PREVALENCE AND RISK FACTORS FOR REFRACTIVE ERRORS AND THEIR ASSOCIATIONS WITH MAJOR AGE-RELATED EYE DISEASES IN ADULT SINGAPORE INDIANS

PAN CHENWEI

(B. Med, Fudan University)

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DECLARATION

I hereby declare that the thesis is my original work and it has been written by me in its entirety. I have duly acknowledged all the sources of information which have been used in the thesis.
This thesis has also not been submitted for any degree in any university previously.

Pan Chenwei
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LIST OF ACRONYMS

D	diopters
SE	spherical equivalent
AL	axial length
GWAS	genome-wide association study
ACD	anterior chamber depth
LT	lens thickness
NHANES	National Health and Nutrition Examination Survey
CI	confidence interval
PAR%	population attributable risk percentage
RESC	Refractive Error Study in Children
SCORM	Singapore Cohort Study of Risk factors for Myopia
STARS	Strabismus, Amblyopia and Refractive error Study in Singapore Preschool Children
SMS	Sydney Myopia Study
OLSM	Orinda Longitudinal Study of Myopia
CLEERE	Collaborative Longitudinal Evaluation of Ethnicity and Refractive Error
OR	odds ratio
ECM	extracellular matrix
CR	corneal radius of curvature
VCD	vitreous chamber depth
AMD	Age-Related Macular Degeneration
DR	Diabetic Retinopathy
WESDR	Wisconsin Epidemiologic Study of Diabetic Retinopathy
PSC	posterior subcapsular cataract
POAG	Primary Open Angle Glaucoma
IOP	intraocular pressure
CCT	central corneal thickness
SERI	Singapore Eye Research Institute
IRB	Institutional Review Board
HDL	high density lipoprotein cholesterol
LDL	low density lipoprotein cholesterol
HbA1c	hemoglobin A1c
HPLC	high-performance liquid chromatography
RPE	retinal pigment epithelium
NPDR	non-proliferative diabetic retinopathy
PDR	proliferative diabetic retinopathy
CSME	clinically significant macular edema
VTDR	vision-threatening diabetic retinopathy
LOCS III	Lens Opacity Classification System III system
CDR	cup-disc ratio
GEE	generalized estimating equation
HR	hazards ratios
IQR	inter quartile range

BMI	body mass index
SINDI	Singapore Indian Eye Study
SiMES	Singapore Malay Eye Study
HLA	human leukocyte antigen

SUMMARY

Myopia is a global public health concern and there may be an epidemic of myopia in Singapore. Current data revealed racial differences in myopia prevalence even after adjusting for education, suggesting that other factors, including genetic factors, may be responsible for the racial variation. Detailed inter-ethnic comparisons among middle-aged and elderly Indians, Chinese and Malays in Singapore have not been conducted. The prevalence of myopia among Indian adults in Singapore may be different from Indian adults in India. Possible ocular complications of myopia including cataract, age-related macular degeneration (AMD), diabetic retinopathy (DR) and primary open angle glaucoma (POAG) have been reported in Caucasians and Chinese, and should be carefully delineated in Indians.

Population-based cross-sectional data in the Singapore Indian Eye Study on Indians aged 40-84 years were analyzed in this study. The overall aim of the thesis is to determine the prevalence and patterns of myopia and other refractive errors and theirs associations with major age-related eye diseases in adult Singapore Indians. The aims include: i) To determine the prevalence and risk factors for refractive errors in middle-aged to elderly Singaporeans of Indian ethnicity, ii) To describe the distribution and determinants of ocular biometric parameters in adult Singapore Indians, iii) To assess the influence of factors related to migration and acculturation on myopia in migrant Indians in Singapore. iv) To determine the associations of myopia and axial length (AL) with major age-related eye diseases including AMD, DR, age-related cataract and POAG. v) To determine the associations between refractive errors and AMD by a systematic review and meta-analysis of observational studies

In this study, 28.0% of Singaporeans of Indian ethnicity aged over 40 years had myopia, which is similar to that of Singapore Malays but lower than Singapore Chinese of the same age. The higher myopia prevalence rates recorded among Indians in India compared with Singaporean Indians may be due to the high nuclear cataract rates in older adults in India. The prevalence of myopia decreased with age in adults without nuclear cataract and increased with age in adults with nuclear cataract, suggesting that the U-shape curve may be explained by differences in patterns for adults with and without nuclear cataract. A more myopic refraction was predominately explained by longer AL or greater AL/corneal radius (CR) ratio throughout the whole age range, although lens nuclear opacity was also a predictor of refraction in older age groups. Height, time spent reading and educational level were the most important predictors of AL. Myopia was more prevalent and ALs were longer among second (or higher) generation immigrants compared with first generation immigrants. Among first generation immigrants, those who migrated to Singapore at an early age and those who preferred to be and were interviewed in English were more likely to be myopic than their counterparts. Myopic eyes were less likely to have AMD and DR, but more likely to have nuclear cataract, posterior subcapsular cataract and POAG. In addition, the variation in AL explained most of the associations of refractive error with AMD, DR or POAG, but not the associations with age-related nuclear cataract, which results from changes in the refractive power of the lens associated with nuclear cataract.

CHAPTER 1

LITERATURE REVIEW

1.1 Nature Development of Myopia

Myopia is the most common eye disorder.[1] It refers to the state of refraction in which parallel rays of light are brought to focus in front of the retina of a resting eye.[2-3] In myopic eyes, the images of distant objects are focused in front of the retina when the accommodation system is relaxed. Therefore, light entering the eye has to originate from near objects in order to be focused on the retina of the myopic eye. (**Figure 1**) It is measured by the spherical power in diopters (D) of the diverging lens needed to focus light onto the retina, which can be expressed as the spherical equivalent (SE). Most commonly used definitions of myopia in epidemiologic studies include SE of at least -0.50 D, -0.75 D, and -1.00 D.[4] Myopia is generally classified as high myopia when it exceeds 6 D.[3] Most infants are usually born hyperopic.[5] Normally, the eyes shift from neonatal hypeopia to emmetropia in the first year of life.[6] Myopia typically develops during the school years, progressing until adulthood though sometimes it may also develop in adults. Progression typically ceases in the teenage years. Generally, the annual progression is close to -0.50D for children aged 8 to 12 years.[7] Investigators found that the final refractive status is correlated with the age of onset in adulthood, that is, children who become myopic at an earlier age may have a higher risk for myopia progression and higher degree of myopia later on.[7-8] Later in life of age over 60 years, a myopic refractive shift may result from crystalline lens changes.[9]

1.2 Axial Length as an Endophenotype of Myopia

Axial Length (AL) is considered as an endophenotype of myopia. Both AL and myopia can be analyzed as a quantitative trait using linkage studies. However, AL is much more suitable. The phenotype of myopia, especially high myopia, is commonly accompanied with other eye disorders such as cataract, glaucoma and chorioretinal abnormalities, thus would inevitably involve some confounders and may lead to biased conclusions. However, AL, as a clean trait, could be studied in general optical healthy populations and subjects with low myopia to avoid those confounders. Some reported that the heritability of myopia varies significantly among studies with different family structures, while the heritability of AL remains quite consistent [10] . Thus, using AL as an endophenotype could avoid or minimize the substantial bias caused by a more complex myopic trait due to instability of heritability. AL as a clean and simple endophenotype may bring some advantages to the research field of myopia. This conclusion was partly supported by the first genome-wide association study (GWAS) on myopia.[11]

1.3 Measurement of Refraction and Ocular Biometry.

It was suggested that subjective refraction using a phoroptor is usually preferred in cooperative patients. Subjective refraction data were preferred for analysis since the reproducibility of subjective refraction has been found to be within 0.50 D for spherical equivalent, sphere power, and cylinder power.[12-13] Auto-refraction is adequate for a preliminary refraction but is not a good substitute for subjective refraction.[12] Cycloplegic auto-refraction is the gold standard technique for refractive error measurement.[14] Non-cycloplegic refraction might have overestimated the myopia rates, but this effect seems to be marginal on subjects were middle-aged to elderly adults over 40 years who

may have lower amplitude of accommodation.[15-16]

In previous studies[17-20], AL was measured by A-scan ultrasound biometry which requires corneal surface contact and the measurement is more time-consuming. The non-contact optical biometry measurement which uses partial coherence interferometry technology (IOL Master) eliminates the deficiency of A-scan ultrasound measurement. It was suggested that the IOL Master is a better predictor of normative ocular biometric data than ultrasound biometry.[21] Biometry data from ultrasound and laser interferometry may be slightly different.[22] Anterior chamber depth (ACD) using ultrasound were found to be significantly shorter than non-contact measures.[23] Compared with A-scan ultrasound, IOL Master could either overestimate[24] or underestimate[25] AL. IOL Master also does not provide lens thickness (LT) measurement.

1.4 Socioeconomic Burden of Myopia

Myopia is a significant public health problem and its rapid increase in prevalence in recent decades is associated with a significant financial burden. Direct myopia related cost includes prescription of spectacles and contact lenses, contact lenses solutions and repeat optometry visits.[26] In Singapore, the mean annual direct cost of myopia for each Singaporean school children aged 7 to 9 years was estimated to be US$148.[27] In the United States, the National Health and Nutrition Examination Survey (NHANES) reported the annual direct cost of correcting distance vision impairment due to refractive errors to be between US$3.9 billion and US$7.2 billion.[28] Globally, the annual cost for myopia was estimated to be US$4.6 billion in 1990.[29] There are also medical cost associated with treating myopia induced morbidities such as retinal detachment,

glaucoma, cataract, and associated visual disability and blindness.[26]

1.5 Prevalence of Myopia

1.5.1 Worldwide Prevalence of Myopia in Adults

In mainland China, the prevalence of myopia for definitions of SE of <-0.50 D, <-1.0 D, <-6.0 D, and <-8.0 D were reported to be 22.9% (95% confidence interval [CI], 21.7, 24.2), 16.9% (95% CI, 15.8, 18.0), 2.6% (95% CI, 2.2, 3.1), and 1.5% (95% CI, 1.1, 1.9) respectively, in the Beijing Eye Study (n=4,439, aged 40-90 years).[30] The limitation of this study is that refraction was not performed on subjects with an uncorrected visual acuity of 0.0 logMAR (Snellen 6/6) or better. The Shihpai Eye study in Taiwanese adults aged over 65 years reported the prevalence to be 19.4% and 14.5% for myopia of SE<-0.5 D and SE <-1.0 D, respectively. The prevalence of myopia in Taiwan seems to be lower than that of Beijing Eye Study. The difference in prevalence of less than 3.5% between Taiwan and Beijing is marginal. This difference in prevalence is attributed to the older sample in Taiwan leading to a hyperopic shift in refraction, but this difference in age would also work in the opposite direction with a potential myopic shift due to the onset of nuclear cataract in the older population.[31] In Japanese adults aged over 40 years, the prevalence was reported to be 41.8% for myopia of SE < -0.5D.[32] The Japanese study may have overestimated the prevalence of myopia due to younger participants and non-cycloplegic refraction.

In India, three population-based studies have been conducted to estimate the prevalence of myopia.[33-35] The prevalence of myopia for SE < -0.5D in 40 year and older Indian adults in both urban and rural areas was reported to be 34.6% (n=3,723) in the

Indian state of Andhra Pradesh, with a prevalence of 38.0% in rural areas and 31.9% in urban areas. The higher prevalence of myopia in the rural Indian population could be explained by higher rates of nuclear cataract in rural India leading to a myopic shift in refraction.[33] This study was the first to provide the population attributable risk percentage (PAR%) data on different types of refractive errors in adult Asians. Data from this population-based study demonstrated the expected association between age and different types of refractive errors. In another study of rural Indian adults aged over 39 year in Chennai (n=2,508), the prevalence was reported to be 31% for myopia of SE< -0.5D.[34] The association between myopia and age almost disappeared after adjustment for nuclear sclerosis, indicating that nuclear sclerosis is responsible for the increase in myopia with age. The extent of non-participation bias cannot be elucidated as neither of the studies in India revealed details about the respondents and non-respondents. In the Central India Eye and Medical Study, which included 4711 subjects (aged 30 years or older) of 5885 eligible subjects, myopia of more than -0.50 D, -1.0 D, more than -6.0 D, and more than -8 D occurred in 17.0%, 13.0%, 0.9%, and 0.4% of the subjects, respectively.[35]This study demonstrated that the rural population of Central India has not experienced a myopic shift as described for many urban populations at the Pacific Rim.

In Bangladesh and Pakistani adults aged over 30 years, the prevalence of myopia (SE < -0.5D) has been reported to be 23.8% (n=11,624) and 36.5% (n=14,490) respectively whereas it is about 48.1% in Indonesian young adults aged over 21 years (n=1,043).[36-38] The prevalence of myopia in Mongolian adults over 40 years was reported to be 17.2% (n=1,617).[20] In the WHO National Blindness and Low Vision Surveys in Bangladesh, non-cycloplegic refraction and subjective refraction were only performed on

those with visual acuity worse than 0.30 logMAR (Snellen 6/12). Thus, the prevalence of myopia may have been overestimated.

The Tanjong Pagar Survey (TPS) and the Singapore Malay Eyes Study (SiMES) analyzed the prevalence of myopia of SE < -0.50D in Singaporean Chinese and Malay adults aged over 40 years and reported it to be 38.7% [39] and 26.2%[40], respectively.

In the United States, the 1999-2004 NHANES used an autorefractor to measure refractive data on a US non-institutionalized, civilian population aged 20 years or older. The age-standardized prevalence of myopia (SE <−1.0 D or less) was 33.1% (95% CI, 31.5% to 34.7%) in 12,010 participants.[41] In this study, non-cycloplegic refraction may have caused an overestimation of myopic persons among younger participants. In the Baltimore Eye Survey (n=5,028), the prevalence of myopia (SE < -0.5D) was 28.1% among the white and 19.4% among the black.[42] The Los Angeles Latino Eye Study reported a myopia prevalence of 16.8% in 40 years or older adults (n=5,927) in the worse eye.[43] In the Beaver Dam Eye Study, the age-gender adjusted prevalence of myopia (SE < -0.5D) was 26.2% based on the data of the right eye.[44] The Barbados Eye Study examined the prevalence of myopia in African–Americans aged 40 to 84 years (n=4,709). The age-gender adjusted prevalence of myopia (SE<-0.5D) was 21.9% (95 CI, 20.6-23.2) based on objective refraction data.[45] The Beaver Dam Eye study of adults aged over 43 years may have overestimated the prevalence of myopia in terms of the younger respondents. On the contrary, the NHANES on people aged over 20 years may have underestimated the prevalence of myopia since the younger working adults were more difficult to recruit than the older ones.

