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Title: 15-year Incidence rate of Primary Angle Closure Disease in the Andhra Pradesh Eye Disease Study

Running Head: 15-year incident rate primary angle closure disease in India

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INTRODUCTION

Glaucoma is one of the leading causes of irreversible blindness.[1] Primary angle closure disease (PACD) includes the pre-disease states [primary angle closure suspect (PACS) and primary angle closure (PAC)], and overt disease [primary angle closure glaucoma (PACG)]. With an estimated global prevalence of 0.5% [(95% Confidence Interval (CI): 0.11 to 1.36)], PACG affected more than 20 million people aged 40 to 80 years in 2013, which is predicted to increase to 32 million by 2040.[2] The prevalence of PACG varies across geographic regions and ethnic groups, and is highest in Asia 1.09% (95% CI: 0.43 to 2.32).[2] Although PACG is less common than POAG, the prevalence of blindness is higher in people with PACG than in those with POAG.[3] In addition, most forms of the disease are asymptomatic and difficult to diagnose.[4-6]

In the recent past, several population-based surveys reported the prevalence of glaucoma, especially from Asia. However, data on the incidence rate of PACD are limited.[7] Incidence studies are important as they determine the risk of developing the disease over a period of time.[8] Studies have estimated the incidence of new cases of PACD[9-11] or have explored the natural history by determining the risk of conversion from one form of the disease to an another over time.[12-17] There is considerably less published literature on the former than the latter.

The Andhra Pradesh Eye Disease Study (APEDS) is a large, population-based survey conducted in Southern India. The study was designed to determine the prevalence of eye diseases and their risk factors, to estimate the magnitude of blindness and low vision and their impact on quality of life, and to describe the barriers to accessing eye care services.[18] The original survey had urban and rural samples. In this publication, we report the incidence of PACD, derived from the mean 15-year follow up examination, in the three rural areas as the urban area could no longer be identified due to rapid urbanization. We also report risk factors associated with the development of the disease.

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 (LVPEI), Hyderabad, India and the London School of Hygiene & Tropical Medicine (LSHTM), London. Written informed consent was obtained from all participants. The first phase of the APEDS (APEDS I) was conducted from 1996 to 2000 and included 10,293 participants of all ages. The sample was selected using a multistage cluster sampling procedure from one urban and three rural areas of the then undivided Andhra Pradesh state in southern India. The urban area was Hyderabad and the rural areas were located in West Godavari district (affluent rural), and Adilabad and Mahabubnagar districts (poor rural).[18] This was one of the most rigorous population-based surveys conducted in a low-income setting. Findings from this study significantly contributed to the development of eye care policies in India.[18,19]

Between 2009 and 2010, a feasibility study called APEDS II was conducted to trace participants examined in APEDS I to estimate migration and mortality rates, and to identify participants willing to be re-examined. The three rural areas were revisited wherein 5447 (70.1%) of the 7771 rural participants examined in APEDS I were traced.[20] Re-examination of this cohort of participants after 15 years (range 13-17 years) between 2012 and 2016 constitutes APEDS III. In this manuscript, we report the incidence of PACD among participants aged 40 or more years at baseline, i.e., in APEDS I. Details of the design and methodology for APEDS III have been described previously[21] and relevant details are summarized here.

A comprehensive eye examination was performed on all participants using similar methods to APEDS I. The study team was trained on the procedures. All four clinical investigators underwent inter-observer agreement assessments with the principal investigator (PI, a glaucoma specialist) for lens grading, gonioscopy as well as optic disc assessment prior to joining the study. There was only one investigator at any given time and the investigators underwent agreement with the PI for lens grading, gonioscopy as well as optic disc assessment prior to joining the study. Agreement between the PI and other investigators in the binary 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.

Participants with a presenting distance or near visual acuity < logMAR 0.0 underwent streak retinoscopy followed by subjective refraction and acceptance. Each eye was tested separately and then binocularly. Refraction was performed by a trained optometrist / vision technician. Intraocular pressure (IOP) was measured with Goldmann applanation tonometer (Haag-Streit, Bern, Switzerland). 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. A NMR-K 2-mirror lens (Ocular instruments, Bellevue, WA) as well as Sussman 4 mirror lens (Ocular Instrument, Washington, USA) were used. The angle was considered occludable if the pigmented posterior trabecular meshwork was not visible for ≥ 180° of the angle circumferences in the primary position, without manipulation under dim illumination.

All participants underwent pupillary dilatation; participants with occludable angles were dilated after laser iridotomy. The optic disc and peripapillary area were assessed with a 78-diopter (D) lens (Volk, OH, USA) at the slit lamp and the entire fundus was assessed by indirect ophthalmoscopy using a 20-D lens (Volk, OH, USA).

