Baseline Demographics, Rationale, and Methods of Jiri Eye Disease Incidence Study

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ABSTRACT

Introduction: Anthropological and biomedical studies have been undertaken in the Jirel population for more than three decades. The Jirel pedigree is one of the most powerful documented human pedigree's currently available for genetic studies.

Objective: To estimate the incidence of cataract, glaucoma and retinal diseases among the Jirel population aged 50 years or more over a period of 10 years.

Methodology: Jiri Eye Disease Incidence Study (JEDIS) is population-based cohort study that will enroll all participants of Jiri Eye Study (JES) aged 50 years and above, once every four years up to the year 2028. Detailed clinical examinations and investigations following the same clinical protocols of the JES will be carried out.

Result: Baseline demographics of 690 participants aged 50 years and above revealed 50.4% were males and 49.6% females and the average age (standard deviation) was 61.5 (8.6) years for males and 62.2 (8.7) years for females. At the end of 5 years, 483 participants completed the follow up, a response rate of 80%.

Conclusion: Epidemiological information derived from this study will help understand the natural history of eye diseases and implement health care programs for the prevention of blindness in the Jirel population.

Key words: Cataract; epidemiology; glaucoma; Jirel; retinal diseases.

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INTRODUCTION

For more than three decades anthropological and biomedical studies have been undertaken in the Jirel population. The studies include anthropological investigations (Williams-Blangero, and Blangero, 1989), assessments of population structure (Williams-Blangero, and Blangero, 1990), genetic susceptibility to parasitic worm infection (Williams-Blangero et al., 2002) and genetics of growth and development (Williams et al., 2013). As part of Jiri Eye Study (JES) conducted from 2015-2018 (Johnson et.al, 2019), the population was focus for genetic and clinical epidemiology of ocular traits and disorder. The extensive genealogical information for the population was available through the long history of genetic research conducted. The current ocular study participants belong to a single-extended pedigree, which makes it an extremely powerful resource for genetic epidemiological studies (Williams-Blangero, and Blangero, 2006) as they represent all individuals (≈3,000) that had participated in the previous studies.

The JES revealed prevalence of glaucoma was 4.2% among ≥40 years in this ethnic population (Miller et al., 2022). This is high compared to another Nepali study (Thapa et al., 2012), which had more diverse ethnic representation. Taking high response rate (80%) into consideration in five-year follow-up (year 2024), success of conducting previous studies in this less migratory population over long periods of time, and high glaucoma prevalence, Jiri Eye Disease Incidence Study (JEDIS) cohort study was decided to be ideal to understand natural history of chronic eye diseases over 10-year duration in this ethnic population.

The objectives of JEDIS were: i) to estimate incidence of cataract, glaucoma, and retinal diseases among subjects >50 years over 10-year duration; ii) to estimate incidence of visual impairment and blindness among subjects >50 years over 10-year duration; and iii) to investigate associated risk factors such as age, sex, intraocular pressure, central corneal thickness, axial length refractive error, hypertension, and diabetes.

METHODOLOGY

The JEDIS is a population-based cohort study of a duration of 10 years, conducted to study the clinical epidemiology of ocular traits and disorders among the Jirel ethnic group residing in Jiri. This study included participants 50 years and above who had previously been enrolled in the baseline JES (2015- 2018).

The JES was a study of genetic and clinical epidemiology of ocular traits and disorders that was conducted from 2015 to 2018 among those who were 18 years and above. They were recruited from seven Jirel villages that were most easily accessible. A sample size of 2000 was calculated from the observed Jirel pedigree structure to assess the statistical power to detect heritability of ocular trait measures. Calculations showed that the study would have 80% (the benchmark for statistical genetic power calculations) power to detect heritability (h^2) of an ocular trait as low as 6.5%. A sample size of 2000 participants was able to detect significant genetic effects for normal and diseased ocular trait measures in the large and powerful pedigree-based cohort.