In the UK, among a total of 2,487 randomly selected 44-year-old members of the

1958 British birth cohort, 1214 individuals (49%; 95% CI, 48.8-50.8) were myopic. Refraction was measured by autorefraction using the Nikon Retinomax 2 (Nikon Corp., Tokyo, Japan), under non-cycloplegic conditions. Thus, myopia prevalence may have been overestimated.[46] In Norway, non-cycloplegic refraction was measured in a population-based sample of young (20-25 years) and middle-aged (40-45 years) adults. A total of 3,137 persons (1,248 young and 1,889 middle-aged adults) with corrected visual acuity worse than 0.3 logMAR (Snellen 6/12) in either eye were included in the study. The prevalence of myopia (SE < -0.5D) was 35.0% in the young adult group and 30.3% in the middle-aged group. Prevalence of myopia was overestimated especially for the young adult group due to the non-cycloplegic refraction.[47]

In Australia, the Blue Mountains Study reported a prevalence of myopia in adults aged 40-97 years of 15.0% (n=3,654).[48] The Visual Impairment Project reported a myopia (SE < −0.5 D) prevalence of 17.0% (95% CI 15.8, 18.0).[49] A meta-analysis by the Eye Diseases Prevalence Research Group estimated the crude prevalence rates for myopia of −1.0 D or less as 25.4%, 26.6%, and 16.4% in the United States, Western Europe and Australia, respectively.[50]

Based on the published data of myopia prevalence on adults, it is still unclear whether the myopia prevalence is higher in East Asian Countries than in Western Countries. The prevalence of myopia is 38.7% in Singaporean Chinese (SE < -0.5 D).[39] However, the meta-analysis by Kempen *et al.* showed that the prevalence of myopia is 25.4% and 26.6% for White subjects in the United States and Western Europe using a more conservative definition of myopia (SE < -1.0 D), respectively.[50] The cut off used to define myopia is arbitrary but the prevalence might change significantly by a small shift

in this cut-off value.[49] In Singapore, the Chinese have a higher prevalence of myopia compared with Malays living in the same country and the myopia prevalence in South Asia in the Indian population is only marginally lower than the Singaporean Chinese. The myopia prevalence reported in the Singaporean Malays[40] is also lower than those from North America.[42, 44] (**Table 1**)

1.5.2 Worldwide Prevalence of Myopia in Children

The Refractive Error Study in Children (RESC) was conducted in different countries using the same sampling strategies, procedures to measure refraction and definitions of myopia, in order to compare the prevalence of myopia across different study populations. In Nepal, the prevalence of myopia ranged from 10.9% in 10-year-old children, 16.5% in 12-year-olds, to 27.3% in 15-year-old children living in the urban region, whereas it was less than 3% in 5 to 15 year old children in rural Nepal [51-52]. In urban India, the prevalence of myopia was 4.7%, 7.0% and 10.8% in 5, 10 and 15 year-olds, respectively. On the other hand, the prevalence of myopia was 2.8%, 4.1% and 6.7% in 7, 10 and 15-year-olds, respectively in the rural region [53-54]. Among urban Chinese children the prevalence of myopia ranged from 5.7% in 5-year-olds, 30.1% in 10-year-olds and increased to 78.4% in the 15-year-olds.[55] In rural parts of northern China, the prevalence of myopia was almost nil in 5-year-olds and steadily increased to 36.7% and 55.0% in 15-year-old males and females respectively.[56] In the rural region of Southern China, 36.8% of 13-year-olds, 43.0% of 15-year-olds and 53.9% of 17-year-olds were found to be myopic.[57] In brief, the prevalence of myopia was highest (78.4%) in 15-year-old urban Chinese children [55] and lowest (1.2%) in 5 to 15 year old

rural Nepalese children.[52] (**Figure 2**)

In Singapore, the prevalence of myopia was 29.0% in 7-year-olds, 34.7% in 8-year-olds and 53.1% in 9-year-olds in the school-based population of the Singapore Cohort Study of Risk factors for Myopia (SCORM) [58] while the Strabismus, Amblyopia and Refractive error Study in Singapore Preschool Children (STARS) reported that the prevalence of myopia was 11.0% in Chinese children aged 6 to 72 months[59]. In Hong Kong, a large cross-sectional survey reported that the prevalence was 17.0% in children aged less than 7 years and which increased to 37.5% among those aged 8 years and 53.1% in children aged more than 11 years.[60] The prevalence of myopia among Taiwanese Chinese primary school children aged 7 years was 5.8% in 1983, 3.0% in 1986, 6.6% in 1990, 12.0% in 1995 and 20.0% in 2000. Among Taiwanese children aged 12 years, the myopic rates were 36.7%, 27.5%, 35.2%, 55.5% and 61.0% correspondingly. At the junior high school level, the prevalence was 64.2%, 61.6%, 74.0%, 76.0% and 81.0% respectively. Among children aged 16 to 18 years, the myopia prevalence was almost constant at around 74% to 75% in studies conducted in 1983, 1986 and 1990. However, the prevalence rate increased to 84% in studies in 1995 and 2000.[61]

The prevalence of myopia has also been reported in non-Asian populations. Among South African children, the prevalence of myopia was about 3% or 4% increasing to 6.3% in 14-year-olds and 9.6% in 15-year-olds [62]. In Chile, 3.4% of the 5-year-olds were myopic and the prevalence rate increased to 19.4% and 14.7% in the 15-year-old males and females respectively[63]. In Australia, the Sydney Myopia Study (SMS) reported the myopia prevalence to be 1.4% among 6-year-olds (n=1,765) with 0.8% in the White children and 2.7% among other ethnic groups [64]. Among 12-year-old children (n=2,353),

the overall myopia prevalence was 11.9%, which was lower among European Caucasian children (4.6%) and Middle Eastern children (6.1%) and higher among East Asian (39.5%) and South Asian (31.5%) children [65], although the sample size of non-White groups in SMS was very small. In the Orinda Longitudinal Study of Myopia (OLSM), the prevalence of myopia increased from 4.5% in 6 to 7-year-old children to 28% in 12-year-old children in a predominantly white population in the United States [66]. In the USA Collaborative Longitudinal Evaluation of Ethnicity and Refractive Error (CLEERE), Asians had the highest prevalence (18.5%), followed by Hispanics (13.2%). Whites had the lowest prevalence of myopia (4.4%), which was not significantly different from African Americans (6.6%). In the CLEERE study, however, children with different ethnicities were from different geographical areas so that the comparison of prevalence was affected by both genetic and environmental factors.[67]

In a Swedish school-based sample of 1,045 children aged from 12 to 13 years, refraction was performed using 1 drop of 0.5% tropicamide and measured by retinoscopy. The prevalence of myopia (SE ≤ -0.5D) was reported to be 49.7% and the prevalence of bilateral myopia was reported to be 39.0%.[68] In another study in the UK, non-cycloplegic autorefraction data were available for 7,554 children at the age of 7 from a birth cohort study. Using a definition of 'likely to be myopic' as SE ≤-1.50D, this study reported a prevalence of myopia of 1.5% in seven-year-old white children.[69] The Northern Ireland Childhood Errors of Refraction study, a population-based cross-sectional study, examined 661 white 12-13-year-olds and 392 white 6-7-year-old children between 2006 and 2008. The prevalence of myopia was reported to be 2.8% (95% CI 1.3%, 4.3%) in the 6-7-year-old age group and 17.7% (95% CI 13.2%, 22.2%) in the 12-13-year-old age

group.[70] The Aston Eye Study, an ongoing multi-racial sample of school children from the metropolitan area of Birmingham, England, reported preliminary cross-sectional data on 213 South Asian, 44 black African Caribbean and 70 white European children aged 6-7 years and 114 South Asian, 40 black African Caribbean and 115 white European children aged 12-13 years and found that myopia prevalence was 9.4% and 29.4% for the two age groups, respectively. Ethnic differences in myopia prevalence were found with South Asian children having higher levels than white European children (36.8% vs. 18.6%) for the children aged 12-13 years.[71] The Child Heart and Health Study in England used population-based sampling stratified by socioeconomic status and reported the prevalence of myopia to be 3.4% in White children aged 10 to 11 years. However, non-cycloplegic refraction in this study might have led to an overestimation of the myopia prevalence.[72] In Greece and Bulgaria, four schools from the centre of a Greek city were chosen and two schools from the centre of a Bulgarian city. Non-cycloplegic auto-refraction was performed on children aged 10-15 years. The prevalence of myopia (SE≤-0.75D) was 37.2% in Greek children and 13.5% in Bulgarian children.[73]

In summary, the prevalence of myopia in Chinese children is higher than other ethnic groups. Moreover, the prevalence of myopia in European children seems to be lower than that in Asian children generally. Data from most studies have also documented a clear urban–rural difference in the prevalence of myopia. Studies on populations with very similar genetic backgrounds growing up in different environments in India, Nepal and China have shown that those growing up in rural environments have a lower prevalence of myopia. For the Chinese ethnicity, the prevalence of myopia in cities such as Guangzhou and Hong Kong is comparable to those reported for Singapore and urban

areas of Taiwan. However, recent evidence showed that the prevalence in rural southern China is also very high. Whether this high prevalence of myopia in rural China is due to rapid economic development and high educational achievement is unclear. (**Table 2 & 3**)

1.6 Major Risk Factors of Myopia

1.6.1 Outdoor Activities as a Protective Factor for Myopia

In Australia, students who performed high levels of near work but low levels of outdoor activity had the least hyperopic mean refraction. On the other hand, those who carried out low levels of near work but high levels of outdoor activity had the most hyperopic mean refraction. Furthermore, in an analysis combining the amount of outdoor activity and near work activity spent, children with low outdoor time and high near work were 2 to 3 times more likely to be myopic compared to those performing low near work and high outdoor activities.[74]

In Singapore, a cross-sectional study was conducted to analyze the effect of outdoor activities on 1,249 teenagers aged 11 to 20 years (71.1%, Chinese, 20.7% Malays and 0.8% other ethnicities). After adjusting for confounders, there was a significant negative association between myopia and outdoor activity. Adjusting for the same confounders, for each hour increase in outdoor activity per day, SE increased by 0.17 D (i.e. a hyperopic shift) and the AL decreased by 0.06 mm.[75]

The OLSM found that children who became myopic (SE < -0.75 D) by the 8th grade spent less time in sports and outdoor activity (hours per week) at the 3rd grade compared to those who did not become myopic (7.98 ± 6.54 hours vs. 11.65 ± 6.97 hours). In predictive models for future myopia, the combined amount of sports and

outdoor hours per week was predictive of future myopia.[76]

Additional recent studies have found that outdoor activity is an independent factor negatively associated with myopia. The Sydney Myopia Study measured both near work and outdoor activities simultaneously and found that near work activities had little impact on refraction.[74] This study also found no effect of indoor sport on myopia, which implicates that more time spent outdoors, rather than sport itself, as the essential protective factor. A recent animal study on chicks found that light intensity modulates the process of emmetropization and that a low intensity of ambient light is a risk factor for developing myopia.[77] The biological mechanism behind this association is not yet clearly understood. It is postulated that higher light intensity outdoors could make the depth of field greater and reduce image blur. In addition, the release of dopamine from the retina is stimulated by light, and dopamine can inhibit eye growth.[74] However, the hypothesis that it is the high light intensity outdoors that is crucial has been contradicted by a study suggesting that it is the spectral composition of the light, rather than the intensity, which is the primary cause of the tendency for myopia to be associated with more time indoors.[78] In a recent animal study, chicks exposed to high illuminances (15,000 lux) for 5 hours per day significantly slowed compensation for negative lenses compared with those under 500 lux. Compensation for positive lenses was accelerated by exposure to high illuminances but the end point refraction was unchanged, compared with that of the 500-lux group. High illuminance also reduced deprivation myopia by roughly 60%, compared with that seen under 500 lux. This protective effect was abolished by the daily injection of spiperone, a dopamine receptor antagonist. This study showed that the retardation of myopia development by light is partially mediated by dopamine.[79] A very

recent animal study (Smith et al, 2011 ARVO e-abstract 3922) showed that high-light-reared monkeys exhibited significantly lower average degrees of myopic anisometropia (+0.14 ± 4.12 vs. -3.56 ± 3.33 D, p = 0.04) and average treated-eye refractive errors that were significantly more hyperopic than those observed in monocularly form-deprived monkeys reared under normal light levels (+4.44 ± 5.24 vs. -0.65 ± 3.84 D, p = 0.03). Thus, high ambient light levels can dramatically retard the development of form-deprivation myopia. This study indicated that absolute light levels are a fundamental variable impacting the vision-dependent regulation of ocular growth in primates and suggested that the seemingly protective effects of outdoor activities against myopia in children are due to exposure to the higher light levels normally encountered in outdoor environments. In a recent publication, Charman hypothesized that a consistent relationship between the astigmatic image fields and the retina are likely to be favourable to peripherally-based emmetropization. This condition is satisfied by outdoor environments, since dioptric stimuli may not vary widely across the visual field.[80] (**Table 4**)

1.6.2 Near Work as a Risk Factor for Myopia

In the SMS, near work was quantified by the continuous time and close reading distance in 12- year-old children.[81] Children who read continuously for more than 30 minutes were more likely to develop myopia compared to those who read for less than 30 minutes continuously. Meanwhile, children who performed near-work at a distance of less than 30 cm were 2.5 times more likely to have myopia than those who worked at a longer distance. Similarly, children who spent a longer time reading for pleasure and

those who read at a distance closer than 30 cm were more likely have higher myopic refractions.

The SCORM study found that children who read more than two books per week were about 3 times more likely to have higher myopia (SE< -3.0 D) compared with those who read less than two books per week. Children who read for more than two hours a day were 1.5 times more likely to have higher myopia compared to those who read less than 2 hours, but this was not significant. Every book read per week, was associated with an AL elongation of 0.04 mm. Children who read more than two books per week had 0.17 mm longer axial lengths compared to children who read two or fewer books per week. [58]

The OLSM examined 366 eighth-grade predominantly Caucasian children and found that the Odds Ratio (OR) of myopia (SE < -0.75 D) was 1.02 (95% CI 1.008, 1.032) for every dioptre-hours of near work spent per week, after controlling for parental myopia and achievement scores.[82]

Near work was also shown not to be associated with myopia in several other studies.[83-84] In a 5-year follow-up longitudinal study on 1,318 children aged 6 to 14 years, hours per week spent reading or using a computer did not differ between the groups before myopia onset. Studying and TV watching were also not significantly different before myopia onset. This study failed to show evidence of a relationship between near visual activities and the development of myopia.[85] Most studies on myopia and near work are cross-sectional which cannot examine the temporal relationship between outcomes and predictors. It is also likely that myopes engage in more near work as it is more difficult to take part in some sporting tasks due to spectacle wear. A prospective study reported that myopic children may be more at risk of having lower levels of physical

activity than their non-myopic peers.[86] This argument should be resolved by more prospective studies with longitudinal evidence. In addition, most information on near work and time outdoors in previous studies were reported by parents. Thus, recall bias or reporting bias may have occurred. In the future more accurate and more tightly standardised methodology for quantifying near work needs to be used, which should facilitate precise comparison between different studies. Some modifiable kinds of near work, such as reading posture, breaks during reading, and proper lighting should also be studied so that children could benefit through health promotion efforts of modifiable behaviour.[87] (**Table 5**)

1.6.3 Role of Education

Numerous studies that have examined the effect of education on myopia have found a consistent correlation between higher educational level and higher prevalence of myopia.[42, 44, 49, 88] There appears to be an association between myopia and higher academic achievements as well.[82, 89-90] In a study on the Chinese children in Singapore and Sydney, early schooling in Singapore has also been found to be associated with the high levels of myopia compared with schooling in Sydney.[91] This study indicated that exposure to a more intensive schooling system at an early age may be an independent risk factor for myopia. Higher educational level was also positively associated with longer AL. In Singapore Malay adults, increasing AL was associated with higher educational levels (standardized regression coefficient = 0.118, $p < 0.001$).[92] In Singapore Chinese adults, an AL increase of 0.60 mm is associated with every 10 years of education.[17]

In epidemiological studies, educational level is usually measured either as years of

formal education or level of academic achievement. Both the duration and level of education are highly correlated with time spent on reading and writing. Hence, educational level may be a surrogate for near work.[6] Meanwhile, the association between education and myopia may also reflect common genetics of intelligence and refraction.

1.6.4 Parental Myopia as a Risk Factor for Myopia

In the SMS, children with one and two myopic parents had 2 times and 8 times higher risks, respectively, of developing myopia (SE ≤-0.5 D) compared to those with no myopic parents. In addition, an increasing severity of parental myopia led to a greater risk of myopia. The odds ratios for mild myopia (SE -0.5 to -3 D), moderate myopia (SE -3 to -6 D) and high myopia (SE at least -6 D) were 6.4 (95% CI 1.5, 27.8), 10.2 (95% CI 2.6, 40.1) and 21.8 (95% CI 5.3, 89.4), respectively.[93]

It was also reported that children with myopic parents have longer AL than those without myopic parents. Zadnik *et al* investigated 716 Caucasian children aged 6 to 14 years and demonstrated that the pre-myopic eyes in children with myopic parents had a longer AL than those without myopic parents. This suggests that the size of the pre-myopic eyes might be already influenced by parental myopia. Moreover, it was found that children with 2 myopic parents developed myopia more often (11%) than children with 1 myopic parent (5%) or children without myopic parents (2%). (SE ≤-0.75 D).[94]

The SCORM cohort showed that having one and two myopic parents was associated with an increase in AL of 0.14 mm and 0.32 mm, respectively, compared with no myopic parents. The study also showed that having one myopic parent and two myopic parents increased the degree of myopia by 0.39 D and 0.74D, respectively.[58]

Most studies have shown a consistently higher prevalence of myopia among those with myopic parents as compared with those without. Parental myopia is considered as a marker for both genes and a shared family environmental exposure. Myopic parents are more likely to create myopigenic environments such as more intensive education or less time spent outdoors.[82, 93, 95]

The gene-environment interaction for myopia is still inconclusive. The SCORM study found an interaction between parental myopia and near-work. However, both the OLSM and the SMS found all children are protected by outdoor activities but the risk declined in parallel for children with and without myopic parents, indicating there might be no interaction between outdoor activities and parental myopia. Since myopic parents may create myopigenic environments for their children, interaction observed between parental myopia and near-work may not represent gene-environment interaction. (**Table 6**)

1.6.5 Myopia in Animal Models

In animal models, macaque monkeys with surgically fused eyelids, i.e. form deprivation, experienced excessive axial length (AL) elongation and eventually developed myopia.[96] Another early study on chicks found that monocular deprivation of form vision also produced myopia and eye enlargement.[97] These landmark studies ushered a new era in experimental myopia study and in the years since, models of form deprivation of myopia have been developed in a wide variety of animal species, including chicks, [98-99] tree shrews, [100-101] guinea pigs [102-103] and adult monkeys.[104] Other experimental methods using positive or negative lens as modulators of refractive error in

chicks showed that the eye grows more slowly (developed hyperopia) or more rapidly (developed myopia), respectively.[98] Recent experiments also indicated that the low levels of lighting in laboratories played a major part in the development of myopia in these animal models of myopia, as they appear to be directly countered by high light levels.[79] (Smith et al, 2011 ARVO e-abstract 3922) The experimental models of myopia suggest that both retinal image degradation (hyperopic and myopic defocus) and accommodation play important roles in AL elongation and myopia formation in animals.[105] Experimental models of myopia appear to suggest an important role of environmental factors in degradation of image quality, which could lead to myopia development.[96-97, 100] The latest animal study on chicks also found that genetic factors are the major determinant of susceptibility to myopia induced by retinal image degradation. Selective breeding for susceptibility to myopia reveals a gene-environment interaction on refractive development.[106] However, questions remain on the applicability of animal models of myopia to physiological human myopia.[107]

1.6.6 Genetic Risk Factors for Myopia

Genetic analysis has shown that a few genes were reported to be associated with myopia. Many genes associated with human refractive error can be clustered into common biological networks. The largest set of these genes is involved in connective tissue growth and extracellular matrix (ECM) reorganization.[108] This group includes genes that encode matrix metalloproteinases (*MMP1*, *MMP2*, *MMP3*, and *MMP9*), growth factors and growth factor receptors (*HGF*, *TGFB1*, *TGFB2*, and *MET*), collagens (*COL1A1* and *COL2A1*), and proteoglycans (*LUM*).[109] Mitochondrial-mediated apoptosis

as a novel mechanism for refractive error regulation was found recently. Other possible sources of refractive variation in humans involves a pathway that includes Ras protein-specific guanine nucleotide-releasing factor 1[110] and muscarinic acetylcholine receptor genes.[111] Another study implicated a role for genetic modifiers of rod-mediated visual signal transmission.[112] These biological mechanisms will require external validation from experimental studies.