Participants unable to attend the study centre due to frailty or physical morbidity were examined at home using similar methods, i.e., they had visual acuity assessment, slit lamp examination, IOP measurement with a Perkins tonometer (Perkins Mk3, Haag-Streit, Bern, Switzerland), gonioscopy with NMR-K 2-mirror as well as Sussman 4 mirror lens and optic disc assessment with a 78-diopter (D) lens at the slit lamp. Indirect ophthalmoscopy using a 20-D lens was performed to examine the posterior segment. The anterior segments of those who were bedridden were examined with hand held slit lamp (BA 904, Haag-Streit, Bern, Switzerland).

Automated visual field analysis a using Humphrey Visual Field (HVF) analyzer (Humphrey Instruments Inc., San Leandro, CA) was attempted for all participants with any of the following optic disc features: asymmetry in CDR of > 0.2 between the eyes, a vertical CDR of ≥ 0.65; neuro-retinal rim < 0.2 at any clock hour; notch in the disc; disc hemorrhage; and obvious peripapillary nerve fiber layer defect in either eye. Visual fields were also assessed if the IOP was ≥ 22 mmHg in either eye, or if there was an IOP difference of ≥ 6 mmHg between the two eyes, using the threshold central 24-2 strategy (stimulus size III). If the visual field was abnormal or unreliable, the test was repeated. The criteria used to determine glaucomatous visual field defects included a field defect that correlated with optic disc damage and met ≥2 of Anderson's three criteria.

Definitions

Definitions for an occludable angle and PACG were based on the International Society for Geographical and Epidemiologic Ophthalmology (ISGEO) classification[22] which uses 97.5th and 99.5th percentiles of IOP and vertical CDR of the normal population. In APEDS I, visual field testing was not performed on the entire sample, so normative data could not be used. Hence, as in our previous publication on prevalence,[5] we used normative data from the Chennai Glaucoma Study (CGS) for the 97.5th and 99.5th percentile cutoffs for the IOP and CDR. The CGS and the APEDS populations were both located in south India and are likely of similar ethnicity (Dravidians). The 97.5th and the 99.5th percentile cutoffs for IOP were 21 and 24 mmHg, respectively, while those for CDR were 0.7 and 0.8, respectively for the rural population.[6]

Glaucoma was classified according to three levels of evidence.[22] In level 1, the diagnosis was based on structural damage and functional changes i.e., CDR ratio or CDR asymmetry ≥ 97.5th percentile for the normal population, and a neuro-retinal rim width reduced to 0.1 CDR (between 10 and 1 o'clock or 5 and 7 o'clock) with definite visual field defects consistent with glaucoma. Level 2 was based on advanced structural damage with unproven field loss. This comprised participants in whom visual fields could not be determined or were unreliable, with CDR or CDR asymmetry of ≥ 99.5th percentile for the normal population. Category 3 included persons with an IOP of ≥ 99.5th percentile for the normal population, whose optic discs could not be examined because of media opacity. In this category, additional criteria such as visual acuity, clinical evidence of glaucoma filtering surgery and information in medical records were also taken into consideration.[22]

A PACS was defined as an eye with an occludable angle. PAC was defined as an eye with PACS and peripheral anterior synechiae and/or elevated IOP without glaucomatous optic disc damage. PACG was defined as PAC with evidence of glaucoma as defined by the ISGEO.[22] The entire spectrum of PACD consisted of PACS, PAC as well as PACG.

The definitions and relevant denominators for each are shown in **Table 1**. For each participant, the form of PACD was defined on the basis of the more affected eye.

At baseline, hyperopia was defined as a spherical equivalent of ≥ 0.5 D in phakic eyes, and myopia was defined as spherical equivalent of -0.5 D or greater in phakic eyes. Nuclear sclerosis was graded using the LOCS III classification system; nuclear opalescence above grade 2 was considered to be nuclear sclerosis. Hypertension (HTN) was determined by either one or a combination of the following factors: history of high blood pressure diagnosed by a physician; current use of anti-hypertensive medication; and/or a blood pressure reading of ≥ 140/90 mmHg. Diabetes mellitus (DM) was determined by a history of DM and/or diabetic retinopathy on clinical examination.

Two-hundred and seventy-three of the 1470 participants (18.5%) were excluded for the following reasons: A) participants with following diagnosis at the baseline: PACD (32), POAG (13), and suspicion of glaucoma on the basis of the clinical appearance of the optic disc (1); B) participants who underwent cataract surgery in the intervening period (180); and C) no data available on gonioscopy at baseline (45) or an iridotomy had been performed (2) (**Figure 1**).

