Fifteen-year incidence rate and risk factors of pterygium in the Southern Indian state of Andhra Pradesh

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ABSTRACT

Purpose To report 15-year incidence rate and associated risk factors of pterygium among people aged 30 years and above at baseline in the rural clusters of longitudinal Andhra Pradesh Eye Disease Study (APEDS III).

Methods The baseline APEDS I included 7771 participants of which 6447 (83%) were traced and 5395 (83.7%) were re-examined in APEDS III. To estimate the incidence of pterygium, we selected participants who were 30 years and above at baseline (4188), of which 2976 were traced and 2627 (88.3%) were examined, and based on inclusion criteria, 2290 participants were included in the study. The incidence rate of pterygium was defined as the proportion of people free of pterygium at baseline who had developed the condition at 15-year follow-up (range 13–17 years). Univariate and multivariable analyses for risk factors were undertaken.

Results The sex-adjusted incidence rate of pterygium was 25.2 per 100 person-years (95% CI 24.8 to 25.7) which was significantly higher for men than women (26.3 per 100 person-years (95% CI 25.6 to 27.0) and 24.7 (95% CI 24.1 to 25.3) respectively). At the multivariable analysis, male gender (RR: 1.35, 95% CI 1.0 to 1.83), no formal education (RR: 2.46, 95% CI 1.12 to 4.93), outdoor occupation (RR: 1.47, 95% CI 1.14 to 1.9) and lower body mass index (BMI) (<18.5) (RR: 1.25, 95% CI 1.02 to 1.55) were associated with increased risk of pterygium.

Conclusions The overall incidence rate of pterygium was high in this rural population, especially in men and those engaged in outdoor activities, lack of formal education and with lower BMI. It is likely that greater exposure to ultraviolet light is a major contributing factor, thus warranting preventive strategies.

INTRODUCTION

Pterygium is an elevated, superficial, fibro-vascular proliferation which typically extends from the nasal perlimbal conjunctiva, which can extend onto the corneal surface.1–4 In advanced cases, pterygium can distort the corneal topography and obscure the optical axis, leading to significant irregular astigmatism and visual impairment.2,4 Several studies have reported the prevalence and risk factors for pterygium.2–23 According to a recent meta-analysis, the global prevalence of pterygium was 12% which ranged from 3% in those aged 10–20 years to 19.5% in those aged 80 years and above.23 The lowest prevalence was reported in Saudi Arabia (0.07%, age range: 17–82 years), while the highest was from China (53%, age range: 40–87 years).23 Risk factors include demographic, environmental and lifestyle factors, with increasing age and outdoor occupation (a surrogate for ultraviolet (UV) light exposure) being more common across multiple studies.2–7,10–16,18–23 Outdoor occupation leads to increased exposure to UV light, resulting in cellular changes at the medial limbus.24 Other factors, such as sex, education, smoking, diabetes and hypertension, have given inconsistent findings.2,5–7,12–14,16,18,21,23 However, as all these studies were cross-sectional, causality cannot be as implied as readily as in longitudinal, cohort studies. To the best of our knowledge, only four cohort studies have been reported from African, Chinese and South Korean populations with incidence data ranging from 4.9% to 11.6%, depending on the number of years of follow-up.5–8

The Andhra Pradesh Eye Disease Study I (APEDS I) was a cross-sectional survey conducted between 1996 and 2000 in three rural (West Godavari, Adilabad and Mahbubnagar districts, n=7771) and one urban area (Hyderabad, n=2522) in Andhra Pradesh state in Southern India.29–30 The follow-up, APEDS III, was conducted from 2012 to 2016 in rural areas of APEDS I, to estimate the long-term incidence and progression of visual loss from the major eye diseases in this region. The urban area was excluded, due to rapid urbanisation in the past decade, it was not possible to trace the urban population in Hyderabad.31

The prevalence of pterygium is high in the ‘pterygium belt’, which lies between 30° north and 30° south of the equator.32 Andhra Pradesh region also lies in ‘pterygium belt’ and has very high UV exposure and thus the prevalence of diseases related to UV can be high.33 A large part of the population is engaged in agriculture and several other outdoor occupations. Data from APEDS I reported a prevalence of 11% and risk factors for pterygium.34 This high prevalence is reflected by the fact that between 2010 and 2019, almost 10% of the 1.6 million outpatients who attended eye care services in our institution had pterygium,35 and
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removal was the second most common surgical procedure after cataract surgery. We now report the 15-year incidence rate of pterygium and its risk factors among people who were ≥30 years at baseline (1996–2000).