1.7 Axial Length

1.7.1 Axial Length and Refractive Error

Myopia is a consequence of uncoordinated contributions of ocular components to overall eye structures. In other words, the cornea and lens fail to compensate for AL elongation. Thus, parameters closely linked to measurements of these parts such as corneal radius of curvature (CR), ACD, LT, vitreous chamber depth (VCD) and AL are widely evaluated, among which, AL received the most attention as a main parameter for refractive error.

The distribution of AL is reported to be positively skewed in the general population, and it is under a normal distribution in some selected cohorts.[113-114] Ophthalmologists use ultrasound velocity reading machinery and optical partial coherence interferometry to determine the AL of their patients to clarify the severity of myopia. A great number of reports have shown a negative relationship between AL and myopia.[109] AL, lens power and corneal power can explain up to 96% of the variation of refraction in populations.[115] Age-related AL differences were discovered in some population-based studies. Older people tend to have shorter AL than younger participants[17], which may be explained by cohort effects. For example, near work was

more intensive in the younger age group, which is a factor increasing AL probably due to a defocus-induced disturbance of emmetropisation. AL has some predicted values for the onset of myopia but only within the 2–4 years preceding onset. It reaches its fastest rate of change during the year before the onset of myopia and then axial elongation follows relatively slowly, with more stable rates of change after onset.[116]

1.7.2 Mean Axial Length in Population-Based Studies

The means of AL adults were reported to be 23.23 mm in Singapore Chinese[17], 23.55 mm in Singapore Malays[92], 22.6 mm in India Indians[117], 23.38 mm in Latinos[18], 23.13 mm in Mogolians[20] and 22.76 mm in Burmese[19]. The age-patterns of AL in different studies are diverse among different studies. Older adults were observed to have shorter ALs in Singaporean Chinese[17] and Malays[118], but not in Latinos[18], Burmese[19] and Mongolians[20]. These observations implicate that the higher rates of myopia and longer ALs in younger Singaporeans are probably due to differences in ocular dimension between birth cohorts or are part of the aging phenomenon.

The SMS surveyed AL of predominantly European Caucasian children. The mean AL ranged from 22.58 mm in the 6-year-old children and 22.67 mm in the 7-year-olds, [64] to 23.38 mm in the children aged 11.1 to 14.4 years.[119] The OLSM analyzed predominantly Caucasian population using ultrasound biometry and reported mean AL of 22.49 mm in the 6-year-olds, 22.65 mm in the 7-year-olds, 23.31 mm in the 11-year-olds and 23.09 mm in the 12-year-olds.[120] In the SCORM which used ultrasound biometry, the mean AL was 23.1mm in the 7-year-olds, 23.4 mm in the 8-year-olds and 23.8 mm in the 9-year-old Chinese children. [58] Thus, the mean AL in Sydney children was lower than

Singapore children, suggesting that differences are attributed to both genetic and environmental influences.

1.7.3 Axial Length and Ocular Biometric Components

In general, AL increases rapidly in the early stage of life, then slowly increases until adulthood, then decreases in old age. Average AL for full-term infants increases from 16.8 to 23.6 mm when they become adults.[121] This increase in AL would cause a shift to myopia, which was offset by corresponding changes in other parts of the ocular components. The lens will reduce its refractive power when AL increases.[122] A 1-mm elongation of AL without other compensation is equivalent to a myopia shift of –2 to –2.5 diopters. Each component of the visual system has close interaction with the other components during the maturation process. If the lens were removed from human eyes at an early age, a retardation of eye growth would occur.[123] The AL of eyes after cataract surgery is shorter than in age-matched controls.[124] A decrease in lens power is correlated with the elongation of AL but whether this is an active or a passive emmetropisation process is inconclusive. AL was also reported to be significantly negatively correlated with corneal power and documented to have a positive correlation with ACD and a negative correlation with lens thickness[125-126] .

1.8 Migration Studies on Myopia

Dramatic increases in the prevalence of myopia over the past few decades suggest that refractive errors in humans are sensitive to environmental pressures across a wide range of physical situations, communities and lifestyles. One way of investigating the

influence of lifestyle on the prevalence of refractive errors is to examine the changing patterns of refractive errors in migrant populations. Studies on the Inuit populations showed that the prevalence of myopia increased among generations as people moved into new settlements.[127-130] The Los Angeles Latino Eye Study reported that US-born Latino immigrants had higher prevalence of myopia than those born outside US (22.66% vs. 13.99%).[43] The refractive errors of Asian immigrants have received the most attention. In a study on Chinese Children living in Singapore and Sydney, the prevalence of myopia in 6- and 7-year-old children of Chinese ethnicity was significantly lower in Sydney (3.3%) than in Singapore (29.1%) ($P<0.001$).[91] The lower prevalence of myopia in Sydney was associated with increased hours of outdoor activities. The authors hypothesized that the differences in the prevalence of myopia may be due to the early educational pressures in Singapore but not in Sydney. Similarly, another study reported the relatively low prevalence of myopia of second-generation Australian schoolchildren coming from a predominantly Lebanese Middle Eastern Arabic background is similar to that found for other metropolitan Australian school children but higher than that reported in the Middle East. The authors suggested that lifestyle and educational practices may be a significant influence in the progression of myopic refractive errors.[131] In the late 1980s and early 90s, a large number of Chinese people from Asian countries such as Hong Kong, China, and Taiwan migrated to Western countries for political and educational reasons. A study on Chinese-Canadian Children found that Chinese children living in Canada developed myopia comparable in prevalence and magnitude to those living in urban East Asian countries. Recent migration of the children and their families to Canada did not appear to lower their myopia risk.[132]

1.9 Refractive Error and Major Age-Related Eye Disease

1.9.1 Refractive Error and Age-Related Macular Degeneration

The association between refractive error and AMD was initially reported in several case-control studies, [133-135] and then further assessed in population-based studies. For example, among white populations, the Rotterdam Study reported that increasing hyperopic refraction was associated with both prevalent and incident AMD.[136] The Blue Mountains Eye Study in Australia reported a weak association of hyperopic refraction with prevalent early AMD.[137] In Asians, both the Singapore Malay Eye Study and the Beijing Eye Study found a significant association between hyperopia and AMD in cross-sectional designs.[138-139] However, evidences from longitudinal population-based data have not supported this cross-sectional association. The U.S. Beaver Dam Eye Study reported that baseline refraction was not associated with either incident early or late AMD.[140-141] The Blue Mountains Eye Study also found no significant association between hyperopia and the 5-year incidence of early or late AMD.[142] It is possible, however, that longitudinal population-based studies which have assessed this association to date have lacked sufficient study power for incident AMD. Meanwhile, the impact of increasing age-related nuclear cataract with its secondary effect on refractive error (through induced index myopia) could also have confounded the ability to assess this longitudinal association using refractive measures rather than AL. Differences in study design and methods could possibly explain the inconsistent results observed among different ethnic groups as well. Examining the relationship between AL and AMD may provide further insights into possible mechanisms underlying the association of hyperopic refraction and AMD. However, only two studies to date have evaluated the relationship

between AMD and AL with inconsistent results. A Norwegian prevalence survey examined AL and AMD but found no relationship.[143] On the other hand, the Singapore Malay Eye Study found that each millimeter decrease in AL was associated with 29% increased odds of early AMD.[138](**Table 7**)

1.9.2 Refractive Error and Diabetic Retinopathy

The relationship between refractive errors and DR is not clear. In some clinical-based studies, myopic refraction was found to be associated with lower risk of DR.[144-145] However, clinic-based studies may be biased because myopic diabetics may undergo a routine eye examination. Only three population-based studies assessed this association with inconsistent results. The Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) demonstrated that myopia was not associated with incident DR in univariate analyses, but showed a protective effect against progression to proliferative diabetic retinopathy in persons with younger-onset diabetes in multivariate models.[146] The Visual Impairment Project did not find any significant association between DR and myopia in a cross-sectional design.[147] In Malays living in Singapore, myopic refraction is associated with a lower risk of DR, particularly vision-threatening retinopathy, without any evidence of a threshold.[148] The inconsistent results require further studies to exam the association between myopia and DR. (**Table 8**)

1.9.3 Refractive Error and Age-Related Cataract

Cataract is the leading cause of blindness worldwide. The relationship between refractive errors and age-related cataract is not clear. In the US, the Beaver Dam Eye

Study of adults 43–84 years supported the cross-sectional association between myopia and nuclear cataract (OR, 1.67; 95% CI, 1.23, 2.27), but provide no evidence of a relationship between myopia and 5-year incident cataract.[149] The Australian Blue Mountain Eye Study of adults aged over 49 years reported that PSC was associated with low myopia (OR 2.1; 95% 95%CI 1.4, 3.5), moderate myopia (OR 3.1; 95% CI 1.6, 5.7) and high myopia (OR 5.5; 95% CI 2.8, 10.9) while high myopia was associated with all three types of cataract.[150] The multivariate adjusted OR of incident nuclear cataract in myopic adults (SE < –0.5 D) in the Barbados Eye Study of adults aged 40–84 years (n = 2,609; follow up = 4 years) was 2.8 (95% CI 2.0, 4.0) (PSC and cortical cataract results were not reported).[151] In cross-sectional studies, refractive associations with PSC, cortical and nuclear cataract were examined in the Visual Impairment Project in Australia (n = 5,147) of adults 40 years and older. Only cortical cataract was found to be associated with myopia (SE < -1.0D).[152] A population-based study on Singaporean Chinese supported the associations between nuclear cataract or PSC and myopia. This study also indicated the PSC is also associated with deeper anterior chamber, thinner lens, and longer vitreous chamber, with vitreous chamber depth explaining most of the association between PSC and myopia.[153](**Table 9**)

1.9.4 Refractive Error and Primary Open Angle Glaucoma

Glaucoma is a group of diseases, which have a final common pathway of progressive nerve fiber layer thinning and concomitant ganglion cell loss. The association of glaucoma and myopia has been investigated in several population-based studies. In the Beaver Dam Eye Study[5], OR of POAG for mild myopia was 2.9 (95% CI 1.3, 6.9); for moderate myopia was 2.1(95% CI 1.0, 4.6); for severe myopia was 3.9 (95% CI 1.6, 9.5).

In the Blue Mountains Eye Study, OR of prevalent OAG was 3.3 (95% CI 1.7, 6.4) for moderate to high myopia (SE at least –3.0 D) and 2.3 (95% CI 1.3, 4.1) for patients with low myopia (SE < -3.0 D and >1.0 D) which implied that glaucoma risks increased with more severe myopia. In Tajimi Study in Japan, OR of POAG for low myopia (SE>-1.0D and SE<-3.0D) was 1.85 (95% CI 1.03, 3.31) and for 2.60 (95% CI, 1.56, 4.35) for moderate to high myopia (SE> -3D). In developing countries such as China, India and Burma, myopia is also described as a risk factor of glaucoma. Xu *et al* classified glaucoma as 'Optic Disc Glaucoma' and 'Optic Disc Glaucoma' and found presence of glaucoma was significantly associated with the myopic refractive error (P<0.001). [9] In India, Ramakrishnan *et al* also examined the association of glaucoma with mild, moderate and severe myopia and the result was OR of POAG for mild myopia was 2.9 (95% CI 1.3,6.9), for moderate myopia was 2.1(95% CI 1.0,4.6), for severe myopia was 3.9 (95% CI 1.6,9.5)[10]. However, the Chennai Glaucoma Study[11] found no associations between POAG and myopia (OR= 0.68 95%CI 0.40, 1.17). The Meiktila Eye Study[12] in Burma reported the positive association of AL and glaucoma. The OR of POAG for AL was 1.36 (95%CI 1.01, 1.77) in univariate analysis but in multivariate analysis, the association disappeared (P>0.05). One of the largest screening surveys of myopia and glaucoma was performed in the Malmo survey in Sweden, covering 32,918 individuals aged 57 to 79 years examined for glaucoma with refraction measured by autorefractors and glaucoma defined as reproducible perimetric disease.[154] The prevalence of newly detected glaucoma increased with increasing myopia (P<0.0001) across all age groups. The Los Angles Latino Eye Study group aimed to examine the association between myopia and glaucoma by measuring refractive error, AL, and corneal power.[155] A total of

5,927 Latinos aged 40 years and older were included out of 6,357 examined. The unadjusted prevalence of glaucoma among myopes was 8.1%, compared with 3.7% among nonmyopes (OR, 2.34; CI, 1.7, 3.1). After adjusting for age, sex, IOP, CCT, diabetes, and family history, myopes still had an OR of 1.86 (CI, 1.32, 2.59) compared with nonmyopes for glaucoma. Adjusted OR for the stratified myopic groups was significant only for the moderate to high myopia (OR, 2.0; CI, 1.1, 3.7) as low myopia was (OR, 1.6; CI 0.9, 2.6). The most important result was that each millimeter longer in AL was associated with a 26% higher prevalence of glaucoma, as a continuous variable from 21mm to 27mm (OR, 1.26; CI, 1.1, 1.4), independent of myopic refractive error. As AL only changes during youth, and known covariates in this population have been accounted for, the study strongly supports the collective prior evidence of the association between moderate-to-high myopia and glaucoma. The Singapore Malay Eye Survey examined 3,280 of 4,168 eligible persons aged 40 to 80 years to determine the relationship between AL and glaucoma.[156] Longer AL was associated with glaucoma (ORs: 2.49, 3.61, and 2.88, respectively; comparing quartiles: 2, 3, and 4 of AL with quartile 1; P=0.03 for trend), even after controlling for CCT. Persons with moderate or high myopia were also more likely to have glaucoma after adjusting for covariates (OR, 2.80; CI, 1.07, 7.37). Finally, the association of myopia with POAG has been confirmed by a meta-analysis of 13 population-based studies.[157] (**Table 10 & Fig 3-5**)

1.10 Summary of the Literature Review

The prevalence of myopia in adults over 40 years has been reported in several population-based studies with different results. It is still unclear whether myopia

prevalence is higher in East Asian Countries than in Western Countries. Inter-ethnic variation seems to exist in the prevalence of myopia. The refractive status is influenced by ocular biometric parameters such as AL and CR. Understanding the inter-relationship between refraction and ocular biometry may help to explain the trends and patterns of refractive errors observed in different populations and ethnicities. However, while the epidemiology of refractive errors has been reported in different countries and ethnicities worldwide, only a small fraction of population-based studies have described ocular biometry distribution.

It is well known that both genetic and environmental factors contribute to the etiology of myopia. Because the prevalence of myopia has increased significantly in many urban Asian cities, it has been suggested that this reflects major shifts in environmental factors such as increasing education pressure and urbanization. Migrant studies may provide further clues to the role of environmental effects on myopia. In migrant studies, people moving from one country to another are compared with people born in the new country of the same genetic heritage and thus help to tease the effects of environmental exposures from genetics. Such information is also important from a public health perspective, considering that there are more than 200 million people travelling internationally and another 750 million people migrating within their own country around the world.[158] There have been few migration studies on myopia in urbanized Asian countries.

AMD, DR, age-related cataract and POAG are four of the most common ocular diseases, which lead to visual impairment and blindness. Since myopia and other refractive errors have been linked with potential ocular complications and morbidity[159-160],

a clearer understanding of the associations between refractive errors and these major ocular diseases is important for clinicians, epidemiologists and patients. In addition, although the associations of refractive error and other ocular diseases have been assessed, few population-based studies have assessed whether these observed associations were explained by AL, reflective of axial myopia. Considering the inconsistent associations between refractive error and AMD among different studies, a systematic approach to quantitatively combine the results of all available studies assessing the association would be informative.