In the baseline JES, a total number of 2045

participants aged 18 years and above was included. From this sample 690 participants were 50 years and above. All 690 participants were included in the 10-year follow-up study. An annual clinical examination and data collection of participants was commenced in 2021 following which a five-year follow up was completed in 2024. From 2025 participants will be examined annually until 2028 to complete the 10 years follow up study.

Jiri is located in Dolakha District of Bagmati Province of Nepal (Figure 1). It is approximately 190 kilometres (km) east of Kathmandu, the capital of Nepal. It is a geographically well-defined area of approximately 211 km^2 bounded on the east and west by two important rivers, the Tama Koshi and the Likhu Khola. The total population according to the census of 2021 was 16,109 living in nine wards (Central Bureau of Statistics Nepal, 2021). The region is named for the Jirels.

Subject recruitment and examination activities are conducted annually in Jiri and has commenced since 2021 and will continue until 2028. Study participants are contacted prior to every visit by the local recruitment staff to explain the purpose and benefits of the study. They will provide them with a Nepali-translated consent form (read to individuals who are illiterate) to obtain verbal agreement to participate in the study. Thereafter an appointment date and time will be arranged for the participants to attend the field research clinic that will coincide with the forthcoming field site visit.

Participants aged ≥50 years who had participated in the baseline JES were included. Further, participants were only included if they had

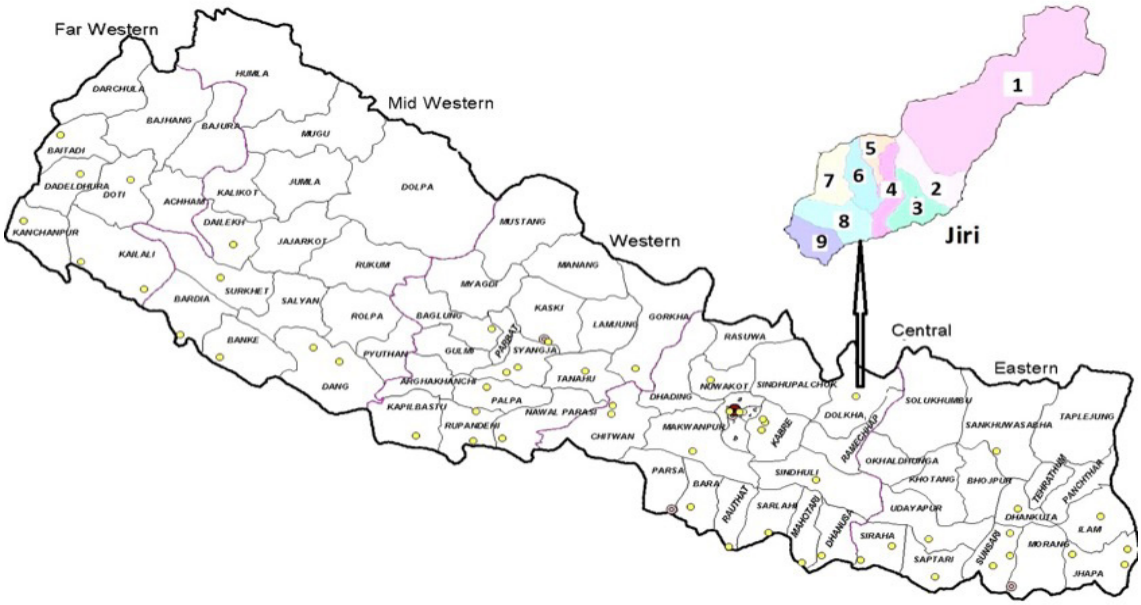

Figure 1: Map of Nepal showing Jiri located in Dolakha district.

resided in the sample area for a minimum of 12 months, to allow future longitudinal studies to take place. Participants <50 years were excluded from the study or those who were planning to reside in the study area for less than 12 months or who had not participated in the JES.

Those who declined to answer general questions on history of eye disease or refused to undergo eye examination were excluded from the study. The demographic characteristics of individuals who did not participate were collected in order to compare them with the study participants.

The clinical examination and investigations were conducted by an ophthalmologist and the research team at the community eye centre of Tilganga Institute of Ophthalmology established in Jiri. The clinical examination and investigations were conducted using the same protocol for JEDIS and JES for accurate comparison between the two studies.