METHODS
The study adhered to the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board of the L V Prasad Eye Institute, Hyderabad, India, and the London School of Hygiene & Tropical Medicine, London. Written informed consent was obtained from all participants. Details of the methods for APEDS III, which was carried out between 2012 and 2016, are provided elsewhere. The two earlier studies, APEDS I and APEDSIII, have also been described earlier and all the participants in APEDS III were re-examined using the same methodology as APEDS I.

Data were collected during APEDS I on a range of socio-demographic factors, including systemic risk factors, age, occupation, education, residence, history of smoking, hypertension and diabetes, and use of spectacles for distance correction. Occupation was classified using 18 different categories, and participants were asked whether during regular working hours (9:00 to 17:00) their occupation demanded more than 4 hours of outdoor work. If so, it was classified as outdoor; if not, their occupation was classified as indoor. All underwent a comprehensive eye examination and their anthropometric measurements (weight and height) were recorded.

Details of the ophthalmic examination procedure have already been reported. In brief, the clinical team comprised of an ophthalmologist, an optometrist and a vision technician trained to assess visual acuity (VA), perform refraction and examine the anterior and posterior segment. Presenting distance VA was measured using a standard, illuminated (at least 200 lux) logarithm of minimum angle of resolution chart at 3 m, with the participant’s current refractive correction, if any. Undilated slit-lamp examination (SL 120 Carl Zeiss Meditec, Dublin, California, USA) was performed by the clinician, including intraocular pressure measurement by Goldman applanation tonometry (Carl Zeiss Meditec), before and after pupil dilatation. Gonioscopy was performed in all participants using NMR-K two-mirror lens (Ocular Instrument, Bellevue, Washington, USA) and graded as previously described. In addition, a four-mirror gonioscopy was performed by the optometrist with an indirect gonioscopic lens (Volk Opticals, Mentor, Ohio, USA) and any abnormality in the angle was documented. Following gonioscopy, pupils were dilated with tropicamide 1% and phenylephrine hydrochloride 2.5% for lens grading and posterior segment examination, unless contraindicated (ie, risk of angle-closure acute glaucoma or active infection).

Pterygium was defined as a raised conjunctival fibro-vascular growth crossing the limbus invading onto the clear cornea, which was classified as present or absent by the examining ophthalmologist. Variables at baseline were defined as follows: age (30–39 years, 40–49 years, 50–59 years, 60 years or above), sex (men, women), education (no formal education, classes 1–5, classes 6–10, and classes 11 and above), occupation (indoor, outdoor), history of smoking (non-smoker, past smoker, current smoker), body mass index (BMI) (<18.5, 18.5–24.99, 25–29.99, ≥30), systemic hypertension (defined as a systolic blood pressure of 140 mm Hg and above and/or diastolic blood pressure of 90 mm Hg and above and/or those on antihypertensive medication regardless of their blood pressure readings), and history of diabetes mellitus and use of spectacles (for near or distance correction or sunglasses). A positive history of diabetes mellitus was based on the self-report or the detection of diabetic retinopathy at baseline.

Participants in whom the presence of pterygium could not be assessed (due to corneal scarring for example) at APEDS I or APEDS III were excluded from further analysis. The incidence of pterygium was defined as the proportion of people free from pterygium at baseline who had developed the condition by the 15-year follow-up.