Statistical Analysis

Data were analyzed for participants aged ≥ 40 years at baseline who were also examined during APEDS III. The Shapiro-Wilk test was used to check the normality of distribution. Data are presented as means (Standard Deviation; SD) and medians (1^{st}, 3^{rd} quartile), as appropriate. The incidence estimates were adjusted for the age and sex distribution of the population. Participants were classified into three groups on the basis of their age at baseline, i.e., APEDS 1, as 40 to 49 years, 50 to 59 years and 60 years and above. For categorical variables in univariable analysis,

Chi-square or Fisher's exact tests were used. T-tests and one-way ANOVA were used to compare continuous variables. Age was used as a continuous variable; the age interval was per 1-year increase. The association of PACD with age, sex, hyperopia, myopia, nuclear sclerosis, HTN, DM, and body mass index (BMI) were evaluated first with univariable analysis followed by multivariable analysis using logistic regression. Multivariable regression model included variables which achieved definite ($p<0.05$) or borderline significance ($p<0.1$) in the univariable model. We also used the AIC (Akaike Information Criterion) while selecting the regression model. Multicollinearity was checked by calculating the variance inflation factor (VIF), and the goodness of fit for logistic regression models was checked using the Hosmer–Lemeshow test. Statistical analyses were undertaken using Stata 12.1 (StataCorp, College Station, TX). A two-sided p value <0.05 was considered statistically significant.

RESULTS

A total of 2790 participants aged ≥ 40 years were examined in APEDS I. After a mean 15 years, 1470 (52.6%) were re-examined. The mean (SD) age of these participants was 50.2 (SD 8.1) years; median (1^{st}, 3^{rd} quartiles) age was 48 (44, 55) years and ranged between 40 and 82 years at baseline, i.e., APEDS I. The distribution of participants by age group was as follows: 774 (52.6%) 40 to 49 years, 454 (30.8%) 50 to 59 years, and 242 (16.4%) 60 years and above. There were 670 (45.5%) males. Perimetry was performed in 380 participants, 256 (67.3%) of whom underwent repeat tests as per the study protocol.[21]

We compared baseline demographic characteristics of participants and a) all non-participants (i.e., those who had died since APEDS I and those who did not respond in APEDS III) and b) those who did not respond in APEDS III ("non-responders" i.e., participants who migrated,

could not be traced or refused to participate) (**Table 2**). Comparing participants with all non-participants, participants were younger, were more likely to be male, to have nuclear sclerosis and myopia but not hyperopia, to have HT and DM and a leaner body mass index. There was also no difference in baseline PACD between participants and non-participants. Comparing participants with non-responders, participants were more likely to be younger, to be male, non-myopic and not to have nuclear sclerosis.

The role of natural lens in the pathogenesis of PACD was assessed by studying the relationship between the incidence of PACD and the rate of cataract surgery in the different age groups. With increasing age, the rate of cataract surgery increased while the incidence of PACD declined (**Figure 2**).

Overall, 102 participants developed PACS and 73 developed PAC (69 were classified as normal and four were classified as PACS in APEDS I; the latter four progressed to PAC despite a functional laser iridotomy performed at the baseline) over 15 years (**Table 3 and Figure 3**). The 15-year cumulative incidence of PACS [95% confidence interval (CI)] was 8.52% (7, 10.24) or about 0.5% per year. The 15-year cumulative incidence of PAC (95% CI) was 6.01% (4.74, 7.5) or about 0.4% per year. Overall, 19 participants (all were classified as normal in APEDS I) developed PACG while 190 developed any form of PACD over 15 years. In the 19 participants with PACG, the diagnosis was based on ISGEO classification level 1 evidence in 10 participants and level 2 evidence in nine participants. The 15-year cumulative incidence (95% CI) of PACG was 1.56% (0.94, 2.43) or about 0.1% per year. The 15-year cumulative incidence (95% CI) of PACD was 15.87% (13.84, 18.06) or about 1% per year.

In univariable analysis, female sex and hyperopia were significant risk factors for incident PACD. Systemic hypertension was of borderline significance, and myopia was protective (**Table 4**). However, in multivariable analysis, the only significant risk factors were female sex which increased the risk (OR: 2.72; 95% CI: 1.91–3.86) and myopia which was protective (OR: 0.54; 95% CI: 0.35-0.85). There was also no significant multicollinearity in the model and the Hosmer-Lemeshow test indicated a good fit of the logistic regression model (P= 0.35).

DISCUSSION

APEDS is the second longitudinal study of eye diseases in India after the Chennai Eye Disease Incidence Study (CEDIS)[11] to report the incidence of PACD in a large south Indian population. APEDS is the longest incidence study of PACD and the first to report the incidence rate of the disease. We found the overall 15 years incidence of PACS to be 8.52%, incidence of PAC to be 6.01%, PACG to be 1.56% and PACD to be 15.87% with female sex being a significant risk factor while presence of myopia was protective.