CHAPTER 2

AIMS AND OBJECTIVES OF THESIS

The overall aim of this thesis is to describe the prevalence and patterns of refractive errors and to evaluate the associations of refractive errors with other major ocular disorders in Indian adults living in Singapore.

Aim 1: To determine the prevalence and risk factors for refractive errors in middle-aged to elderly Singaporeans of Indian ethnicity.

Aim 2: To describe the distribution and determinants of ocular biometric parameters in adult Singapore Indians.

Aim 3: To assess the influence of factors related to migration and acculturation on myopia and AL in migrant Indians in Singapore

Aim 4: To investigate the associations of refractive errors and AL with major ocular diseases including AMD, DR, age-related cataract and POAG.

Aim 5: To determine the association between refractive errors and AMD by systematic review and meta-analysis of observational studies.

CHAPTER 3

METHODS

3.1 Study Design

The Singapore Indian Eye Study was a population-based, cross-sectional epidemiological study of Indian adults aged 40–84 years living in Singapore. The study followed the principles of the Declaration of Helsinki, and ethics approval was obtained from the Singapore Eye Research Institute (SERI) Institutional Review Board (IRB). All participants were given a choice to provide their written, informed consent in either Tamil or English. Consent was explained by bilingual study interviewers. Both versions of the patient information sheet and informed consent form were approved by the SERI Institutional Review Board.

3.2 Sampling Frame

The criterion for identifying Indian ethnicity was set by the Singapore census. This definition referred to all persons of Indian origin, as indicated on the National Registration Identity Card, which was provided to all Singapore citizens and permanent residents. According to the data provided by the Singapore census, of the 4.02 million resident populations in Singapore, 76.8% are ethnic Chinese, 7.9% are ethnic Indians and 13.6% are ethnic Malays.

The sampling area was located on the South-Western part of Singapore including the postal sector code areas 8 (Duxton/Tanjong Pagar), 9 (Telok Blangah/Bukit Purmei/Sentosa), 10 (Telok Blangah/Depot Road), 11 (Alexandra/Kent Ridge/Pasir

Panjang), 12 (Clementi/West Coast), 59 (Eng Kong/Toh Yi), 60 (Jurong East/Teban Garden), 61 (Chin Bee/Corporation/Taman Jurong), 62 (Gul/Pioneer sector/Jurong Island), 64 (Boon Lay/Jurong West/Jalan Bahar) and 65 (Bukit Bartok) provided by the Ministry of Home Affairs. The list includes the name, NRIC number, gender, age, date of birth, ethnic group, address and postal code of each person. Choosing this area as the study area has some advantages. Firstly, the residents in this area were fairly representative of the whole Singapore population in terms of age distribution, housing type, and socioeconomic status according to the 2000 Singapore Census. So the study result of this area could be representative of the whole country. Secondly, the amount of Indian residents is sufficient enough to satisfy the sample size. Thirdly, the area is along the track of the Singapore subway train which makes it more convenient both for the participant to go to the clinic for eye examination. This might have been conducive to improving the participation rate. Finally, the area is population-intensity which covers a 15.8% of the country's total land area. (**Figure 6**)

The Ministry of Home Affairs provided an initial list of 12,000 ethnic Indian names together with gender, addresses, date of birth and the National Registration Identity Card numbers, derived from a simple random sampling of all ethnic Indian aged 40–80+ years of age residing in South-Western Singapore. From this list, we derived a final sampling frame of 6,350 ethnic Indian residents using an age-stratified random sampling strategy. Assuming an eligibility rate of 70%, and a response rate of 75%, the estimated target sample size was 3,300. (**Figure 7**)

3.3 Sample Size Calculation

Disproportionate stratified sampling by 10-year age groups was conducted to select 6,350 potential Indian participants, so as to recruit 3,300 Indians, assuming an ineligibility rate of 30% and a non-response rate of 25% (6,350× 0.70 × 0.75 = 3,333). The expected prevalence of myopia is 35%, cataract 30%, AMD 10%, and glaucoma 3%. A sample size of 3,300 Indians was optimal to provide sufficient precision to detect prevalence of all these conditions. For example, for glaucoma, a sample size of 3,258 would provide a prevalence of 3% with a 95% confidence interval of 2.5%-3.5%

3.4 Recruitment Strategies

The sample list includes the name, NRIC, date of birth, address and postal code. Several measures were taken to recruit potential subjects and these included: a cover letter inviting the residents and for eye screening was mailed to their home address. The hand phone or pager numbers of the Project Manager and Assistant Project Manager were listed to facilitate communication between the study staff and the participants. A few days later, a telephone call was made to the resident and the nature of the screening exercise was explained to the resident. The resident was invited for a free eye check-up at SERI at an appointed date and time if eligibility criteria are fulfilled. An appointment letter was sent to the house. If the resident is not contactable by telephone, a house visit by study staff will be made and at least 6 visits, including a weekday night and weekend was made before the resident is deemed non-contactable.

3.5 Clinical Examinations

Once the subject agreed to participate in the study, the recruitment officer set up an

appointment date to have an eye examination at the clinic. The clinical examinations were conducted at the Singapore Eye Research Institute. The subject was requested to bring along the appointment card and their IC together with medication and spectacles they are currently on. At the registration counter, the interviewer explained the nature of the study and obtained the informed consent. The study ID was issued and barcode was printed out and tagged on to the subject's case report form. For the purpose of identification, the subject must wear the nametag throughout examination. (**Figure 8**)

Anthropometry

Height was measured in centimeters using a wall-mounted measuring tape. Weight was measured in kilograms using a digital scale (SECA, model 782 2321009; Vogel & Halke, Germany).

Blood Pressure and Pulse Rate

Blood pressure was taken with the participant seated and after 5 minutes of rest. Systolic and diastolic blood pressure and pulse rate were measured with a digital automatic blood pressure monitor (Dinamap model Pro Series DP110X-RW, 100V2; GE Medical Systems Information Technologies, Inc., USA). Blood pressure was measured on two occasions 5 minutes apart. If the blood pressures differed by more than 10 mmHg systolic and 5 mmHg diastolic, a third measurement was made. The blood pressure of the individual was then taken as the mean between the two closest readings.

Visual Acuity

Distance presenting visual acuity was measured using a logarithm of the minimum angle of resolution (Log MAR) number chart (Lighthouse International, New York, USA) at a distance of 4 meters, with the participant wearing their current optical correction (spectacles or contact lenses), if any. A number chart was used for participants who were unable to identify the Latin alphabets. If no number could be read at 4 meters, the participant was moved to 3, 2 or 1 meters consecutively and finally visual acuity was assessed as counting fingers, hand movements, perception of light, or no perception of light. Subjective refraction and distance best-corrected visual acuity in Log MAR scores were measured by trained and certified study optometrists. Near vision acuity test was done using the Log MAR near vision chart.

Refraction

The refraction (sphere, cylinder and axis) was measured using an autorefractor machine (Canon RK 5 Auto Ref-Keratometer, Canon Inc. Ltd., Tochigiken, Japan) operated by optometrists or trained technicians. The first five valid readings were used and averaged using vector methods to give a single estimate of refractive error. All five readings should be at most 0.50 D apart in both the spherical and cylinder components.

Ocular Biometry

Ocular biometry was performed using an optical biometry machine (Zeiss IOL Master, version: 3.01.0294). This device is a non-contact optical biometry machine that is non-invasive as opposed to the ultrasound A-scan biometry machine. The axial length, anterior chamber depth and corneal curvature radii in the horizontal and vertical meridian

will be measured in the right and left eye.

The acceptance range of the auto-keratometry measurement should be ±0.03mm for the 3 readings. As for the anterior chamber depth, the range would be ±0.1mm. If unable to perform IOL master readings then proceed with A – scan machine e.g. dense cataracts.

Retinal Imaging

Fundus photography was performed using a digital non-mydriatic retinal camera (Canon CRDGi with a 20Diopter SLR backing, Canon, Japan). Optic disc imaging using the Heidelberg Retina Tomograph II (HRT II, Heidelberg Engineering, Germany) was performed for all participants.

Slit Lamp Examination

Anterior and posterior segment examinations were performed at the slit-lamp (Haag-Streit model BQ-900; Haag-Streit, Switzerland) using a 78 Diopter lens, which included measurements of vertical dimensions of the optic disc and cup with an eyepiece graticule, etched in 0.1 mm units.

Central Corneal Thickness and Intraocular Pressure

Central corneal thickness (CCT) was measured in each eye with an ultrasound pachymeter (Advent; Mentor O & O Inc, Norwell, Massachusetts). Goldmann applanation tonometry (AT900, Haag-Streit AG International, Switzerland) was used to measure intraocular pressure (IOP) of each eye.

Biochemistry Tests

Non-fasting venous blood samples were drawn and sent for biochemistry tests, including analysis of total cholesterol, high density lipoprotein cholesterol (HDL), low density lipoprotein cholesterol (LDL), triglycerides, glucose, and hemoglobin A1c (HbA1c). HbA1c was measured by high-performance liquid chromatography (HPLC).

3.6 Questionnaire and Interview

The questionnaire was administered by a trained interviewer. After dilation, or as and when the study participant was waiting for the any one of the photographic station, the clinical interview was conducted. Before conducting the questionnaire, the purpose of the survey was explained and assured them that the information provided would be strictly confidential. The questionnaires were administered in three languages, including English, Tamil, and Malay. English questionnaires were culturally adapted and translated into the other two languages using a standard "forward-backward" translation procedure. English interviewers made the first contact with the participants, and assigned those who experienced language difficulties to the interviewers who were fluent in Tamil or Malay.

Demography consisted of race (as in IC), number of individuals living in the house, country of birth, marital status, length of stay in Singapore, religion, current job and literacy level.

Socioeconomic status was evaluated by 'educational level', 'type of housing', and 'monthly income'. Educational level was assessed in five categories: no formal education/primary education/ high school/polytechnic/university; four types of housing were included for evaluating the living condition: 1-2 room HDB flat/3-4 room HDB

flat/5 room or executive HDB flat/others; total income per month was sorted into 5 groups: Less than S$1000/ S$1000 - <S$2000/ S$2000 - <S$3000/More than S$3000/ Retired.

Near work activities: To assess the near work of subjects, this questionnaire included the questions regarding time of reading and writing per day (Currently, how many hours per day do you read and write?), time of computer work per day (Currently, how many hours per day do you spend using the computer?), time of watching TV or playing television video games per day (Currently, how many hours per day do you spend watching television or playing games on the television screen?)

Smoking status: Smoking status was asked: Have you ever smoked cigarettes, cigars or a pipe regularly? (Regularly being at least weekly); Have you given up smoking? Smoking Status were defined by 3 categories: Never smoked/ Current smokers/ Past smokers

3.7 Definition of Immigrant Status

Participants were categorized as two cohorts based on the country of birth: Singaporean Indian residents born outside of Singapore were defined as 'first generation' immigrants, while Singaporean Indian residents born in Singapore were defined as 'second (or higher) generation' immigrants.

3.8 Disease Definitions

3.8.1 Refractive Error

SE was defined as sphere plus half cylinder. Myopia was defined as a SE of -0.5

diopters (D) or less, hyperopia as a SE of 0.5D or more, and emmetropia as a SE of between -0.5 and 0.5D. Moderate myopia was defined as a SE of -3.0 D or less. High Myopia was defined as SE less than -5.0 D. Other definitions of myopia such as SE less than -0.75 D or SE less than -1.00 D were also used for analyses to compare the prevalence with other studies. Other definitions of hyperopia (SE > 2D) were also analyzed. Astigmatism was defined as cylinder less than -0.50 D, -1.00 D, or -1.50 D and anisometropia as the difference in SE greater than 1.00 D. "With the rule" astigmatism was defined when the axis was 0° to 15°, "against the rule" when 75° to 105°, and "oblique" when axes were located from 20° to 70° and 110° to 160°.

3.8.2 Age-Related Macular Degeneration

A digital retinal camera (Canon CR-DGi with a 10-D SLR back; Canon, Tokyo, Japan) was used to obtain color photographs centered at the optic disc and macula of each eye. The photographs were graded for AMD signs based on the Wisconsin Age-Related Maculopathy Grading System.[161] Early AMD was defined as soft indistinct drusen, or soft distinct drusen plus retinal pigment epithelium (RPE) abnormalities. Neovascular AMD lesions were defined as the presence of RPE detachment; neurosensory detachment; subretinal or sub-RPE hemorrhages; or intraretinal, subretinal, or sub-RPE scar tissue. Subretinal hemorrhages or hard exudates within the macular area also were considered signs of neovascular AMD if other retinal vascular diseases as the alternative causes were excluded. Geographic atrophy was defined by presence of visible choroidal vessels and a discrete atrophic area with a sharp border with an area of at least 175 μm in diameter. Late AMD was defined as the presence of either neovascular AMD or geographic

atrophy. Any AMD was defined as the presence of early AMD or late AMD.

3.8.3 Diabetic Retinopathy

Retinopathy lesions were graded according to the Airlie House classification system.[162] Retinopathy severity was categorized into minimal non-proliferative diabetic retinopathy (NPDR; level 15 through 20), mild NPDR (level 35), moderate NPDR (level 43 through 47), severe NPDR (level 53), and proliferative diabetic retinopathy (PDR, level more than 60). Macular edema was defined by hard exudates in the presence of microaneurysms and blot hemorrhage with one disc diameter from the foveal center or presence of focal photocoagulation scars in the macular areas. Those with macular edema were further divided into cases with clinically significant macular edema (CSME) and without CSME. CSME was defined by macular edema within 550 μm of the foveal center or if focal photocoagulation scars were present in the macular area.
Vision-threatening diabetic retinopathy (VTDR) was defined as the presence of severe NPDR, PDR, or CSME.

3.8.4 Age-Related Cataract

Age-related cataract was diagnosed clinically using the Lens Opacity Classification System (LOCS) III system.[163] LOCS III includes an assessment of nuclear opalescence (NO), cortical cataract (C), and posterior subcapsular cataract (P). A LOCS III score of 4.0 or more for NO was defined as significant nuclear cataract, a score of 2.0 or more for C as significant cortical cataract, and a score of 2.0 or more for P as significant posterior subcapsular cataract.

3.8.5 Glaucoma

Glaucoma cases were defined according to the International Society for Geographical and Epidemiological Ophthalmology criteria based on 3 categories.[164] Category 1 cases were defined based on structural and functional evidence. It required cup-disc ratio (CDR) or CDR asymmetry ≥ 97.5th percentile for the normal population or a neuroretinal rim width reduced to ≤ 0.1 CDR (between 11- and 1-o'clock or 5- and 7-o'clock) with a definite glaucomatous visual field defect. Category 2 was based on advanced structural damage with unproved field loss. This included those subjects in whom visual field could not be determined or were unreliable, with CDR or CDR asymmetry ≥ 99.5th percentile for the normal population. Category 3 consisted of persons with an IOP ≥ 99.5th percentile for the normal population, whose optic discs could not be examined because of media opacities. POAG was defined as an eye with evidence of glaucomatous optic neuropathy with an angle appearance in which the pigmented/posterior trabecular meshwork was seen for 270° or more of the angle circumference during static gonioscopy, in the absence of secondary pathologic processes.

3.9 Data Management and Quality Control

Data were collected in a combination of paper and digital formats. Clinical examination records, questionnaire responses, printouts, and biochemistry results were compiled into participant-specific case report forms that were labeled with the participant's unique study number. Imaging data, including digital fundus and lens

photographs, were retrieved directly from the imaging equipments and stored in their respective computers, identifiable only by the study number, date created, file path, format, and size. Data were manually inspected prior to discharging the participant to ensure completeness. All variables of interest were entered into a password-protected Microsoft Office Access database by a data entry clerk and manually cross-checked by a second clerk to detect and rectify data entry errors. Frequency and range checks were conducted monthly by the study statisticians to identify outliers. For all digital information, original data were copied into external hard disks daily and written onto DVDs for storage in the medical records office together the respective case report forms.

3.10 Statistical Analyses

Statistical analyses were performed in SPSS (Statistical Package for Social Science, SPSS V16.0, SPSS Inc., Chicago, IL). Two-tailed P-value less than 0.05 was considered statistically significant.