Data were analysed using STATA (version 13) software (Stata Corp, College Station, Texas, USA). The incidence rate was assessed and presented with 95% CIs. Baseline descriptive statistics included a comparison of the socio-demographics and clinical findings of those who did and did not participate, and between participants with and without incident pterygium using χ^2 tests. Multiple logistic regression models, including stepwise methods, were used to calculate the OR and 95% CI for each risk factor, using incident pterygium as the outcome measure. Variance inflation factors were used to test for collinearity between the covariates after fitting a multiple regression model. The Hosmer-Lemeshow test for goodness of fit was used to assess the model fitness. The statistical significance was determined at p<0.05 (two-tailed).

RESULTS
The baseline APEDS I included 7771 people in three rural areas in the Andhra Pradesh state in Southern India. At APEDS III (2012–2016), 6447 (83%) of the 7771 rural participants originally included in APEDS I were traced and available for examination and remaining 1324 (17%) had died. Of these, 5395 (83.7%) were re-examined after a mean of 15 years (range 13–17).

Among the 4188 participants aged ≥30 years at baseline, 1212 (28.9%) had died and 2976 (71.1%) were available for follow-up; 2627 (88.3%) were examined (figure 1). For those not examined, the reasons were migration (n=168, 5.7%), declined examination (n=98, 3.3%) and could not be traced (83, 2.8%). Excluded were 337 (12.8%) as they either had pterygium at baseline or could not be assessed for pterygium. Finally, 2290 participants were included in the study (figure 1).

Those who had died between APEDS I and APEDS III were significantly older than those examined (table 1). Mortality was also significantly higher in men, those with lower levels of formal education or who stayed indoors, spectacle users and smokers, and people with hypertension, diabetes and a lower BMI. Non-participants were significantly older (p=0.001), better educated (p=0.003), hypertensive (p=0.040) and were less likely to perform outdoor activities

Figure 1 Flow chart showing the number of participants included in analysis. APEDS, Andhra Pradesh Eye Disease Study.

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There were no differences by sex, smoking or diabetes status, use of spectacles or BMI.

The overall age- and sex-adjusted incidence rate of pterygium was 25.2 per 100 person-years (95% CI 24.8 to 25.7) (table 2). Rates were significantly higher in men than in women: 26.3 per 100 person-years (95% CI 25.6 to 27.0) and 24.7 (95% CI 24.1 to 25.3), respectively, but did not increase with age in either sex.

Participants with incident pterygium differed from those without in terms of educational status (p<0.001), BMI (p=0.036) and occupation (outdoor vs indoor work; p<0.001) (table 3).

In multivariable analysis, male sex (p=0.050), lack of formal education (p=0.011), greater outdoor activities (p=0.003) and lower BMI (<18.5) (p=0.034) were all associated with incident pterygium (table 4).

### DISCUSSION

In this study, we assessed the mean 15-year incidence of pterygium in three rural areas of undivided Andhra Pradesh. To the best of our knowledge, this is the first large-scale study to report the incidence of pterygium in India.

The overall incidence was 25.4 per 100 person-years which was slightly higher in men than in women. This is one of the highest incidences reported. Among the four previous longitudinal studies, two were undertaken in countries in the ‘pterygium belt’—the Barbados Incidence Study of Eye Diseases (BISED) and the Yunnan Minority Eye Studies (YMES)—and two were outside the pterygium belt—the Beijing Eye Incidence Study and the Korean cohort study (KCS). As three of these studies reported cumulative incidence, the annual incidence has been estimated for each study, by dividing the cumulative incidence percentage by the mean follow-up in years (table 5). This gave values of 1.3% per year for the BISED and 1.4% per year for the YMES, the two countries in the pterygium belt, and 0.5% per year for the BES which is outside the pterygium belt. The fourth study, KCS, which was again outside the pterygium belt, reported incidence rate as 2.1 per 1000 person-years.

In our study, the crude annual incidence was higher than these earlier studies, that is, 1.7% per year in those 30 years and above and 2.4% per year in those 40 years and above (data not shown), being comparable to BISED and YMES. The higher rate incidence in our analysis indicates pterygium to be a public health issue in Southern India, mostly due to high UV exposure. Hence, appropriate preventive strategies are warranted.