The published literature on the natural history of PACD is limited and the majority of studies report variable rates of progression of different forms of the disease in high-risk populations.[12-17] For example, Yip, et al followed up a high-risk subgroup in a Mongolian population in a screening study on the basis of central anterior chamber depth (ACD) of < 2.53 mm. The incidence of PACS according to the ISGEO definition was 3.4% per year over 6 years of follow up.[16] Wilensky identified 129 clinic patients at risk of developing PACG in the United States, on the basis of a central ACD of < 2 mm. The rate of progression to acute or sub-acute angle closure was 7.17% per year over a mean of 2.7 years follow up.[15] Another study involving a high risk sample of Greenland Inuit with shallow peripheral ACs, reported 3.5% per year progression of PACS to PAC or PACG over 10 years,[12] which was lower than in a longitudinal study of individuals with PACS in south India. In

the latter study, the annual progression of PACS to PAC was 4.4%[13], with 5.7% progression of PAC to PACG over five years.[14] On the other hand, a randomized controlled trial in an urban district of China identified only 0.6% per year progression of PACS to PAC in the non-intervention arm.[17] Reasons for the wide variability in the risk of progression of one form of PACD to another are likely to reflect differences in ethnicity, age, sex and location of recruitment between study populations, as well as differences in the definitions of high risk groups and disease, and the methods used.

Studies which have estimated the incidence of all forms of PACD are sparse (**Table 5**),[9-11] and only the CEDIS examined a large sample to estimate the 6-year incidence of the disease. In this study of 5432 eligible participants, 4421 (mean age 56.4 years) underwent a second examination at the base hospital (rural: 2510, urban: 1911, response rate 81.3%). The 6-year cumulative incidence of PACD was 4.0% (95% CI: 3.3 to 4.7%), and has higher in the rural [4.5% (95% CI: 4.5 to 4.6%)] than the urban population [3.2% (95% CI: 3.1 to 3.2%)].[11] The incidence of PACD was higher in our study than in CEDIS (Table 4) which is not explained by differences in age or sex, and a lower proportion of participants had undergone cataract surgery. Possible reasons could be the difference in the gonioscopy mirror used and non-linear incidence of the disease.

The natural lens is known to play a critical role in the pathogenesis of PACD. Central ACD as well as anterior chamber angle width show a significant negative correlation with age,[23,24] which has been attributed to progressive increase in the thickness of the lens with aging. Increasing lens thickness is considered a reasonable explanation for the development of most PACD in individuals over the age of 40 years.[5-7] We found an inverse relationship between the rate of cataract surgery and the incidence of PACD (Figure 2), as in CEDIS.[11]

196 Female sex is a known risk factor for PACD,[25] and females have shorter axial length and shallower anterior chamber depth than men.[26-28]
197 Females were 2.7 times more likely to have PACD in our study. On the other hand, both the Japanese study and CEDIS did not detect a sex
198 difference in the incidence of PACD.[10,11] The difference could be because we did not adjust for ocular biometric parameters in our study.
199 Hyperopia is also a recognized risk factor for PACD. Hyperopic eyes have a shorter axial length and are likely to have a crowded anterior
200 segment, making them susceptible to angle closure. Myopic eyes, on the other hand, have longer axial lengths and deeper anterior chambers
201 which can have a protective effect, as in our study. However, in our study, unlike CEDIS, hyperopia was no longer statistically significant in
202 multivariable analysis. This may be explained by inter-individual variability in the thickness or the relative position of the lens with respect to
203 the scleral spur. Our understanding of the role of the iris and choroid, and the diurnal variation in their physical properties under different
204 physiological states, is evolving.[7]
205 Two meta-analyses have demonstrated a significant association between systemic hypertension and POAG,[29,30] but the role of systemic
206 hypertension and its adverse effect on vessel function in the development of PACG has not been elucidated. In our study, systemic hypertension
207 was not associated with PACD in multivariable analysis, and was also not significant in CEDIS.[11]
208 The relationship between DM and glaucoma is complex in terms of variation in the duration of disease, level of metabolic control, and
209 the functional and metabolic dysregulations associated with diabetes. A recent meta-analysis did show a significant association between
210 diabetes, diabetes duration, and fasting glucose levels with increased risk of open angle glaucoma,[31] but no studies are available on PACD.

Diabetes was not a significant risk factor in the development of PACD in our study, nor in CEDIS. However, the number of participants with DM was small in our study.

The major strengths of our study include the population-based design, long-term follow up with well-defined criteria, adherence to standard protocols and completeness of data collection. Our estimate of incident PACD has several implications for planning and policy making in eye care service delivery.