Participants with prior cataract surgery were excluded from these analyses. As the Spearman correlation coefficient for SE in the left and right eye was high ($r = 0.85$, $P<0.001$), only right eye data were used for analyses. Anisometropia was analyzed only in participants with refractive error data for both eyes and with no history of cataract surgery in either eye. The prevalence of different refractive errors was estimated for the overall sample, and then stratified by age and gender. The age-adjusted prevalence was calculated by direct standardization of the study samples to the Singapore ethnic Indian population, using the 2000 Singapore census data (http://www.singstat.gov.sg). For risk factors, variables of interest were first analyzed in univariate models. The potential

confounders considered were age, gender, education, occupation, marital status, time for reading and writing per day, time for computer use per day, alcohol use, smoking, diabetes mellitus, hypertension, height, BMI, and presence of cataract. If the *P* value was less than 0.05 in univariate models, these possible predictors were included in multiple logistic regression models and manual backward stepwise elimination procedures were performed to choose the most parsimonious model. To control the effects of age, gender and other potential confounders, multiple logistic regression models with sampling weights were performed. Sampling weights are the actual proportions of Indians in each age group among the whole Singapore Indian population obtained from Singapore Census 2000. The interaction terms age*cataract, age*gender and age*education were also evaluated in multivariate models. OR and 95% CI were shown.

Mean biometry data were compared across each age group stratified by gender, and linear test for trend was used to investigate significance for each age group. Possible predictors for each biometric parameter were assessed in univariate analyses. Variables with a $p < 0.05$ in univariate analyses and of scientific importance were included in multiple linear regression models, and manual backward stepwise elimination procedures were performed based on a criterion of $p < 0.05$ to achieve the final, most parsimonious model. Linear regression models were then constructed to evaluate independent effects of lens opacity and ocular biometric components (independent variables) on refraction (dependent variable) in all age groups. Standardized regression coefficients in these models were used to determine the relative importance of nuclear opacity and each biometric component on refraction.

The age and gender standardized prevalence was calculated by direct

standardization of the study samples to the Singapore ethnic Indian population, using the 2000 Singapore census data. We also calculated the mean refraction, AL, ACD and CR in both first and second generation immigrants, using analysis of covariance to adjust first for age and gender and then further for educational level, height and lens nuclear opacity. Multivariate regression models were fitted to estimate the associations of acculturation factors (age at migration and preferred language for interview) with the prevalence of myopia, SE and AL adjusting for age, gender, educational level, lens nuclear opacity score and height. To evaluate the extent that educational level and other risk factors may explain the excess prevalence of myopia and high myopia in second generation immigrants compared with first generation immigrants, we estimated the percentage reduction in odds associated with adjustment for these factors according to the following formula: (Ra-Rb)/(Ra-1)×100, where Ra is the odds ratio of myopia in second immigrants compared with first generation immigrants, adjusted for age and gender only (reference model), and Rb is the odds ratio in models after additional adjustment.

For the analyses related to DR, the diabetes cohort as a whole was analyzed. AMD or early AMD lesions including drusen or retinal pigmentary abnormality, DR or VTDR, POAG, and age-related cataract were analyzed as binary outcome variables. Generalized estimating equation (GEE) models with the right and left eye data combined were fitted to estimate the associations (ORs and 95% CIs) between refractive errors or AL and the four ocular outcomes. For multivariate analysis, only age, gender and factors that were significantly different in univariate comparison ($P < 0.10$) or of scientific importance were retained in the model. Finally, AL was entered into analysis of covariance models to determine whether it explains the difference in mean refraction

between eyes with and without a specific eye disease. The relative proportion of the association explained by AL (%) was defined as [(Difference in mean refraction in the reference model – Difference in mean refraction in models with AL added)/Difference in mean refraction in the reference model]. The reference model adjusted for age, gender, and factors that were significantly different in univariate comparison ($P < 0.10$) or of scientific importance for a specific ocular disease.

We followed the Meta-analysis of Observational Studies in Epidemiology guidelines.[165] We searched the electronic database of PubMed for relevant papers on the association between refractive error and AMD published up to March 27, 2012, with the following search terms: ((("myopia"[MeSH Terms] OR "myopia"[All Fields]) OR ("hyperopia"[MeSH Terms] OR "hyperopia"[All Fields]) OR ("refractive errors"[MeSH Terms] OR ("refractive"[All Fields] AND "errors"[All Fields]) OR "refractive errors"[All Fields] OR ("refractive"[All Fields] AND "error"[All Fields]) OR "refractive error"[All Fields]) AND ("age-related maculopathy"[All Fields] OR "age related maculopathy"[All Fields] OR "age-related macular degeneration"[All Fields] OR "age related macular degeneration"[All Fields] OR "macular degeneration"[All Fields]) AND (("risk factors"[MeSH Terms] OR ("risk"[All Fields] AND "factors"[All Fields]) OR "risk factors"[All Fields] OR ("risk"[All Fields] AND "factor"[All Fields]) OR "risk factor"[All Fields]) OR ("risk factors"[MeSH Terms] OR ("risk"[All Fields] AND "factors"[All Fields]) OR "risk factors"[All Fields]) OR ("association"[MeSH Terms] OR "association"[All Fields]) OR associated[All Fields])). In addition, the reference lists of all identified studies were examined.

Studies were included if they reported refractive error as an independent covariate

and AMD or early AMD as the outcome measure. AMD was assessed based on standardized protocols such as the Wisconsin grading system[161] or the international classification proposed by the International ARM Epidemiological Study Group[166]. The association estimate as odds ratio (OR) or hazards ratios (HR) with 95% confidence interval (CI) was reported in the paper, or allowed for the calculation of it based on the data presented in the paper. Studies were excluded if they were clinical-based studies or published in a non-English language.

For each study, the following information were extracted: (i) first author, (ii) publication year, (iii) study name, (iv) sample size, (v) age range of the study participants, (vi) definitions of refractive errors and AMD, (vii) effect estimate including OR(HR) and 95%CI, (viii) confounding factors adjusted for.

The study quality was assessed with the tool described by Sanderson et al.[167] The variables examined included the methods for selecting study participants, methods for measuring exposure (refractive error) and outcome variable (AMD), design-specific sources of bias (excluding confounding), methods for controlling confounding, statistical methods (excluding control of confounding), and conflict of interest.

Meta-analysis was performed using Stata version 12.0 (StataCorp, College Station, TX). The fully-adjusted, study-specific ORs or HRs were combined to estimate the pooled OR or HRs with 95% CI using the random effects model, which accounts for both within-study and inter-study variability. Any AMD including both early AMD and late AMD was analyzed as an outcome variable. For the studies only reported the result of early AMD, we assumed early AMD is equal to any AMD since the prevalence and incidence of late AMD is extremely low in general populations. Myopia, hyperopia and

per diopter increase in SE were analyzed as an independent covariate. We also included the unpublished data from the Singapore Indian Eye Study, which was conducted by our team using the same study protocols as the Singapore Malay Eye Study[138], in this meta-analysis. For the Singapore Prospect Study which reported results for male and female cohorts separately, we combined the two ORs and subsequently included the pooled OR in the meta-analysis.[168] For studies that only reported stratified ORs or HRs, we pooled the ORs or HRs to obtain an overall estimate for any myopia or hyperopia. Most studies defined myopia and hyperopia using cutoff values, with a group of emmetropic eyes as reference category. Myopia was treated as the reference category in the Singapore Malay Eye Study. We therefore converted the OR by using emmetropia as the reference category in conformity with other studies.[138] No refractive error cutoff values were reported in the Central India Eye and Medical Study[169] , we therefore contacted the principle investigator to obtain the full dataset and calculated the OR of myopia and hyperopia with AMD for the Central India Eye and Medical Study. Statistical heterogeneity among studies was evaluated using I^2 Statistic.[170] Values of 0 to 24%, 25% to 49%, 50% to 74%, and more than 75% denote no, low, moderate, and high heterogeneity, respectively.[171] Heterogeneity due to study design was avoided by separating the meta-analysis into cross-sectional studies and cohort studies. Publication bias was evaluated with the use of Egger regression asymmetry test[172] and the Begg's test[173]. Forest plots of association estimates between myopia and prevalent AMD, myopia and incident AMD, hyperopia and prevalent AMD and hyperopia and incident AMD were presented, respectively.

CHAPTER 4

RESULTS

4.1 Characteristics and Demographics of the Study Population

A total of 3,400 Singaporean Indians (response rate = 75.6%) aged 40 to 84 years participated in the study. (**Figure 9**)

Table 11 and **Figure 10** show the age and gender distribution of the study subjects. 1,706 (50.2%) were men and 1,694 (49.8%) were women. The mean age of the study participants was 57.8 years (SD = 10.1). There was no significant difference in mean age between men (58.1 years, SD = 10.2) and women (57.5 years, SD = 57.5, p = 0.09). There were 869 (6.3%), 1,098 (17.9%), 894 (17.1%) and 512 (19.2%) participants in the age groups 40-49 years, 50-59 years, 60-69 years and 70-84 years, respectively. There was no significant difference in the proportion of gender in each age group (p = 0.35)

Table 12 and **Figure 11-13** show the distribution of educational level, individual income and housing type of the study subjects. There were 317 (9.3%), 1,581 (46.4%), 819 (24.1%), 358 (10.5%) and 319 (9.4%) study participants whose highest attained education level were ‘No formal education’, ‘Primary education’, ‘High school’, ’Polytechnic’ and ’University’, respectively. There were 1,092 (33.0%), 539 (16.3%), 1,209 (36.5%) and 417 (14.2%) study participants whose monthly income were ‘less than 1000’, ‘1000 to 2000’, ‘more than 2000’ and ’Retired’, respectively. There were 160 (4.7%), 2,021 (16.3%) and 1,212 (14.2%) study participants who lived in ‘1-2 room HDB flat’, ‘3-4 room HDB flat’, ‘5 room, executive HDB flat or private housing’, respectively.

Figure 14 shows the distribution of smoking categories. Most of the study subjects never smoked; **Figure 15** shows the distribution of height and weight. **Figure 16** shows the distribution of blood pressure. **Figure 17** shows the distribution of IOP. **Figure 18** shows the distribution of cup disc ratio. **Figure 19** shows the distribution of CCT. **Figure 20** shows the distribution of hypertension. **Figure 21** shows the distribution of diabetes. The prevalence of hypertension and diabetes increased with age.

4.2 Prevalence and Risk Factors for Refractive Errors

Adults with previous cataract surgery were excluded from analysis. **Table 13** compares age, gender, educational level, height and weight between those with and without previous cataract surgery. In general, those with cataract surgery tended to be older ($P<0.001$), less educated ($P<0.001$), shorter ($P<0.001$) and lighter ($P<0.001$) compared with those without cataract surgery. There was no gender difference between the two groups. ($P =0.48$)

Table 14 shows the comparison of subjects included in and excluded from refraction data analyses. In general, subjects included in the analyses tended to be younger ($P<0.001$), more educated ($P<0.001$), taller ($P<0.001$) and heavier ($P<0.001$) compared with those excluded from analysis. There was no gender difference between the two groups. ($P =0.39$)

Of the 2,805 subjects with right eye refraction data and no cataract surgery history, 1,417 (50.5%) were male and 1,388 (49.5%) female. The age ranged from 43 to 84 years with a mean of 55.5 ± 8.8 years. The mean ages of men and women were 55.9 ± 9.1 and 55.0 ± 8.3 years, respectively ($P = 0.006$).

Figure 22 shows the distribution of refraction in SE in different age groups among 2,805 subjects in the analyses. The distribution of SE was skewed towards more myopic values in all age groups. The skewness values for the SE distribution were -2.74, -2.46,-1.84 and -0.80, while the kurtosis values were 11.87, 9.82, 6.68 and 0.61 for age groups 40-49, 50-59, 60-69 and 70 years or older, respectively. Both the skewness and kurtosis of the SE distribution decreased with age. The mean and median SE for this sample, were -0.05 D and 0.25 D, respectively. **Figure 23** shows the box plot of SEs by age groups.

Table 15 shows crude and age-standardized prevalence of myopia and high myopia by different definitions. The crude prevalence of myopia for three different definitions was: 26.1% (for SE < -0.5 D); 21.8% (for SE < -0.75 D) and 19.0% (for SE< -1.0 D). The age-standardized prevalence of myopia for three different definitions was: 28.0% (for SE < -0.5 D); 23.5% (for SE < -0.75 D) and 20.4% (for SE< -1.0 D). The prevalence of myopia was slightly higher in women (28.5%) than men (26.9%), but this difference was not statistically significant (P = 0.48). Further, the age-standardized prevalence of high myopia (SE < -5.0 D) was 4.1% (95% CI 3.3, 5.0) with significantly higher rates in females (4.7%) than males (3.1%) (P = 0.02). The prevalence of myopia (SE < -0.5 D) was 33.3%, 23.8%, 20.3% and 26.9% for age groups 40-49, 50-59, 60-69, and 70 years or older, respectively. The prevalence of myopia (SE < -0.75 D) was 28.0%, 19.3%, 17.3% and 23.2% for age groups 40-49, 50-59, 60-69, and 70 years or older, respectively. The prevalence of myopia (SE < -1.0 D) was 24.5%, 17.5%, 14.2% and 19.4% for age groups 40-49, 50-59, 60-69, and 70 years or older, respectively. The prevalence of high myopia (SE < -5.0 D) was 5.3%, 4.1%, 2.3% and 1.9% for age groups 40-49, 50-59,

60-69, and 70 years or older, respectively. There is a trend of decreasing in prevalence with age for both myopia (P<0.001) and high myopia (P = 0.009).

Figure 24 shows the prevalence of myopia by educational level. Generally, prevalence of myopia increased with increasing educational level.

Table 16 shows the mean spherical equivalent by age group and gender. The pattern is similar to the prevalence of myopia with 40-49 having the most myopic refraction.

A U-shaped relationship was observed between myopia prevalence and increasing age. The prevalence of myopia followed a bimodal pattern, initially decreasing with age and then increasing in older adults. The association was modified by nuclear cataract defined as LOCS III score for nuclear opalescence or nuclear color of 4 or more. Myopia prevalence increased with age among subjects with nuclear cataract (n = 323), while decreasing with age among subjects without nuclear cataract (n=2,482). (**Figure 25**)

Table 17 shows the nuclear cataract-specific prevalence of myopia within each age group. Prevalence of myopia increased significant with increasing nuclear opacity score in 60-69 years and 70-83 years age groups.

Table 18 shows the age-specific prevalence of myopia by nuclear lens opacity. When nuclear opacity score was less than 2.0 or between 2.0 to 4.0, the prevalence of myopia decreased significantly with increasing age.

Crude and age-standardized prevalence of astigmatism, hyperopia and anisometropia are shown in **Table 19**. Age-standardized prevalence of astigmatism, hyperopia and anisometropia were 54.9%, 35.9% and 9.8%, respectively. Prevalence of other definitions of astigmatism and hyperopia are also shown. The prevalence of

hyperopia (SE > + 2.0D) was 8.6%. The prevalence of astigmatism was 21.3% or 10.2% when using the definitions of less than 1.0 or 1.5 cylinder, respectively. The prevalence of both astigmatism and anisometropia increased with age. Prevalence of hyperopia initially increased with age and then decreased, with the highest rate in the 60-69 year age group (60.7%). There were no gender differences in the prevalence of astigmatism (P = 0.14), hyperopia (P = 0.27), or anisometropia (P = 0.20). In addition, amongst those with astigmatism (n=1,585), 62.9% had "against the rule" astigmatism, 3.2% had "with the rule" astigmatism, and 33.9% had "oblique" astigmatism. The axis of astigmatism showed a peak at 90° (against-the-rule astigmatism). However, there were no statistically significant differences in the axis of astigmatism by gender (P=0.92) or age group (P=0.15).

Table 20 shows the univariate analysis between refraction and potential myopia risk factors. Occupation (P<0.001), individual income (P<0.001), educational level (P<0.001), hours for reading and writing (P<0.001), hours for computer using (P<0.001), height (P<0.001), weight (P=0.004), pulse pressure (P<0.001), cataract (P<0.001) and astigmatism (P<0.001) were found to be significantly related to refraction in univariate comparisons.

Table 21 shows the multivariate analysis of risk factors for refractive errors. Factors that were significant in univariate analysis were included in multivariate analysis. In multivariate analysis, myopia was associated with time spent on reading and writing per day (OR=1.19), height (OR=1.04) and astigmatism (OR=3.59), after adjusting for age and gender. The interaction between age and cataract was also significant in the multivariate model (P = 0.03). Age (OR=1.07), myopia (OR=3.59) and diabetes

(OR=1.58) were associated with astigmatism, after adjusting for other confounders, while age and astigmatism were associated with both hyperopia and anisometropia.

Figure 26 compared the age-specific prevalence of myopia (SE < -0.5D) in Andhra Pradesh Eye Disease Study, Chennai Glaucoma Study and Singapore Indian Eye Study. Prevalence of myopia is higher in Singapore in 40-49 years age group. In 50-59 years, 60-69 years and 70 years or older age group, prevalence of myopia is higher in India.

Figure 27&28 compared the age-specific prevalence of myopia (SE < -0.5D) in Chinese, Malays and Indians in Singapore. In general, prevalence of myopia is highest in Chinese among all age groups. The prevalence of myopia in Malays and Indians is similar.

