methodology be used for future studies to enable comparisons between regions.

SUMMARY

What was known before

- The incidence of Pseudo-exfoliation (PXF) shows large geographic variation though the incidence studies are few.
- Only a few studies have investigated ocular, systemic and lifestyle variables as potential risk factors for incidence of PXF.

What this study adds

- This study reports incidence rate of PXF.
- There was no incident case of PXF in individuals below age of 30 years at baseline, over mean 15 years of follow up.
- We found regional difference in the incidence of PXF. Variation in ultraviolet exposure might be the explanation.

DATA AVAILABILITY

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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AUTHOR CONTRIBUTIONS

NSC was responsible for data analysis, drafted the manuscript, approved the final version and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. RCK conceived and designed the work that led to the submission, acquired data, and played an important role in interpreting the results, revised the manuscript, approved the final version and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. CG played an important role in interpreting the results, revised the manuscript, approved the final version and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All the remaining authors acquired data, played a role in interpreting the results, revised the manuscript, approved the final version and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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COMPETING INTERESTS

The authors declare no competing interests.

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