Our study has a few limitations. The association between ocular biometric parameters and PACD, as well as the role of the lens in the development and progression of the disease has evolved over time. In the early stages of the APEDS we did not perform ocular biometry, although this was added in the follow up study. Loss to follow up is another weakness of our study, which is a frequent problem in incidence studies. However, the main cause of loss to follow-up was mortality and the response rate from living participants was reasonably high. The relatively high number of deaths reflects the long duration of the study. Higher mortality rates have been observed in other long-duration studies as well. At median follow-up of 13.2 years in Beaver Dam eye study, 32.3% of the baseline population had died.[32] Similarly, in the Blue Mountains Eye Study, after 15 years, 43.9% of baseline participants had died.[33] Non-response was higher in females, myopes and those with nuclear sclerosis, which may introduce different biases. Higher non-response by females and those with nuclear sclerosis could have underestimated the incidence, while non-response by myopes may have overestimated the incidence. The prevalence of PACD was comparable between participants and non-participants at baseline (Table 2), and our estimates and not therefore, likely to be biased by non-response. Apart from this, in the risk factor analysis, all the factors were fixed at baseline, whereas in real life these factors can vary over time. We also accept

the limitations of 2-mirror gonioscopy lens; this lens has a contact diameter of 15 mm which reduces the ability to detect synechiae than a smaller lens such as the Zeiss or Sussman 4-mirror gonioscopy lens. Moreover, the angle may appear shallower during manipulation using a 2-mirror lens. In the follow up component of our study, gonioscopy was performed using a 2-mirror gonio-lens as well as a Sussman 4-mirror lens but we limited analysis to the data obtained using the former, as this method was used at the baseline.

In conclusion, this long-term population-based study reports the incidence rate of PACD. The results show that women were at a higher risk of developing PACD and myopia was protective.

Appendix:

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Figure Legends:

Figure 1: Flow chart showing the number of participants included in analysis

Figure 2: The relationship between the incidence of primary angle closure disease and the rate of cataract surgery (n= 180)

Figure 3: Numerators and denominators for the different forms of primary angle closure disease at baseline and follow up

Table 1. Definitions and denominators for angle closure disease

Form of angle closure disease	Population at risk (denominator)	Incidence
For PACS[#]	Normal at baseline (X)	PACS at follow-up (A)
For PAC^	Normal (X) or PACS (Y) at baseline	PAC at follow up (B)
For PACG[@]	Normal (X) or PACS (Y) or PAC (Z) at baseline	PACG at follow-up (C)
For PACD[&]	Normal at baseline (X)	PACS or PAC or PACG at follow up (A+B+C)

#PACS: Primary angle closure suspect; ^PAC: Primary angle closure; @PACG: Primary angle closure glaucoma; [&]PACD: Primary angle closure disease

Table 2: Comparison of baseline demographic characteristics between participants and non-participants in Andhra Pradesh Eye Disease Study 3

Variable	Participants (n=1470, 52.6%)		Non-participants (n=1320, 47.4%)		Sub-division of non-participants				P value[1]	P value[2]
					Died (n=1106, 39.6%)		No response# (n=214, 7.6%)			
Mean baseline age (SD, years)	50.2 (8.1)		59.6 (10.4)		61 (9.9)		52.4 (9.5)		<0.01	<0.01
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**		
Female	800	54.4	668	50.6	535	48.3	133	62.1	<0.01	0.03
Hyperopia	259	17.6	211	15.9	162	14.6	49	22.9	<0.01	0.06
Myopia	397	27.0	623	47.2	551	49.8	72	33.6	<0.01	0.04
Nuclear sclerosis	181	12.5	520	41.6	473	45.2	47	22.9	<0.01	<0.01
PACD	32	2.1	34	2.5	31	2.8	3	1.4	0.48	0.3
Hypertension	545	37.7	654	50.4	560	51.6	94	44.1	<0.01	0.07
Diabetes mellitus	20	1.3	51	3.8	48	4.3	3	1.4	<0.01	0.9
Body mass index:										
18.5-24.99	705	49.2	547	44.3	437	42.6	110	52.8	<0.01	0.71
<18.5	583	40.7	575	46.6	497	48.4	78	37.5		
25-29.99	116	8.1	90	7.3	75	7.3	15	7.2		
>+30	27	1.8	21	1.7	16	1.5	5	2.3		

335 # No response includes participants who migrated, could not be traced or refused to participate.

336 n: Number, SD: Standard Deviation, PACD: Primary Angle Closure Disease

337 P value[1] is between participants and non-participants while P value[2] is between participants and non-respondents.

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350 **Table 3**: Incidence of Primary Angle Closure Suspect (PACS), Primary Angle Closure (PAC), Primary Angle Closure glaucoma (PACG), and
351 Primary Angle Closure disease (PACD)