In the present study, the incidence of pterygium was estimated using baseline data from the APEDS. The baseline APEDS I reported a prevalence of 11.7%. Significant associations in the cross-sectional analysis were older age, low educational level, outdoor occupation and living in a rural area. Interestingly, the longitudinal studies failed to find an association between age at baseline and the incidence of pterygium, including the APEDS III. One possible explanation which could justify the lack of association between older age and pterygium rate in the APEDS III is that individuals at the highest risk of pterygium may have already developed pterygium at baseline, thus being excluded from the present investigation. Another possible explanation is behavioural change, with less outdoor exposure over time.

In our study, sex was an independent risk factor for pterygium, with men being at increased risk. This finding might be discordant with a recently published study carried on in our hospital-based data, which reported a higher prevalence of pterygium in women. The reason for the difference could be explained by the study methodology as well as population included in these studies. The study from Das et al is a cross-sectional investigation, calculating the prevalence of pterygium in a hospital-based cohort. Our study is a longitudinal sample-based epidemiological observation reporting on the incidence of pterygium. The median age of the former study was 55 years, while only 17% of our sample

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**Table 1** Baseline characteristics of participants in the Andhra Pradesh Eye Disease Study III (n=4188)

| Available and examined | Available not examined | Died before examination | P value |
|------------------------|------------------------|-------------------------|---------|
| (n=2627)               | (n=349)                | (n=1212)                |         |

**Age (years)**

| n | % | n | % | n | % |
|---|---|---|---|---|---|
| 30–39 | 1157 | 44 | 135 | 38.7 | 106 | 8.7 |
| 40–49 | 774 | 29.5 | 94 | 26.9 | 161 | 13.3 |
| 50–59 | 454 | 17.3 | 64 | 18.3 | 269 | 22.2 |
| 60 and above | 242 | 9.2 | 56 | 16.1 | 676 | 55.8 |

**Sex**

| n | % |
|---|---|
| Men | 1179 | 44.9 |
| Women | 1448 | 55.1 |

**Education**

| n | % |
|---|---|
| Classes 11 or above | 84 | 3.2 |
| Classes 6–10 | 362 | 13.8 |
| Classes 1–5 | 539 | 20.5 |
| No formal education | 1642 | 62.5 |

**Smoking status**

| n | % |
|---|---|
| Non-smoker | 1735 | 66 |
| Past smoker | 137 | 5.3 |
| Current smoker | 755 | 28.7 |

**Systemic hypertension**

| n | % |
|---|---|
| No | 1759 | 67 |
| Yes | 829 | 31.6 |

**History of diabetes mellitus**

| n | % |
|---|---|
| No | 2605 | 99.2 |
| Yes | 22 | 0.8 |

**Occupation**

| n | % |
|---|---|
| Indoor | 701 | 26.7 |
| Outdoor | 1919 | 73 |

**Spectacles**

| n | % |
|---|---|
| No | 2315 | 88.1 |
| Yes | 312 | 11.9 |

**BMI**

| n | % |
|---|---|
| 18.5–24.9 | 1288 | 49 |
| <18.5 | 1063 | 40.5 |
| 25–29.9 | 185 | 7 |

*Statistically significant value at χ² test.
†Data not available for 7 (0.3%) available and examined and 3 (0.3%) died before examination.
‡Data not available for 51 (2%) available and examined, 74 (6.1%) died before examination, and 9 (2.6%) available but not examined.
§Data not available for 39 (1.4%) available and examined, 24 (2%) died before examination, and 2 (0.6%) available but not examined.
BMI, body mass index.