Informed written consent was taken on the day of arrival at the clinic. Participants had to read the consent form or have it read to them in front of a witness and were given time understand and ask questions. A signature or thumb print was documented on the informed consent form. All study procedures were conducted in accordance with a protocol approved by the Tilganga Institutional Review Board and the Nepal Health Research Council in accordance with the Declaration of Helsinki.

Medical and ocular history were taken regarding ocular conditions such as history of wearing glasses, using eye drops, trauma to the eyes and any other existing eye problems. A history regarding systemic diseases, high blood pressure, diabetes and a family history of glaucoma or any eye disease was taken.

Visual acuity and refraction were conducted by an ophthalmic assistant with a three-year certified training in ophthalmology. The vision was recorded using a log MAR E chart placed at four-metre distance. The unaided presenting visual acuity and the best corrected visual acuity were recorded. LogMAR unit measurements were converted to decimal acuity for analyses according to the formula: decimal acuity = $10^{-\text{LogMAR}}$ (Holladay, 1997). Objective refraction was carried out using a streak retinoscope (Beta 200, Heine, Germany), which was followed by a subjective refraction. If the subject was unable to read the logMAR 1.0 line then the vision was checked at one metre. If the subject was unable to identify any of the largest optotypes, then perception of hand movement was checked. If hand movements could not be identified, then presence of light perception was checked and recorded.

Perimetry was performed on all subjects with a visual acuity of LogMAR 0.6 or better, a 24-2 visual field test was performed using a Humphrey HFA II 745i Visual Field Analyser (Carl Zeiss, Bangalore, India).

Pachymetry was used to measure central corneal thickness (CCT) on all subjects using Sonogage (Cleveland, OH 44128 USA). The ocular surface was anaesthetised with proparacaine 0.5% (Cipla Ltd. Mumbai, India). The measurement was taken with subjects in the sitting position while fixing on a distant target. The average from five measurements was recorded.

External examination of the face and eyes with the help of a hand-held flashlight included examination for the presence of strabismus,

extraocular movement abnormalities or any other gross pathology.

Pupillary evaluation involved asking the subject to fix at a distant object and then the direct and indirect pupillary reflexes of each eye were evaluated. A swinging flashlight test was used to determine the presence or absence of a relative afferent pupillary defect.

Slit lamp biomicroscopy was performed using a Haag Streit BP 900 (Switzerland) slit lamp. The lids and adnexa, conjunctiva, sclera, cornea, anterior chamber, and iris were examined. The van Herrick's method was used to grade peripheral anterior chamber depth (Van et.al, 1969).

Goldmann Applanation tonometry was used to measure intraocular pressure (IOP) on all subjects (AT 900 Haag Streit International) (Kass, 1996). The tonometers were calibrated at three-month interval. The ocular surface was first anaesthetised with Proparacaine 0.5%. (Cipla Ltd. Mumbai, India).

Gonioscopy was done on all subjects with a four-mirror Zeiss gonioscope (Carl Zeiss AG, Oberkochen, Germany) in ambient light with a shortened slit beam that did not fall on the pupil; the iridocorneal angle was graded using the Shafer system (Shaffer, 1960). The subjects with occludable angles were explained the risk of developing angle closure if they did not undergo laser peripheral iridotomy (LPI). Those subjects who consented underwent LPI.

Ocular Biometry was performed on every subject (US 500 Echoscan, Nidek Co. Ltd, Japan). Measurements of axial length and the anterior chamber depth were taken.

Grading of lens opacities was performed after pharmacologically dilating the pupils of all subjects with tropicamide 1% and phenylephrine 5%. Grading of lens opacities was done by comparing the lenticular opacities with a set of photos that represented the Lenticular Opacities Classification System (LOCS 2) (Chylack et al., 1989).

Fundus examination which included detailed evaluation of the optic disc and macula was performed with a 90 Dioptre lens (Volk Optical Inc, Mentor, Ohio, USA). A measuring eye piece graticule (Haag- Streit, Switzerland) was used to measure the vertical cup disc diameter.