	Male		Female		Total		Incidence rate/100 person years (95% CI*)
Age group	**At risk**	**n (%) (95% CI*)**	**At risk**	**n (%) (95% CI*)**	**At risk**	**n (%) (95% CI*)**	
Incidence of PACS							
40 - 49	320	12 (3.75) (1.95, 6.45)	371	53 (14.28) (10.88, 18.26)	691	65 (9.4) (7.33, 11.83)	9.81 (9.24, 10.4)
50 - 59	170	6 (3.52) (1.3, 7.52)	180	22 (12.22) (7.82, 17.91)	350	28 (8) (5.38, 11.35)	8.1 (7.37, 8.88)
≥60	75	4 (5.33) (1.47, 13.09)	81	5 (6.17) (2.03, 13.82)	156	9 (5.76) (2.67, 10.66)	5.89 (4.96, 6.93)
Total	565	22 (3.89) (2.45, 5.83)	632	80 (12.65) (10.16, 15.5)	1197	102 (8.52) (7, 10.24)	8.81 (8.4, 9.24)
Incidence of PAC							
40 - 49	323	13 (4.02) (2.16, 6.78)	374	29 (7.75) (5.25, 10.94)	697	42 (6.02) (4.37, 8.05)	6.33 (5.87, 6.82)
50 - 59	173	8 (4.62) (2.01, 8.9)	184	12 (6.52) (3.41, 11.11)	357	20 (5.6) (3.45, 8.51)	5.73 (5.11, 6.39)
≥ 60	76	4 (5.26) (1.45, 12.93)	83	7 (8.43) (3.45, 16.6)	159	11 (6.91) (3.5, 12.04)	7.07 (6.07, 8.19)
Total	572	25 (4.37) (2.84, 6.38)	641	48 (7.48) (5.57, 9.8)	1213	73 (6.01) (4.74, 7.5)	6.25 (5.9, 6.61)
Incidence of PACG							
40 - 49	323	2 (0.61) (0.07, 2.21)	375	10 (2.66) (1.28, 4.84)	698	12 (1.71) (0.89, 2.98)	1.74 (1.5, 2.01)
50 - 59	173	1 (0.57) (0.01, 3.17)	185	4 (2.16) (0.59, 5.44)	358	5 (1.39) (0.45, 3.22)	1.58 (1.26, 1.95)
≥ 60	76	1 (1.31) (0.03, 7.11)	83	1 (1.2) (0.03, 6.53)	159	2 (1.25) (0.15, 4.46)	1.2 (0.79, 1.73)
Total	572	4 (0.69) (0.19, 1.78)	643	15 (2.33) (1.31, 3.81)	1215	19 (1.56) (0.94, 2.43)	1.62 (1.44, 1.82)

Incidence of PACD							
40 - 49	320	27 (8.43) (5.63, 12.03)	371	91 (24.52) (20.23, 29.23)	691	118 (17.07) (14.34, 20.09)	17.81 (17.07, 18.56)
50 - 59	170	15 (8.82) (5.02, 14.13)	180	36 (20) (14.41, 26.59)	350	51 (14.57) (11.04, 18.7)	14.98 (14.01, 15.99)
≥60	75	9 (12) (5.63, 21.56)	81	12 (14.81) (7.89, 24.44)	156	21 (13.46) (8.52, 19.83)	13.74 (12.35, 15.22)
Total	565	51 (9.02) (6.79, 11.69)	632	139 (21.99) (18.82, 25.42)	1197	190 (15.87) (13.84, 18.06)	16.46 (15.92, 17.02)

*CI: Confidence Interval

362 **Table 4:** Logistic regression to assess the association of primary angle closure disease with its risk factors (at baseline)

Variable	**Sub-Variable**	**Number at Risk (%)**	**Univariate Regression**		**Multivariate Regression**	
			Odds Ratio (95% CI)	P value	Odds Ratio (95% CI)	P value
Baseline age (years) (per 1-yr increase)	-	1197 (100)	0.98 (0.96, 1.00)	0.19		
Sex	Male	565 (47.2)	1.00		1.00	
	Female	632 (52.8)	**2.84 (2.01, 4)**	**<0.01**	**2.72 (1.91, 3.86)**	**<0.01**
Hyperopia (SE ≥ 0.5 D)	Absent	1000 (83.5)	1.00		1.00	
	Present	197 (16.4)	**1.87 (1.29, 2.72)**	**<0.01**	1.33 (0.9, 1.98)	0.15
Myopia (SE -0.5 D or greater)	Absent	910 (76)	1.00		1.00	
	Present	287 (23.9)	**0.49 (0.32, 0.76)**	**<0.01**	**0.54 (0.35, 0.85)**	**<0.01**
Nuclear Sclerosis[#]	Absent	1081 (90.6)	1.00			
	Present	112 (9.3)	0.8 (0.45, 1.41)	0.44		
HTN[$]	Absent	748 (63.3)	1.00		1.00	
	Present	432 (36.6)	**1.36 (0.99, 1.87)**	**0.05**	1.16 (0.84, 1.61)	0.34

DM*	Absent	1184 (98.9)	1.00			
	Present	13 (1)	1.59 (0.43, 5.86)	0.47		
BMI	18.5-24.99	581 (49.7)	1.00			
	<18.5	473 (40.5)	1.04 (0.75, 1.45)	0.77		
	25-29.99	92 (7.8)	1.11 (0.62, 2)	0.7		
	>+30	21 (1.8)	1.25 (0.41, 3.8)	0.69		