Table 22 compares the prevalence of myopia (SE < -0.5D) stratified by LOCS III grade in APEDS and SINDI. In low LOCS III groups (less than 2.0), prevalence of myopia is higher in SINDI than in APEDS. However, in moderate and high LOCS III groups, prevalence of myopia is lower in SINDI than in APEDS.

4.3 Axial Length and Other Ocular Biometric Parameter

Table 23 shows the means of ocular biometric parameters by age and gender. The mean AL, ACD and CR for the overall population were 23.45 ± 1.10 mm, 3.15 ± 0.36 mm, 7.61 ± 0.26 mm, respectively. The mean AL/CR ratio was 3.08 ± 0.13. Men had significant longer AL (P<0.001), deeper ACD (P<0.001) and flatter CR (P<0.001) than women. There was a significant trend of decreasing AL and ACD with increasing age for the population as a whole, and for males and females separately. On average, persons aged 40 to 49 years, when compared with those aged 70 to 83 years, had longer ALs

(mean difference, 0.18 mm) and deeper ACDs (mean difference, 0.32mm). CR did not vary significantly with age (p=0.22). There were no age (p=0.11) and gender (p=0.37) differences seen in AL/CR ratio comparisons.

Table 24 shows the median and distribution of ocular biometric parameters in the study population. The normal distribution was tested by K-S test. The medians of AL, ACD and CR for the overall population were 23.31 mm, 3.15 mm, 7.61 mm, respectively. The ranges of AL, ACD and CR for the overall population were 13.62 mm, 2.56 mm, 2.73 mm, respectively. The inter quartile ranges (IQRs) of AL, ACD and CR for the overall population were 1.22 mm, 0.48 mm, 0.34 mm, respectively. AL was only normally distributed in the oldest age group. ACD and CR were normally distributed in all age groups.

The distribution of ALs is shown in **Figure 29** and **Figure 30**. ALs for the overall population did not demonstrate normal distribution (Kurtosis = 6.1, Skewness = 1.4, p for K-S test < 0.001). When stratified by age groups, ALs only followed a normal distribution in the oldest age group (70-83 years) (Kurtosis = 1.3, Skewness = 0.05, p for K-S test = 0.68). In younger age groups, the distributions of ALs were all positively skewed. The distributions ALs were also positively skewed in both men (Kurtosis = 8.7, Skewness = 1.2, p for K-S test <0.001) and women (Kurtosis = 4.7, Skewness = 1.4, p for K-S test <0.001). The distributions of ACDs and CRs are shown in **Figure 31** and **Figure 32**. Both ACDs and CRs were normally distributed in this population.

Table 25 shows the univariate comparisons of mean ocular biometric parameters by potential determinants. In univariate comparisons, AL was associated with occupation (P<0.001), individual income (P<0.001), educational level (P<0.001), hours for reading

and writing (P<0.001), hours for using computer (P<0.001), height (P<0.001), weight (P<0.001), pulse pressure (P<0.001), HDL (P<0.001), smoking status (P=0.001), alcohol intake (P=0.001), diabetes (P=0.003) and nuclear cataract (P<0.001). ACD was associated with occupation (P<0.001), individual income (P<0.001), educational level (P<0.001), hours for reading and writing (P<0.001), hours for computer usage (P<0.001), height (P<0.001), weight (P<0.001), pulse pressure (P<0.001), HDL (P<0.001), smoking status (P=0.01), alcohol intake (P=0.008), diabetes (P=0.001) and nuclear cataract (P<0.001). CR was associated with occupation (P<0.001), individual income (P<0.001), educational level (P<0.001), hours for reading and writing (P=0.001), hours for using computer (P<0.001), height (P<0.001), weight (P<0.001), BMI (P=0.005), pulse pressure (P=0.002), HDL (P<0.001), smoking status (P<0.001), alcohol intake (P<0.001) and nuclear cataract (P<0.001).

Table 26 shows the multivariate analysis of the determinants of ocular biometric parameters. Factors significant in univariate analysis were retained in multivariate analysis. Three multivariate linear regression models were constructed to explore the determinants for AL, ACD and CR. After adjusting for age, gender, diabetes and nuclear cataract, each centimeter of height increase was associated with 0.034 millimeter increase in AL. For every hour spent more on reading and writing per day, there was a 0.064 millimeter increase in AL. Adults with university educational level had 0.408 millimeter longer mean AL than those with no formal education. Deeper ACDs were found in adults who were younger (regression coefficient = -0.01 mm, $p < 0.001$), taller (regression coefficient = 0.004 mm, $p < 0.001$) and read more per day (regression coefficient = 0.01 mm, $p = 0.02$). Increasing CRs were positively associated with height (regression

coefficient = 0.009 mm, $p = 0.008$).

Table 27 shows the correlations of ocular biometric parameters and SE by refractive status. The correlation between SE and AL/CR (r = -0.78; $p < 0.01$) was stronger than that between SE and AL (r = -0.65; $p < 0.01$). Persons with a more negative SE had longer AL or higher AL/CR ratio. CR showed a weak positive relationship with AL (r = 0.48, $p < 0.05$) but there was no relationship with CR and SE (r = 0.08, P = 0.65). ACD was positively correlated with AL (r = 0.47, $p < 0.01$) but negatively associated with SE (r = -0.31, $p < 0.01$).

Figure 33 shows the LOWESS plot describing the non-linear association between SE and AL. SE showed a decreasing trend with increasing AL. **Figure 34** shows the LOWESS plot describing the non-linear association between SE and AL/CR ratio. SE showed a decreasing trend with increasing AL/CR ratio. **Figure 35** shows the LOWESS plot describing the non-linear association between SE and ACD. SE showed a decreasing trend with increasing ACD. **Figure 36** shows the LOWESS plot describing the non-linear association between SE and CR. SE showed a decreasing trend with increasing CR. SE did not vary significantly with increasing CR.

Figure 37 shows the box plot of AL in different SE groups. AL showed a decreasing trend with increasing SE. **Figure 38** shows the box plot of ACD in different SE groups. ACD showed a decreasing trend with increasing SE. **Figure 39** shows the box plot of CR in different SE groups. CR did not vary significantly with increasing SE. **Figure 40** shows the box plot of AL/CR ratio in different SE groups. AL/CR ratio showed a decreasing trend with increasing SE.

Figure 41 shows the age and gender distribution of AL adjusted for height. After

adjusting for height, women did not have a shorter AL than men. In addition, AL did not decrease with increasing age.

The relationship between AL and SE was different in adults with and without nuclear cataract. In those without nuclear cataract, the relationship between AL and SE (r = 0.70) is stronger than that in nuclear cataract patients (r = 0.46). (**Figure 42**)

When the whole study sample was divided into three subgroups, the relationship between AL and CR was stronger in non-myopic eyes than myopic eyes. (**Figure 43**)

In **Table 28**, linear regression models were constructed to evaluate the independent effect of biometric components on SE in all age groups. In model 1, AL, CR and nuclear opacity (LOCS III) were analyzed as independent variables while SE as dependent variable. In model 2, AL/CR ratio and nuclear opacity (LOCS III) were analyzed as independent variables while SE as dependent variable. Standardized regression coefficient was used to estimate the relative effect of each biometric component on SE. In all age groups, AL or AL/CR ratio was the highest relative predictor of SE with the standardized regression coefficient being the largest. Nuclear opacity was not a significantly predictor of SE in 40-59 years age group. However, nuclear opacity played a more important role in older age groups. The standardized regression coefficients were -0.27 in model 1 and -0.31 in model 2 for nuclear opacity in 70-83 years age group.

Table 29 compared the mean AL and SE in adults aged 40-49 years in different population-based studies. In general, adults with longer AL tended to have more negative SE.

4.4 Myopia Prevalence and Axial Length in the First and Second (or higher)

Generation Immigrants

Figure 44 shows the distribution of birth place in the Singapore Indian Eye Study. Among the 3,400 Indian participants, 2,024 (59.5%) were born in Singapore, 813 (23.9%) were born in India, 495 (14.6%) were born in Malaysia and the other 68 (2.0%) were born in other south-east Asia countries such as Pakistan, Bangladesh, Brunei and Sri Lanka; thus, 1,376 (40.5%) were classified as 'first generation' immigrants and 2,024 (59.5%) were classified as 'second (or higher) generation' immigrants.

Table 30 compares the characteristics of the first and second (or higher) generation immigrants. After excluding participants with previous cataract surgery, 1,109 first generation and 1,877 second or higher generation Asian Indian immigrants contributed to this analysis. 685 (61.8%) first generation immigrants and 1,418 (75.5%) completed the interview in English, respectively. Among the first generation immigrants, the average migration age to Singapore was 20.0 years old (standard deviation [SD] = 12.7). Compared with the second or higher generation immigrants, the first generation immigrants were older ($p < 0.001$), shorter ($p = 0.03$) and less educated ($p < 0.001$). They had lower BMI ($p < 0.001$), lower monthly income ($p < 0.001$), smaller houses ($p = 0.002$) and higher lens opacity score ($p < 0.001$).

Table 31 compares the prevalence of myopia (SE<-0.5D), high myopia (SE<-5.0D) and mean ocular biometric parameters between the first and second or higher generation immigrants. In general, the second or higher generation immigrants had higher prevalence of myopia and high myopia. They also had longer AL after adjusting for age, gender, educational level, height and lens opacity. ACD and CR were not significantly different between the two groups.

Table 32 evaluates the factors that may explain the higher prevalence of myopia and high myopia among the second or higher generation immigrants. The reduction in odds of myopia and high myopia associated with the second or higher generation immigrants was estimated with adjustment of specific factors. Adjustment for height or educational level led to reduction in the excess prevalence of myopia in the second or higher generation immigrants by 7.5% or 37.5%, respectively. On the contrary, adjustment for lens opacity increased the excess prevalence of myopia in the second or higher generation immigrants by 5.0%. For high myopia, prevalence of high myopia in the second or higher generation immigrants was reduced by 33.1% when educational level was adjusted.

Figure 45 shows the distributions of age at migration among the first generation immigrants. There was a peak around 20 years. Most of the first generation immigrants immigrated to Singapore at the age of about 20 years.

Table 33 shows the prevalence of myopia, mean AL and SE by age at migration among the first generation immigrants. In general, those migrated to Singapore before the age of 12 years had the highest prevalence of myopia, most negative SEs and longest ALs compared with others.

Figure 46 shows the mean AL first adjusted for age and gender and further for height, nuclear cataract and educational level in different migration age groups. Even after adjusting for all the confounders, those migrated to Singapore before the age of 12 years still had the longest ALs compared with other groups.

Among the first generation immigrants, younger age at migration (as a continuous variable) was significantly associated with higher prevalence of myopia (OR, 1.02;

95%CI: 1.00, 1.03; p = 0.02), after adjusted for age, gender, educational level, lens opacity and height. Per year decrease in age at migration was associated with a 0.014 D decrease in refraction (95%CI: -0.02, -0.01; p < 0.001) and 0.009 mm increase in AL (95%CI: 0.003, 0.014; p = 0.002). Those who migrated to Singapore before the age of 12 years and thus were schooled in Singapore before 12 years old had higher odds of myopia (OR: 1.58; 95%CI: 1.07, 2.35; p = 0.02), more myopic refraction (regression coefficient: -0.33; 95%CI: -0.49, -0.17; p < 0.001) and longer AL (regression coefficient: 0.27; 95%CI: 0.11, 0.43; p = 0.001) compared with those who migrated and thus were schooled in Singapore after 21 years of age. (**Table 34**)

Among the whole study sample, younger age at migration (as a continuous variable) was significantly associated with higher prevalence of myopia (OR, 1.02; 95%CI: 1.01, 1.03; p = 0.02), after adjusting for age, gender, educational level, lens nuclear opacity score and height. Per year decrease in age at migration was associated with a 0.02 D decrease in refraction (95%CI: -0.03, -0.01; p < 0.001) and 0.01 mm increase in AL (95%CI: 0.007, 0.014; p <0.001). Those who migrated to Singapore before the age of 21 years and thus were educated in Singapore before 21 years old had higher odds of myopia (OR: 1.85; 95%CI: 1.32, 2.59; p <0.001), more myopic refraction (regression coefficient: -0.40; 95%CI: -0.69, -0.11; p = 0.006) and longer AL (regression coefficient: 0.19; 95%CI: 0.11, 0.43; p = 0.001) compared with those who migrated and thus were educated in Singapore after 21 years of age. (**Table 35**)

Table 36 shows the associations of myopia and AL with preferred language for interview. Among the first generation immigrants, the English-interviewed ones had higher prevalence of myopia (OR=1.46; 95%CI: 1.00, 2.17; p = 0.05) compared with the

non-English-interviewed ones after adjusted for age, gender, educational level, lens opacity and height. However, there were no significant differences in the prevalence of myopia between the English-interviewed and non-English-interviewed ones in the second or higher generation immigrants (p = 0.73).

Table 37 shows the risk factors for myopia among the first and second (higher) generation immigrants. Among the first generation immigrants, higher myopia rate is associated with younger age (P=0.02), university educational level (P=0.005), nuclear lens opacity (P<0.001), English as preferred language for interview (P=0.05) and younger migration age (P=0.02). Among the second (or higher) generation immigrants, higher myopia rate is associated with younger age (P<0.001), height (P=0.004), female gender (P<0.001), university educational level (P=0.005) and nuclear lens opacity (P=0.003).

4.5 Refractive Error, Axial Length and Major Age-Related Eye Diseases

3,400 participants were examined (overall response rate 75.6%), of whom 3,337 (98.1%) had sufficient quality photographs for AMD grading in at least one eye. Among the 3,337 participants, there were 188 (5.6%) cases of early AMD, 14 (0.4%) cases of late AMD, totaling 202 (6.1%) cases with any AMD. **Figure 47** shows the distribution of early and late AMD in this cohort. In general, the prevalence of early AMD increases with increasing age while late AMD cases were only found in the oldest age group.

Table 38 compares the characteristics of participants with and without any AMD. In general, AMD patients were significantly older than those without AMD (*P*<0.001). They also had lower income (*P*=0.001), lower cholesterol level (*P*<0.001), were more likely to have hypertension (*P*<0.001) and smoking history (*P*=0.008).

Table 39 shows the multivariate-adjusted associations of refractive error and AL with AMD or specific AMD lesions after adjusting for age, gender, smoking, education, body mass index, hypertension and total cholesterol level. Myopic eyes had lower odds of AMD (OR: 0.45; 95% CI, 0.25, 0.79) than emmetropic eyes. Each mm increase in AL was associated with lower odds of AMD (OR: 0.76; 95% CI 0.65, 0.89). Myopic eyes also had lower odds of drusen (OR: 0.61; 95% CI, 0.43, 0.86) and RPE abnormality (OR: 0.50; 95% CI, 0.35, 0.70) compared with emmetropic eyes. Each mm increase in AL was also associated with decreased odds of drusen (OR: 0.77; 95% CI 0.69, 0.86) and RPE abnormality (OR: 0.79; 95% CI 0.70, 0.89). When myopia was categorized into mild, moderate and high myopia, only mild myopia was significantly correlated with a lower odd of AMD (OR: 0.44; 95% CI 0.23, 0.83). Moderate and high myopia were associated with a lower odd of AMD though the associations were not statistically significant (P = 0.24 for moderate myopia; P = 0.17 for high myopia). Increasing severity of myopia was associated with a decreasing odd of AMD (P for trend = 0.01). (**Table 40**)

Among the 1,119 diabetic subjects, the mean age was 61.0±9.9 years, 537 (48.0%) were female. 1,110 (98.3%) had sufficient quality photographs for DR grading in at least one eye. 403 (36.6%) diabetic subjects had DR. **Figure 48** shows the distribution of DR in this cohort. The prevalence of DR showed an increasing trend with age in women but not in men.

Table 41 compares the characteristics of diabetic patients with and without any DR. In general, DR patients tended to have higher blood glycosylated haemoglobin level ($P<0.001$), greater BMI ($P=0.004$) and higher hypertension rate ($P<0.001$) than diabetic subjects without retinopathy.

DR was present in 21.7% of myopic eyes, 30.3% of emmetropic eyes and 29.4% of hyperopic eyes, respectively. **Table 42** shows the multivariate-adjusted associations of refractive error and AL with DR or VTDR after adjusting for age, gender, education, body mass index, HbA1c, hypertension and total cholesterol level. Myopic eyes had lower odds of DR than emmetropic eyes (OR: 0.68; 95% CI, 0.46, 0.98). Each mm increase in AL was associated with a lower odds of DR (OR: 0.73; 95% CI 0.63, 0.86). However, both refractive error and AL were not significantly associated with VTDR. Increasing severity of myopia was associated with a decreasing odd of DR (P for trend < 0.001). (**Table 43**)

Figure 49 shows the distribution of nuclear cataract in this cohort. The prevalence of nuclear cataract increases with increasing age. **Figure 50** shows the distribution of cortical cataract in this cohort. The prevalence of cortical cataract increases with increasing age. **Figure 51** shows the distribution of PSC in this cohort. The prevalence of PSC increases with increasing age.