Optic disc photography was taken (Topcon 3D Optical Coherence Tomography, Japan).

Optical Coherence Tomography was done (Topcon 3D Optical Coherence Tomography, Japan) of the anterior and posterior segments. The anterior chamber angle configurations, retinal nerve fiber layer and macular thickness were recorded.

Height, weight, and blood pressure were measured in all subjects. A single recording of the seated blood pressure was taken. Screening for diabetes was performed by measuring random blood sugar level from a blood sample (finger prick) taken from all subjects.

Definitions of visual impairment (VI) (best corrected VA) are derived from the International Classification of Diseases, 11^{th} edition (World Health Organisation, 2018). Here, it was defined no VI as VA $\geq$0.5, mild VI as VA of <0.50 but $\geq$0.30, moderate VI as VA <0.30 but $\geq$0.10, severe VI as VA <0.10 but $\geq$0.05, and blindness as VA <0.05 (includes no hand movement or

light perception) with best correction or a visual field <10° from fixation.

Glaucoma cases were defined based on the structural and functional evidence recommended for cross-sectional population-based research, according to the International Society of Geographic and Epidemiologic Ophthalmology (ISGEO) scheme (Table 1) (Foster et.al, 2002). Briefly, the distribution of VCDR from non-glaucomatous subjects with a normal visual field result for both eyes was calculated, where normal visual fields were defined upon application of the ISGEO scheme to this population's distribution. Optic discs were considered normal if the VCDR of one or both discs, or disc asymmetry was less than the 97.5th percentile of this distribution. A glaucomatous visual field defect was present when the hemifield test result was outside normal limits, and a cluster of three or more non-edge, contiguous points, not crossing the horizontal meridian, with a probability of less than 5% of an age-matched normal control on the pattern deviation was noted. In the presence of an open anterior chamber angle (≥ 180° of the pigmented trabecular meshwork), a JES participant was assigned a diagnosis of POAG if one or both eyes had evidence of glaucoma (Table 1), unless there was evidence of retinal or optic nerve disease, pseudoexfoliation, trauma or pigment dispersion. If any of these latter observations were made, a diagnosis of secondary open angle glaucoma was assigned. An occludable angle was diagnosed if the posterior trabecular meshwork was not observed for an angle > 180° on non-indentation gonioscopy. The PACG was defined as an eye with an occludable angle, peripheral anterior synechiae and/or elevated IOP with evidence of glaucoma. JES participants with an occludable angle but no evidence of glaucoma and a normal IOP were diagnosed as primary angle closure suspects (PACS).

Diabetic Retinopathy (DR) was graded using Early Treatment Diabetic Retinopathy Study (ETDRS) criteria (ETDRS report, 1981). DR was graded as non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic

Table 1. Glaucoma diagnosis categories[a].

Category 1: Structural and functional evidence.	Eyes with VCDR or VCDR asymmetry ≥ 97.5th percentile for the normal population combined with a visual field defect consistent with glaucoma.
Category 2: Advanced structural damage where reliable field testing is not possible.	Eyes with VCDR or VCDR asymmetry ≥ 99.5th percentile for the normal population.
Category 3: Optic disc not seen because of media opacity.	Visual acuity < 1.30 and IOP > 99.5th percentile, or Visual acuity < 1.30 and the eye shows evidence of glaucoma filtering surgery.

In diagnosing category 1 or 2 glaucoma, it was required that there should be no alternative explanation for CDR findings (dysplastic disc or marked anisometropia) or the visual field defect (retinal vascular disease, macular degeneration, or cerebrovascular disease). VCDR = vertical cup-to-disc ratio; IOP = intraocular pressure.

retinopathy (PDR). Subjects were categorised to have DR if they presented with any form of NPDR or PDR in at least one eye, irrespective of stage of the disease.

Hypertensive retinopathy was graded according to Modified Scheie Classification (Schubert, 1998). Grade 0: no changes; grade 1: barely detectable arterial narrowing; grade 2: obvious arterial narrowing with focal irregularities; grade 3: grade 2 plus retinal haemorrhage and/or exudates; grade 4: grade 3 plus disc swelling.