(CI: confidence interval, SE: spherical equivalent, D: diopter, HTN: systemic hypertension, DM: diabetes mellitus, BMI: body mass index)

(# nuclear opalescence above grade 2 according to LOCS III classification system

$ History of high blood pressure diagnosed by a physician; current use of anti-hypertensive medication; and/or a blood pressure reading of ≥ 140/90 mmHg

* History of DM and/or diabetic retinopathy on clinical examination)

382 **Table 5.** Comparison with previous studies of primary angle closure disease

Study	Study design	Sample size	Age in years Mean ± SD*	Follow up period (years)	Number of participants developing disease	Incidence per year (%)			
						PACS[#]	PAC^	[@]PACG	[&]PACD
Ponza Eye Study, Italy[9]	[+]Pop. based	398	-	12	2	-	-	0.04	-
Japanese Study, Japan[10]	Cohort study	331	62.5±12.7	5	18	0.66	0.18	0.24	1.08
**CEDIS, South India[11]	Pop. based	3350	56.4±8.9	6	134	0.43	0.18	0.05	0.66
CEDIS, South India (rural cohort)[11]	Pop. based	1883	-	6	82	0.49	0.18	0.04	0.41
***APEDS, South India (rural sample; current study)	Pop. based	1197	49.2±7.65	15	190	0.56	0.4	0.1	1.05

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384 *SD: Standard Deviation; #PACS: Primary angle closure suspect; ^PAC: Primary angle closure; @PACG: Primary angle closure glaucoma; [&]PACD: Primary angle closure
385 disease; [+]Pop: Population; **CEDIS: Chennai Eye Disease Incidence Study; ***APEDS: Andhra Pradesh Eye Disease Study

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Figure 1: Flow chart showing the number of participants included in analysis