Table 44 compares the characteristics of participants with and without any age-related cataract. Cataract patients were older, have lower income (P<0.001) and educational level (P<0.001), more likely to have diabetes (P<0.001) and hypertension (P<0.001), have lower BMI (P<0.001) and cholesterol level (P<0.001) compared with non-cataract subjects.

Nuclear cataract was present in 13.4% of myopic eyes, 8.0% of emmetropic eyes and 11.8% of hyperopic eyes, respectively. Cortical cataract was present in 22.9% of myopic eyes, 20.4% of emmetropic eyes and 33.5% of hyperopic eyes, respectively. PSC was present in 4.9% of myopic eyes, 2.4% of emmetropic eyes and 2.4% of hyperopic

eyes, respectively. **Table 45** shows the multivariate-adjusted associations of refractive error and AL with age-related cataract after adjusting for age, gender, education, diabetes and smoking. Nuclear cataract was more prevalent in myopic eyes (OR: 1.57; 95% CI 1.13, 2.20) and less prevalent in hyperopic eyes (OR: 0.63; 95% CI 0.46, 0.87) than emmetropic eyes. Nuclear cataract was not associated with AL. Cortical cataract was not related to either refractive errors or AL. PSC was found to be more frequent in myopic eyes (OR: 1.73; 95% CI 1.10, 2.27) and positively associated with longer AL (OR: 1.29; 95% CI 1.07, 1.55). When any myopia was categorized into mild, moderate and high myopia, only high myopia was significantly correlated with a higher odd of nuclear cataract (OR: 3.42; 95% CI 1.67, 7.00) and PSC (OR: 5.90; 95% CI 2.68, 12.97) but not with cortical cataract. Increasing severity of myopia was associated with an increasing odd of nuclear cataract (P for trend = 0.02) but not with cortical cataract or PSC (both P for trend > 0.1). (**Table 46**)

Figure 52 shows the distribution of POAG in this cohort. The prevalence of POAG increases with increasing age.

Table 47 compares the characteristics of participants with and without any age-related cataract. POAG subjects were older (P=0.05) and have lower cholesterol level (P=0.08).

Table 48 compares the age and gender adjusted mean SE, AL, ACD, CR, CCT and IOP in eyes with and without any POAG. POAG eyes had more negative SE (P=0.04), longer AL (P=0.02), deeper ACD (P=0.07), thinner CCT (P=0.10) and higher IOP (P=0.02).

Table 49 shows the age and gender adjusted associations of CCT and IOP with

myopia or AL. Myopic eyes had higher IOP (P=0.01) but not thick CCT (P=0.32). AL was associated with thicker CCT (P=0.005) but not with IOP (P=0.45).

POAG was present in 2.3% of moderate myopic eyes, 0.7% of low myopic eyes, 1.0% of emmetropic eyes and 0.8% of hyperopic eyes, respectively. **Table 50 & 51** shows the multivariate-adjusted associations of refractive error and AL with POAG after adjusting for age, gender, education, HbA1c, total cholesterol level, IOP and CCT. Any myopia was not associated with POAG (P=0.68). Only high myopia but not mild or moderate myopia was associated with a higher odd of POAG (OR: 6.97; 95% CI 2.20, 22.16). POAG was associated with each mm increase in AL (OR: 1.43; 95%CI 1.13, 1.80).

Figure 53 & 54 show the LOWESS plots on the non-linear associations of SE and AL with POAG. POAG rate increased dramatically when SE is less than -3 D or AL is more than 24 mm.

Table 52 compares the associations of SE and AL with POAG in High IOP and Normal IOP Groups. The magnitudes of associations of SE and AL with POAG are higher in high IOP groups.

Table 53 explores the combined effect of myopia and IOP on the association with POAG. Myopia was defined as less than -1.0D, -2.0D or -3.0D, respectively. When myopia was defined as less than -1.0D, -2.0D or -3.0D, persons with both myopia and high IOP have 39.3, 35.3, 43.3 higher odds than those with non-myopia and normal IOP, respectively.

In **Table 54**, the difference in mean refraction between eyes, with and without a specific ocular disease, was compared between models with AL entered versus the

reference model without AL. The relative proportion of the refractive association with the ocular condition that is explained by AL was estimated by the amount of attenuation in the association after adding AL in the reference model. In general, adding AL attenuated the difference in mean refraction between eyes with and without AMD, DR or POAG by 76.2%, 76.6% or 64.7%, respectively. AL accounted for only 2.0% or 27.6% of the difference in mean refraction between eyes with and without nuclear cataract or PSC.

4.6 Meta-Analysis of the Association between Refractive Error and Age-Related Macular Degeneration

The literature search yielded 163 titles from PubMed. After screening these titles, we found 32 abstracts which are related to the topic. After screening the abstracts, 15 articles were selected for full paper review. After a thorough review of the 15 full-text to determine whether they met our inclusion critieria, 6 population-based cross-sectional studies[136-137, 168-169] (including the Singapore Indian Eye Study) and 3 population-based longitudinal studies[136, 141-142] were selected for the meta-analysis. Among the 6 cross-sectional studies, 4 were conducted in Asia, 1 was conducted in Australia and the other was conducted in Europe. Among the 3 cohort studies, 1 was conducted in US, 1 was conducted in Australia and the other was conducted in Europe. Characteristics of the studies are presented in **Table 7**.

Table 55 summarizes the pooled effect estimates on associations of refractive error and AMD. In the meta-analysis of 6 cross-sectional studies, hyperopia was associated with higher prevalence of AMD (pooled OR: 1.16, 95% CI, 1.04, 1.29; *P*=0.01) with low heterogeneity among the studies (I^2=29.9%; *P*= 0.21). (**Figure 55**) Persons with myopia

were less likely to have prevalent AMD (pooled OR: 0.75, 95% CI, 0.61, 0.92; *P*=0.005) with no evidence of heterogeneity among the studies (I^2=0%; *P*= 0.49). (**Figure 56**)

In the meta-analysis of 3 longitudinal cohort studies, no significant associations were observed between hyperopia and incident AMD (pooled HR: 0.96, 95% CI, 0.80, 1.14; P=0.63) with low heterogeneity among the studies (I^2=41.7%; *P*= 0.18). However, myopia tended to be related, albeit non-significantly, to a decreased risk of AMD compared with emmetropia. (pooled HR: 0.84, 95% CI, 0.68, 1.04; P=0.10) with no evidence of heterogeneity among the studies (I^2= 4.2%; *P* = 0.35) (**Figures 57 & 58**).

The association of per diopter increase in SE and AMD was reported in 5 cross-sectional studies and 2 cohort studies. (**Table 7**) When combining the effect estimate of these studies, per diopter increase in SE towards hyperopia was associated with both prevalent (pooled OR: 1.09; 95% CI: 1.06, 1.12) and incident (pooled HR: 1.06; 95% CI: 1.02, 1.10) AMD. The data on the association of per mm increase in AL and AMD were available in the Singapore Malay Eye Study, Singapore Indian Eye Study and the Central Indian Eye and Medical Study. When combining the effect estimate of these studies, per mm increase in AL was associated with lower odds of prevalent AMD (pooled OR: 0.76; 95% CI: 0.69, 0.85)

There was no evidence of publication bias as indicated by a non-significant Egger test (all $P > 0.05$) and Begg's test (all $P > 0.05$) in all analyses.

CHAPTER 5

DISSCUSION

5.1 Important Findings of the Study

In this study, 28.0% of Singaporeans of Indian ethnicity aged over 40 years had myopia. In adults without nuclear cataract, prevalence of myopia was higher in Singapore Indians compared India Indians. The mean ocular AL of Indians living in Singapore was longer than that of Indians living in rural India, independent the effect of nuclear cataract. Myopia was also found to be more prevalent and AL was longer among second generation immigrants of Indian residents living in Singapore compared with first generation immigrants. These findings suggest that country-specific environmental factors play a major role in the increasing prevalence of myopia observed in new urbanized Asian societies. Myopic eyes were found to be less likely to have AMD and DR, but more likely to have nuclear cataract, PSC and POAG. In addition, the variation in AL explained most of the associations of refractive error with AMD, DR or POAG, but not the associations with age-related nuclear cataract, which results from changes in the refractive power of the lens associated with nuclear cataract.

5.2 Novelty of the Study

The Indians are the indigenous people residing mainly in the India subcontinent. Asian Indians account for one-sixth of the world population, with a global estimate of more than 1 billion persons.[174] Previous national and regional population-based surveys have provided considerable information regarding the epidemiology of myopia of Indians living in India. However, the data on the pattern of myopia and other refractive errors in

the approximately 25 million migrant Indians who live outside India are lacking. Health of migrants is a major public health challenge faced by governments and policy makers in Singapore. Asian Indians are among the fastest growing migration groups across Asia and the world, but the impact of migration and acculturation on myopia among Indians living in urban Asia remains unclear. This study provides population-based data on the prevalence and patterns of myopia and other refractive errors as well as their associations with other major eye diseases in this particular ethnic group in Singapore. These data may have relevance to many ethnic Indian persons living outside India. Comparisons of our study with data from India may provide important information on the interplay and effects of geographic variation, cultural diversity, environmental differences, and health care systems against a similar background of genetic susceptibility. This study also provided the data on the inter-generation variation in prevalence of myopia and AL, which offer further insights into how environmental exposures impact the risk of myopia. Thus, this study completes a gap in knowledge about adult myopia and other refractive errors in an urban population in Singapore.

5.3 Patterns of Refractive Error and Ocular Biometry

The prevalence of myopia is lower among Singaporean Indians than Indians of a similar age range residing in Southern India. In the Indian state of Andhra Pradesh, a multistage cluster, systematic, stratified random sampling method was used and the age-gender-area adjusted prevalence of myopia of adults aged over 40 years in primarily rural areas was 34.6% (n=3,723).[33] In rural Chennai, the age-gender adjusted prevalence of myopia was 31.0% (n=2,508).[34] Indians in urban Andhra Pradesh had lower myopia

rates (31.9%) than rural Andhra Pradesh (38.0%) but higher myopia rates than Singaporean Indians. Comparing the prevalence of myopia in each age group, myopia is more prevalent in this study than Indian studies for the 40 to 49 years age group, reflecting a potentially 'myopigenic' environment in Singapore. In the 50 to 59 years age group, India Indians exceed Singaporean Indians in the prevalence of myopia due to earlier onset of nuclear cataract or nuclear sclerosis among Indian Indians[33-34]. In the age groups over 60 years, the differences in prevalence of myopia between Indian Indians and Singaporean Indians seem to be enlarged due to the more severity of nuclear opacity. In the Andhra Pradesh Eye Disease Study, the population attributable risk percentage (PAR%) for lens nuclear opacity (NO) 2-3.5 and NO > 3.5 of myopia were estimated to be 76% and 23%, respectively.[33] The high PAR% for nuclear opacity indicates that the main cause of myopia in Indian adults is nuclear cataract. Thus, if we remove the nuclear cataract patients in India from analysis, the prevalence of myopia in Indians residing in India would probably be lower than that of the Singaporean Indians due to the urban versus rural differences as expected.

There are another two studies on the prevalence of myopia in India. Prevalence of myopia has also been reported recently in Central India Eye and Medical Study (n=4711, aged over 30 years)[35] and in subjects with diabetes (n=1414, aged over 40 years).[175] The Central India Eye and Medical Study was conducted in the rural region of Central Maharashtra. The prevalence of myopia was 17% which was significantly lower compared with SINDI. [35] However, this study could not be compared directly due to the difference in age range. The Sankara Nethralaya Diabetic Retinopathy Epidemiology and Molecular Genetic Study reported 19.4% subjects had myopia in a population with

diabetes. [175] Differences in study populations (specific group vs general population) and sampling strategies (age-stratified vs socioeconomic factors-stratified) do not allow direct comparisons.

This study could be directly compared with Singapore Chinese adults (the Tanjong Pagar Survey) and Malay adults (the SiMES) which used identical study protocols, in order to explore the effect of ethnic variation within the same environment.[39-40] However, the sampling process of the Tanjong Pagar Survey was less rigorous than that of SINDI and SiMES. Comparing our results with the Tanjong Pagar Suvery[39] and the SiMES,[40] the prevalence of myopia is highest among Chinese in almost all age groups in both men and women. The Tanjong Pagar Survey was conducted nearly 10 years ago. The difference in the prevalence of Tanjong Pagar Survey, SiMES and SINDI may reflect secular trends over time as well as inter-ethnic variation. The higher prevalence of myopia in Chinese than other ethnicities is possibly attributed to inter-ethnic variability in risk factors such as differences in lifestyle including more time spent on school work, less outdoor activities or ethnic-specific genes relevant to Chinese. In Singapore children, Chinese were reported to spend most time on nearwork[176] but least time outdoors[75]. The mean time outdoors was reported to be 3.05h, 3.94h and 3.21h per day for Chinese, Malays and Indians, respectively ($P<0.001$)[75].

The result of this study is consistent with the studies in children or teenagers. In children or teenagers, the prevalence of myopia has been compared among the three major ethnic groups. In a study on Singapore male conscripts with SE assessed using non-cycloplegic autorefraction and myopia defined as SE ≤ -0.5 D, the Chinese, Indian and Malay prevalence rates were 82.2% (95% CI 81.5, 82.9), 68.7% (95% CI 65.1, 67.1)

and 65% (95% CI 62.9, 67.1), respectively (n=15,095, aged 17-19 years).[177] In the Gombak district of Malaysia, Chinese children had the highest prevalence of myopia (46.4%) among the ethnic groups, followed by Indians (16.2%) and Malays (15.4%) across all ages (n=4,634, aged 7-15 years).[178]

People with high myopia are reported to have a substantially higher risk of cataract, glaucoma, myopic macular degeneration and retinal detachment.[160] Vision in myopia may be restored using optical devices such as spectacles and contact lenses, but high myopia is closely linked to potentially visually disabling eye diseases. The age-standardized prevalence of high myopia (SE < -5.0D) in our study was 4.1%, which is significantly lower than that of Chinese population (9.1%)[39] but slightly higher than that of Malay adults (3.9%)[40] of the same age range. Compared with Indian adults in India, the rate was slightly lower than that of the Andhra Pradesh Eye Disease Study (4.5%)[33] but slightly higher than reported in Chennai Glaucoma Study (3.7%).[34] This rate was also higher than in most other ethnic population such as Whites and Blacks aged over 40 years in the Baltimore Eye Study (1.4%),[42] white persons aged 49-97 years in Blue Mountain Study (3.0%),[48] Indians in Bangladesh (2.2%)[36] aged over 30 years, and Hispanics (2.4%) aged over 40 years in the Los Angeles Latino Eye Study.[43] It has been found that the prevalence of high myopia in children is several times higher than that in older cohorts. The gradual spread of this higher prevalence throughout the population has major public health implications, since a high proportion of those with high myopia develop pathological signs.

A U-shaped relationship between myopia prevalence and increasing age was observed. This similar pattern was also found in Singapore Chinese and Malays of the

same age range [39-40] and was modified by nuclear cataract. In subjects without nuclear cataract, the prevalence of myopia declined with age. This pattern may represent an increase in the prevalence of myopia in younger generations, possibly through a more competitive education system, or an intrinsic age-related decline in myopia prevalence.[179] In subjects with nuclear cataract, the prevalence of myopia increased with age due to increasing nuclear lens opacity in elderly populations.[122] However, the prevalence of myopia increased with age in India. The difference in age-adjusted pattern of myopia prevalence between Singapore and India could be due to a higher prevalence of nuclear cataract in India.[33-34]

The hyperopia prevalence (35.9%) in this study is also higher than that that of Singapore Chinese (28.4%)[7] and Malays (27.4%)[35], but lower than that of white populations in the Beaver Dam Eye Study (49.0%)[44] and the Blue Mountains Eye Study (57.0%)[5]. The prevalence of hyperopia generally increased with age possibly due to a decrease in refractive power of lens,[180] changes in lens position[44] or decreased axial length.[181] In persons aged over 70 years, decreased prevalence of hyperopia was observed in our study, possibly due to lens-induced myopic shift.[32] The increasing trend in myopia and decreasing hyperopia could also be explained by the cohort effect which has been observed in Singapore. In the 1960s and 1970s, only 20–30% or 40–50% of male conscripts were myopic[88] and around 80% of male conscripts were found to be myopic in the 1990s[177]. In view of the limitation of cross-sectional design, we could not separate the age-related hyperopic shift from the cohort effect in our study.