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was aged between 50 and 59 years. Furthermore, nearly 50% of their population belonged to urban or metropolitan districts, while 100% of our cohort included rural areas. This relationship of pterygium and male gender was also not reported in BISED or YMES, but has been stated in several cross-sectional analyses. The fact that nearly 80% of men have outdoor occupations (mainly agriculture) in rural areas probably accounts for these findings. The role of genetics and sex hormones in pterygium development has also been advocated. In vitro studies on corneal fibroblasts have proven that female sex hormones as 17β-estradiol and progesterone inhibit IL-1β-induced collagen degradation and the expression or activation of matrix metalloproteinases (MMPs), which contribute to the pathogenesis of pterygium. By contrast, in vivo analysis have found that oestrogen replacement therapy was associated with a low prevalence of pterygium in postmenopausal women.

We identified lack of formal education as a risk factor in our cohort, which was not reported in other studies. The relatively small number of incident cases in other studies might account for the difference as these studies would have been relatively underpowered to demonstrate this relationship. The way educational categories were classified in (four categories of educational level, as in our study vs binary classification in the studies published previously) might also explain the differences.

Like the BISED and YMES studies, we confirmed the association between outdoor activities and the risk of developing pterygium. This is the most compelling evidence to date, further corroborating the strong association between pterygium and cumulative UV exposure. Although quantifying ocular exposure to UV radiation is very challenging, it is well known that high UV exposure leads to chronic cellular changes at the medial limbus. As nearly 70% of the population of Andhra Pradesh (and the rest of India) lives in rural areas and most are engaged in agricultural activities, a high proportion would be at high risk for developing pterygium during their lifetime.

Unlike the previous study, we found no protective role of regular use of spectacles. However, only 12% of participants wore spectacles which would have reduced the power of the analysis. The BISED study found a negative association between the incidence of pterygium and the use of spectacles, which has been interpreted as a surrogate of office work and decreased UV exposure. In the present study, the usage of spectacles was marked as positive without differentiating refractive correction lenses from sunglasses. It is also likely that there may be a lack of UV filter on the lenses in this cohort. Moreover, adherence to spectacle wearing was not directly assessed, which might be very low especially in rural districts. Both these factors might have reduced

| Variables | Incidence |
|-----------|-----------|
|          | Yes (n=575) | No (n=1715) | Total (n=2290) | P value |
| Age group (years) |          |             |                 |         |
| 30–39     | 246 (42.8) | 812 (47.4)  | 1058 (46.2)     | 0.225   |
| 40–49     | 184 (32)  | 482 (28.1)  | 666 (29.1)      |         |
| 50–59     | 93 (16.2) | 276 (16.1)  | 369 (16.1)      |         |
| ≥60       | 52 (9)    | 145 (8.5)   | 197 (8.8)       |         |
| Sex       |           |             |                 |         |
| Women     | 305 (53)  | 965 (56.3)  | 1270 (55.5)     | 0.178   |
| Men       | 270 (47)  | 750 (43.2)  | 1020 (44.5)     |         |
| Education |           |             |                 |         |
| Classes 11 and above | 11 (1.9) | 63 (3.7) | 74 (3.2) | <0.001 |
| Classes 6–10  | 57 (9.9)  | 276 (16.1) | 333 (14.5)  |         |
| Classes 1–5   | 111 (19.3) | 379 (22.1) | 490 (21.4) |         |
| No formal education | 396 (68.9)| 997 (58.1)| 1393 (60.8)|         |
| Smoking    |           |             |                 |         |
| Non-smoker | 361 (62.8)| 1152 (67.2) | 1513 (66.1) | 0.087 |
| Past smoker | 34 (5.9) | 73 (4.3) | 107 (4.7) |         |
| Current smoker | 180 (31.3)| 490 (28.6)| 670 (29.3)|         |
| Systemic hypertension | No | 387 (68.6)| 1134 (66.9)| 1521 (67.4)| 0.462 |
| History of diabetes | No | 177 (31.4)| 560 (33.1)| 737 (32.6)|         |
| Outdoor work | No | 122 (21.3)| 535 (31.3)| 657 (28.8)| <0.001 |
| Spectacles | No | 501 (87.1)| 1512 (88.2)| 2013 (87.9)| 0.511 |
| BMI        |           |             |                 |         |
| ≤18.5     | 452 (78.8)| 1175 (68.7)| 1627 (71.2)     |         |
| <18.5     | 259 (46)  | 866 (51.6)  | 1125 (50.2)     | 0.036   |
| 25–29.9   | 36 (6.4)  | 129 (7.7)   | 165 (7.4)       |         |
| ≥30       | 9 (1.6)   | 29 (1.7)    | 38 (1.7)        |         |

*Statistically significant value at χ² test.