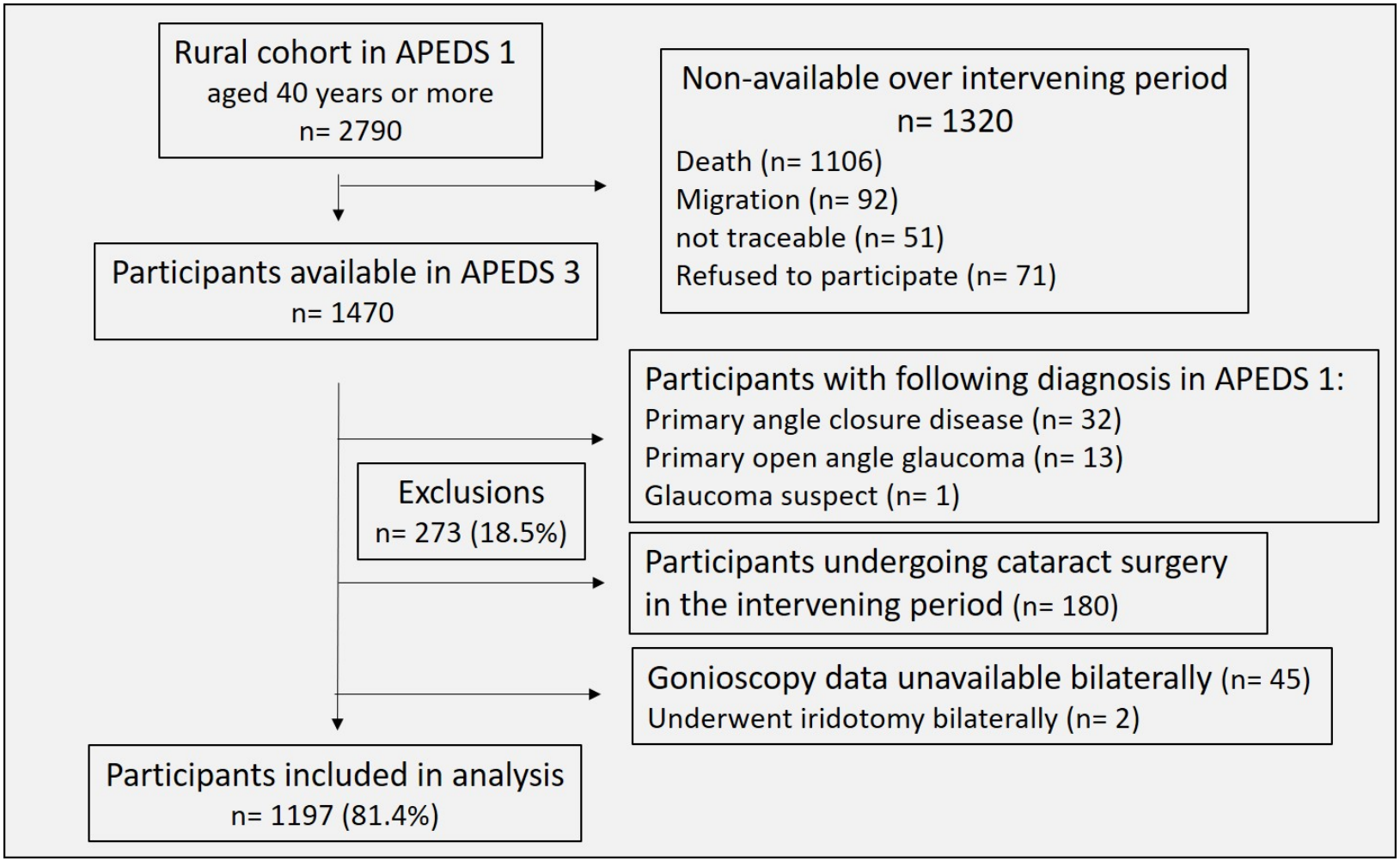

Figure 2: The relationship between the incidence of primary angle closure disease and the rate of cataract surgery (n= 180)

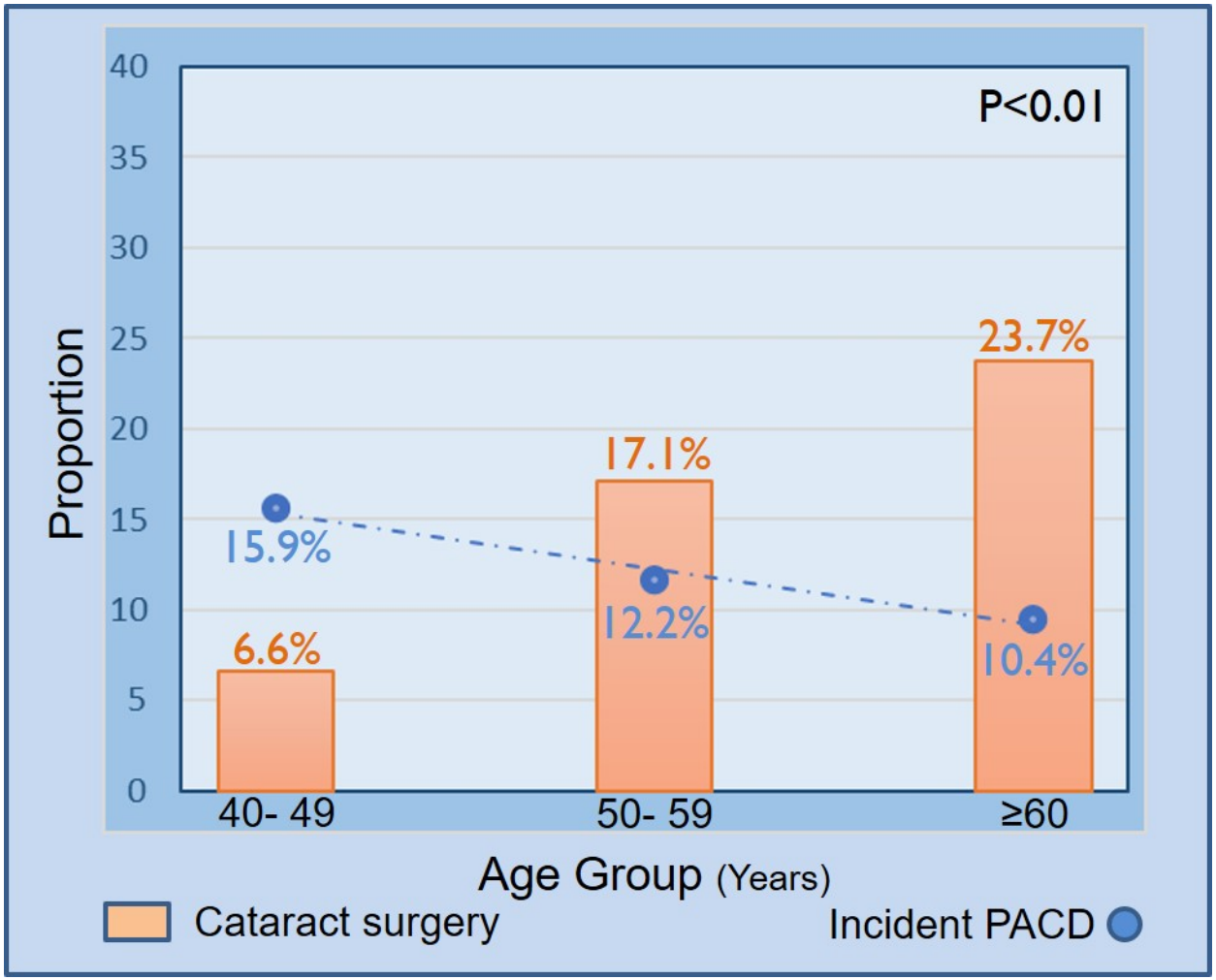

Figure 3: Numerators and denominators for the different forms of primary angle closure disease at baseline and follow up