The AMD was graded according to the classification developed by the International Age-related Maculopathy (ARM) Epidemiological Study Group (Bird et.al, 1995). ARM is a degenerative disorder in persons ≥50 years of age characterised by the presence of any of the following abnormalities in the macula: soft drusen ≥63 microns, hyperpigmentation and/or hypopigmentation of the retinal pigment epithelium (RPE), RPE detachments and associated neurosensory detachment, (peri) retinal haemorrhage, geographic atrophy of the RPE, or (peri) retinal fibrous scarring in the absence of other retinal (vascular) disorders.

Data entry, cleaning, and coding were done in Microsoft Excel sheet. The cleaned data were transported to IBM SPSS Statistics, version 20 (IBM Corp., Armonk, N.Y., USA) for statistical analysis. Chi-square test was used for the association of categorical data, and independent t-test for numerical data. The p-value less than 0.05 was considered as statistically significant.

In diagnosing category 1 or 2 glaucoma, it was required that there should be no alternative explanation for CDR findings (dysplastic disc or marked anisometropia) or the visual field defect (retinal vascular disease, macular degeneration, or cerebrovascular disease). VCDR = vertical cup-to-disc ratio; IOP = intraocular pressure.

RESULT

Overview of participant enrollment, response rate, and demographic profiles at baseline and after five years are tabulated (Tables 2, 3). Among the 690 participants that had been enrolled, 483 had completed the study at five years resulting in a response rate of 79.6% with 80 participants had died. There was no significant difference in the proportion of male and female enrollment (50.4% vs 49%, p = 0.834). The mean age of male (61.5 years) and that of females (62.2 year) was also not significantly different (p = 0.288) indicating that the enrollment of subjects is in equal footing with respect to sex and their ages.

Table 2. Summary of participant enrollment and Response Rate

Year	Baseline Number (%)	Year	Follow Up Number (%)	Response rate (excluding death) %
2015	185 (26.8)	2021	135 (28.0)	84.9
2016	163 (23.6)	2022	127 (26.3)	87.6
2017	155 (22.5)	2023	109 (22.6)	79.6
2018	187 (27.1)	2024	112 (23.2)	67.5
Total	**690 (100)**	**Total**	**483 (100)**	**79.6**

Table 3. Demographic characteristics of study participants at baseline and follow up at 5 year

Variables		Baseline Number (%)	Follow Up Number (%)
Gender	Female	342 (49.6)	244 (50.5)
	Male	348 (50.4)	239 (49.5)
Age group	50-59	317 (45.9)	257 (53.3)
	60-69	232 (33.6)	155 (32.2)
	70-79	115 (16.7)	62 (12.8)
	80-89	26 (3.8)	8 (1.7)
Age	Female, Mean (sd)	62.2 (8.7)	59.8 (7.9)
	Male, Mean (sd)	61.5 (8.6)	60.7 (7.7)
	Total, Mean (sd)	61.9 (8.7)	66.2 (7.8)

Occupation: Agriculture 63.3%, Illiterate: 79.3%

DISCUSSION

Jirels are of the Tibeto-Burman language speaking group which comprise the focal population of the study. Ethnohistorical accounts and population genetic studies support the idea that the Jirels represent a population derived from Sherpas and Sunwars between 10 and 11 generations ago. All individuals who had previously participated in genetic studies of JES conducted in the region belong to a single extended pedigree containing >62,000 pair-wise relationships that are informative and extremely powerful for genetic analyses.

The Jirel pedigree is one of the most powerful documented human pedigrees' currently available for genetic studies.

This study is expected to reveal the incidence of visual impairment, blindness, cataract, glaucoma, and retinal disease in the Jirel population aged 50 years and above at 5 and 10 years duration.

CONCLUSION

The epidemiological information derived from this study will help understand the natural history of eye diseases and implement health care programs for the prevention of blindness in the Jirel population. Epidemiological fieldwork and clinical examination will conclude in April 2028.

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