BMI, body mass index.
The adjusted analysis showed an interesting association between pterygium and low BMI. We can speculate an indirect causative relationship between low weight, low socioeconomic status and exposure to risk factors for pterygium, although the most likely explanation is residual confounding. The role of cigarette smoking in pterygium development is under debate, although recent evidence point towards a protective role. However, this was not confirmed in any of the longitudinal studies indicating that the association might be spurious.

Strengths of our study include its population-based longitudinal design, long-term follow-up, high participation and standardised protocols. Reporting on education status, systemic disease and BMI is also a novelty in comparison with previous studies. Limitations include loss to follow-up during the 15-year study period (due to death and non-participation), which may have led to selection or survivor bias. In the risk factor analysis, all the factors were fixed at baseline, whereas in real life these factors can vary over time. In addition, we only used a binary measure of presence or absence of pterygium at baseline or during follow-up, without accounting for a clinical grading of the disease. In addition, we only used a binary measure of outdoor/indoor activity as a proxy for UV exposure, which may have led to misclassification. This may have been more applicable for women, most of whom described themselves as housewives which was classified as an indoor activity. Similarly, history of smoking was assessed as a categorical variable (ie, non-smoker, past smoker, current smoker), rather then being expressed as pack-years, which would provide a better measure of long-term smoking habits. Another limitation is that interobserver agreement studies were not undertaken for pterygium, but all assessments were made by qualified ophthalmologists after rigorous training. As data were not available on the time of onset of pterygium, the Hazard Ratio would not be calculated. Finally, the urban cluster in APEDS I could not be included in APEDS III due to urbanisation with out-migration of the population, which limits generalisability.

In conclusion, this is the first study to report the incidence of pterygium in India. Our results indicate that the incidence is relatively high in this rural population which lies within the ‘pterygium belt’. The study confirmed that there is an increased risk in men, the uneducated, those with outdoor activities and those with lower BMI. Knowledge of these associations may be useful in the long-term planning of eye care services and public health preventive measures in these regions.

### Table 4 Multiple logistic regression analysis for association between pterygium and demographic, environmental and lifestyle risk factors

| Age (years) | RR† | 95% CI | P value |
|-------------|-----|--------|---------|
| 30–39 (base) |     |        |         |
| 40–49       | 1.24| 0.99–1.57| 0.063 |
| 50–59       | 1.04| 0.78–1.39| 0.795 |
| ≥60         | 1.07| 0.74–1.56| 0.706 |

### Table 5 Cumulative and annual incidence of pterygium in different countries

| Authors          | Year | Region (country)          | Follow-up (years) | Sample size | Age (years), mean ±SD | Number of cases | Cumulative incidence (%), 95% CI | Annual Incidence |
|------------------|------|---------------------------|-------------------|-------------|-----------------------|----------------|----------------------------------|-----------------|
| Nemesure B, et al| 2008 | Barbados (North America)  | 9                 | 1888        | 56.7±10.8             | 218            | 11.6 (10.1–13.1)                 | 1.3             |
| Zhao L, et al    | 2013 | Greater Beijing (China)   | 10                | 2628        | 54.6±9.8              | 129            | 4.9 (NA)                        | 0.5             |
| Li L, et al      | 2015 | Yunnan province (China)   | 5                 | 941         | 63.5±8.3              | 64             | 6.8 (5.2–8.4)                   | 1.4             |
| Rim T, et al     | 2017 | South Korea               | 12                | 10 060 383  | NA                    | 21 465         | NA                              | NA              |
| Our study        | 2012–16 | India                        | 15                | 2290        | 42.7±10               | 575            | 25.2 (24.8–25.7)                | 1.7             |

NA, not available.
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