The prevalence of astigmatism was 54.9% in our study, which was significantly higher than that of Singapore Chinese (37.8%) and Malays (33.3%) of the same age

range[39-40] . This prevalence is also higher than that of Andhra Pradesh Eye Disease Study (37.6%), but similar to that reported from the Chennai Glaucoma Study (54.8%).[33-34] Prevalence of astigmatism increased with age, which is consistent with the findings of previous studies.[31, 37, 42, 48] 'With-the-rule' astigmatism, where the vertical curve is greater than the horizontal, is common in children and adolescents. The dominant proportion of 'against the rule' astigmatism (62.9%) in our study further confirmed that 'with-the-rule' astigmatism tends to disappear or even reverse itself to an 'against-the-rule' astigmatism with increasing age.[182] The main risk factor for astigmatism in our study was diabetes mellitus which was positively associated with astigmatism. In a multivariate logistic model in the SiMES, the association between astigmatism and diabetes mellitus was only of borderline significance (P=0.06).[40] Two cross-sectional studies on diabetic patients have reported quite high prevalence of astigmatism: 87.8 % in Taiwan and 47.4% in India. However, there were no controls. It is possible that diabetes may lead to astigmatism as fluctuating blood sugar levels might alter the refractive index and curvature of the crystalline lens.[183]

It is worthwhile comparing this study with the Central India Eye and Medical Study on Indians living in India. The mean AL in that study (22.6 mm) was significantly shorter than our SINDI study (23.45 mm). The magnitude of the difference is considerable, and it is unlikely to be explained by differences in AL measurement method or age range of the participants. The difference in AL may be explained by a greater degree of urbanization in Singapore and subsequently a higher rate of axial myopia.

Comparing the mean AL among different population-based studies would help to clarify the inter-ethnic variation in AL and its association with refractive errors.

Compared with the other two major ethnic groups in Singapore, the mean AL in this Singaporean Indian cohort is similar to that of the Singaporean Malays in the SiMES, but slightly longer than that of Singaporean Chinese in the Tanjong Pagar Survey. However, different age and gender distributions may account for the differences observed among these population-based studies. In order to compare the association between AL and SE more accurately, the mean AL and SE in different population-based studies in the 40-49 years age group was compared since SE is mostly explained by AL and influence by lens opacity is minimal in this age group. We found longer AL to be associated with more negative SE. Singaporean Chinese with the longest mean AL have the most negative mean SE. There was a trend towards longer AL among the populations with more negative SE, although there was no significant difference (P = 0.08 for men and P = 0.13 for women) due the small sample size.

In this study, older adults tended to have shorter ALs. This has also been observed in Singaporean Chinese[17] and Singaporean Malays[118], but not in Latinos[18], Burmese[19] and Mongolians[20]. In addition, age was only associated with AL in univariate analyses and the association disappeared when height and education were adjusted in the multivariate model in our study. This suggests that younger subjects may be generally taller and more educated, which correspondingly make AL longer than those of older counterparts. In SiMES, age was also associated with AL in univariate analysis ($p<0.001$) but not a significant derterminant of AL in the multiple logistic model ($p = 0.55$). Although AL might decrease with increasing age[181], the age pattern for AL is more likely due to cohort effect than age effect, at least in Singapore.

Gender differences in biometry have been documented in several populations. In

general, men have longer eyes, deeper anterior chambers and flatter corneas than women as measured by A-scan ultrasound and IOLMaster. Much of the variation has been attributed to differences in stature between men and women, particularly height, as adjustment for height in multivariate analyses tended to attenuate the association. For example, the BDES reported that men had generally longer AL and larger eyes, but adjustment for height rendered the association non-significant.[184] In SiMES, however, gender differences in AL and ACD were still significant in multivariate analyses controlling for stature.[92] However, gender was not associated with AL after adjusting for height in this study.

In this study, longer ALs were found in adults who were taller, more educated, and spent more time on reading. Height is the strongest predictor of AL in prior studies.[17-19, 185-187] The association between more time on near work and longer ALs was reported in studies on children and our study confirmed this association. It was found in Singapore that children who read more than two books per week had ALs that were 0.17 mm longer compared with children who read two or fewer books per week.[58] The mechanism of how near work elongate AL may be in terms of the growth induced by excessive accommodation,[188] but this theory remains debatable and has not been supported by animal studies.[189-190] Previous population-based studies on adults have found an association between educational level and AL.[191] In SiMES, increasing AL was associated with higher education level (standardized beta = 0.118, $p < 0.001$)[118]. In the Tanjong Pagar Survey on Singaporean Chinese adults, AL increase by 0.60 mm for every 10 years of education (95% CI: 0.34, 0.85)[17]. This study found that this association only exists at college or university educational level. The implications of AL as an

endophenotype compared to refractive error should be considered. AL is used as an endophenotype for refraction since refraction is affected both by genetic and environmental factors while AL may provide a simpler phenotype.[192] However, our study showed that AL is also associated with environmental factors such as near work and educational level, in addition to height. Moreover, AL may be related to genetic variants too. Thus, AL as an endophenotype for refraction is still controversial and should be further studied. Both refraction and AL should be examined in detail in further epidemiologic studies of myopia.

This association between AL and smoking was not supported by this study. In SiMES, smoking was associated with shorter AL after adjustment for socioeconomic factors.[92] A weak association between smoking and myopia has been suggested from epidemiological studies.[193] In animal models, nicotinic antagonists inhibit experimental myopia in chicks, and these receptors may be activated by nicotine in cigarette smoke.[194] Further research in this area may be useful.

AL is the most important predictor of refraction with standardized regression coefficients of AL being the largest in all age groups. In younger age groups such as 40-49 years and 50-59 years, AL accounts for most of the variation in refraction. While lens opacity became an additional significant predictor of refraction in older age groups, explaining why there was a myopic shift from 60-69 years to 70-83 years. Lens opacity affect refraction through increased power of the more sclerotic lens rather than increased AL.[31, 45, 49, 195] This pattern is supported by the Tanjong Pagar Survey[17] and the Los Angeles Latino Eye Study[18].

In this study, taller adults were also found to have deeper ACDs and flatter corneas,

indicating an overall increase in eye globe size. However, SE was weakly correlated with CR or ACD, confirming other reports that AL was the main determinant of SE, whereas CR and ACD were of relatively minor importance. AL/CR ratio is even more correlated with SE than AL alone in our study. This correlation indicates that longer eyes include those which are long because of overall body stature are not necessarily myopic. Eyes which are long because of excessive axial elongation are in fact myopic. In this study, ALs are less correlated with CRs in myopic eyes than non-myopic eyes, indicating that emmetropisation is substantially based on matching AL to CR, and thus this ratio normalizes for overall eye size and its relationship to height.

5.4 Effects of Migration and Acculturation on Myopia and Axial Length

Migrant studies offer a unique insight into how environmental factors may influence myopia at the population level, by comparing the prevalence and patterns of myopia among different generations of migrants with the same genetic heritage. The pattern of myopia in migrants may be influenced by the retention of ethnic identity and culture after resettlement and by the length of residence in the new country versus the country from which they have derived. However, migrant studies on myopia are few. Our finding is consistent with previous studies, which showed the prevalence of myopia increased spectacularly among generations as people moved into settlements.[43, 127-130] Our study found that second generation immigrants had both more myopic refraction and longer ALs than first generation immigrants. These findings are important given the age range of over 40 years of the study population, as spherical refraction may also reflect the effects of age-related lenticular changes. Unlike refractive error, AL is known not to be

affected by nuclear cataract or nuclear sclerosis.[192] Our study thus demonstrates that second generation immigrants were more likely to have axial myopia than first generation immigrants.

The difference in the prevalence of myopia and AL between the two generations may represent environmental factors unrelated to education. However, these variables may be surrogate measures for some aspect of education not captured by the years-of-schooling measure. Birth country and acculturation may capture the impact of country of education. The fact that the influence of birth country or acculturation is most pronounced in younger age groups, as is the influence of education, is compatible with the idea that acculturation and country of birth may be associated indirectly with myopia through education.

A number of studies have already shown the strong correlation between higher educational level and higher risk of myopia.[42, 49, 88, 196-197] Our study now demonstrated that 37.5% of the excess prevalence of myopia in second as compared to first generation immigrants was explained by higher educational level in second generation immigrants. The mean migration age for first generation immigrants in our study was about 20 years, and therefore most of them completed primary education outside Singapore. They may have been exposed to a less intensive schooling system at an early age and were less likely to receive preschool education compared with Singapore-born Indians. For example, most Singaporean children attend preschool such as kindergarten or a childcare centre, and the syllabus maybe more structured and vigorous, with a greater use of information technology.[198] There may be other early childhood lifestyle factors in Singapore that may contribute to the excess prevalence of myopia including outdoor time,

stress levels, etc. In addition, 90% of the Singaporean children are reported to live in high-rise buildings,[199] which may also reduce outdoor time. Singapore is a small urban city state with more intensive population density and higher per capita gross domestic product compared with India or neighboring countries. Difference in religion, culture or even diet between Singapore and India or neighboring countries may also explain part of the difference in myopia prevalence between the two generation immigrants. Further studies are needed to examine the influence of other factors related to myopia such as time spent outdoors, population density, stress or even diet among different generations of immigrants.

After adjusting for educational level, those migrated to Singapore before the age of 21 and thus were educated in Singapore before 21 years of age had higher prevalence of myopia and longer AL than those migrated after 21 years old and educated outside Singapore before the age of 21. However, myopia rates do not appear to vary much between Indians born outside of Singapore but educated in Singapore and Indians born in Singapore. Thus, our findings could be interpreted that exposure to the Singapore schooling system at early age may be an independent risk factor for myopia. Singapore's schooling is highly competitive, academically oriented and emphasizes on very early educational achievements and passing examinations. Therefore, it is possible that those migrated to Singapore before the age of 21 were under greater education 'pressure' than those who migrated to Singapore after 21 years old. This may reflect a combination of higher level of reading exposure with large amount of near-work activity, corresponding lower levels of outdoor physical activity, and other factors.

The preferred language for interview was reported as a measure for acculturation in

migrant Asians,[200] and we found that first generation immigrants were more myopic if they were interviewed by English. Our finding is consistent with those reported in LALES, which used a nine-item questionnaire that recorded Spanish, English, and preferred language for speech, reading and writing to reflect acculturation level.[43] Preferred language for interview as proxy measures of acculturation may not fully reflect the complex acculturation processes, but it place minimal cognitive demands on participants and can be easily translated as well. Further studies should be conducted to identify the specific factors related to myopia during acculturation.

Other risk factors for myopia between first and second (or higher) generation immigrants are similar. Younger age, higher educational level and higher nuclear lens opacity score are all associated with higher prevalence of myopia in both generation immigrants. These factors are well-known risk factors for myopia, which should be controlled to relieve the public health burden of myopia.

5.5 Protective Effect of Myopia and Longer Axial Length for Age-Related Macular Degeneration and Diabetic Retinopathy

In the present study, myopia was inversely associated with AMD while hyperopia did not confer any increased odds. When any myopia was categorized into mild, moderate and high myopia, only mild myopia was significantly correlated with AMD. The insignificant correlation between moderate and high myopia with AMD may be explained by the small numbers of AMD in moderate and high myopia, leading to a reduction in statistical power. Results from several other population-based studies have shown an inconsistent association between refractive errors and AMD. The Singapore

Prospective Study on multiethnic Asian cohorts reported that myopia was protective for AMD in men (OR: 0.45 95% CI 0.28, 0.70) but not in women (OR: 0.45 95% CI 0.28, 0.70).[168] The baseline report of the Blue Mountain Eye Study[137], Rotterdam Study[136] and the Singapore Malay Eye Study [138] showed that early AMD was more prevalent in hyperopic eyes. The Beaver Dam Eye Study and the Blue Mountain Eye Study found non-significant associations between baseline refractive errors and incident AMD.[141-142]

In the meta-analysis on the association of refractive error with AMD, eyes with hyperopia were more likely to have AMD while eyes with myopia were less likely to have AMD. Longitudinal data support this by showing that myopia tended to be related to a decreased risk of AMD, albeit non-significantly, but in analysis of SE as a continuous variable, each diopter increase in refraction toward hyperopia is associated with a 6-9% risk of both prevalent and incident AMD. Furthermore, longer AL was associated with a reduced risk of AMD.

The biological plausibility of the observed association has not been elucidated. There are several theories. First, one possible explanation is the use of spectacles in myopes may reduce ultraviolet exposure in sunlight, which is known to be a risk factor of AMD.[201-205]

Second, difference in sclera rigidity between myopic and hyperopic eyes may explain this relationship. Longer eyeballs have been observed to have less rigid and compact sclera compared with shorter ones,[206-207] and previous studies have found that increased ocular scleral rigidity may be a significant risk factor for the development of AMD.[208-209]

Third, the observed association may be explained by the variation of the intraocular

concentration of vascular endothelial growth factors (VEGF) between myopic and hyperopic eyes. VEGF is now known to play a key role in AMD pathophysiology.[210] VEGF is a key regulator of angiogenesis, and withdrawal or interference with its function leads to cessation of vascular growth and neovascular regression.[211] Recent finding indicated that the intraocular concentration of VEGF decreased significantly with increasing myopia as well as increasing AL [212], which may partially explain why myopic eyes have a lower prevalence of AMD. AL may be related to ocular volume, and larger intraocular volume of the myopic eyes may lead to a more marked dilution of VEGF, which may lower the risk of AMD.[212]

Fourth, myopic eyes are more likely to have posterior vitreous detachment (PVD).[160, 213] It has been suggested that PVD is associated with a reduced likelihood of progression to neovascularization, which may explain the protective effect of myopia on AMD.[214] This protective effect may be attributed to the removal of the vitreous scaffold for neovascular proliferation, as well as to improved oxygen diffusion across the liquefied vitreous. From a clinical perspective, if a lack of PVD may be one of the causative reasons for the development of AMD, future studies may address the possibilities to induce a PVD as preventive step for AMD.

There were few studies which examined the association of refractive error with late AMD. The refractive association with late AMD was reported in the Singapore Malay Eye Study, Blue Mountain Eye Study and Beaver Dam Eye Study with non-significant findings in all studies. This may be explained by the small number of late AMD cases in population-based sample, leading to an insufficient statistical power to detect a positive association. Further studies with sufficient sample size and late AMD

cases are warranted to examine the association between refractive error and late AMD.

The association between refractive error and DR is less well studied. In population-based studies, the Visual Impairment Project did not find any significant association between prevalent DR and myopia.[147] The Singapore Malay Eye Study showed that myopic refraction was associated with lower prevalence of DR, particularly VTDR.[148] In a longitudinal study, myopia was associated with a lower risk of progression to PDR in younger-onset diabetes.[146] This study now demonstrates that myopia was associated with lower prevalence of DR, consistent with the findings from the Singapore Malay Eye Study. However, this study did not observe a significant association between myopia and VTDR, which differs from findings of the Singapore Malay Eye Study. The mechanisms underlying the protective effect of myopia on DR currently are unclear. The retinal and choroidal thickness in myopic eyes was observed to be thinner than in hyperopic eyes.[215-216] Thus, the myopic retina may be linked with a lower oxygen and nutrients demand compared with hyperopic retina, which may underline the protective effect of myopia on DR. Another explanation may be relatively narrower retinal arterioles in myopic eyes. Myopic eyes with longer AL were observed to have narrower retinal arterioles than non-myopic eyes.[217] Recent studies also support that widening of retinal vascular caliber is associated with increasing risk of DR.[218-220] The mechanisms behind the relationship may involve the impairment of vascular autoregulation and hyperperfusion, tissue hypoxia and ischemia, and aggravating DR risk factors such as hypertension.[221-223] Finally, Quigley *et al* attributed the pressure attenuation in retinal arterioles in myopic eyes to the observed association between myopia and DR.[224] He believed that myopia results in blood flowing through a longer arteriolar tree in the retina

on its course to the capillary bed, the site of disease in clinical diabetic retinopathy.[225] A case control study by comparing 111 insulin-dependent diabetes cases with retinopathy to 81 diabetes cases without retinopathy found that the DR risk was not associated with myopia in patients with human leukocyte antigen (HLA)-DR. In subjects with high-risk HLA-DR phenotypes, however, the retinopathy risk was 10 to 15 times higher in persons with an SE of more than –2.00 D.[226] The interaction between HLA-DR phenotypes and the role of myopia may occur because of changes in vascular flow. Early DR stages are characterized primarily by intravascular and perivascular pathologic features (e.g., basement membrane thickening, microaneurysm formation), whereas vision-threatening stages and complications primarily are extravascular (e.g., exudation, proliferation). Decreased blood flow in myopic eyes may reduce the extravasation of blood components acting as stimuli for macrophages that potentiate proliferation, and the macrophage response in turn may be modulated by the HLA-DR phenotype.

5.6 Associations of Refractive Error and Axial Length with Age-Related Cataract and Primary Open Angle Glaucoma

The cross-sectional association between nuclear cataract and myopia has been demonstrated in several population-based studies.[33, 39-40, 45, 49] This association is believed to reflect increasing nuclear sclerosis of the lens with age, leading to a myopic shift in refraction. In longitudinal cohort studies, the Barbados Eye Study also revealed an associated risk between myopia at baseline and incident nuclear cataract.[151] However, the Beaver Dam Eye Study showed no relationship between baseline refraction and 5-year incident nuclear cataract while eyes with severe nuclear sclerosis at baseline were more

likely to have a myopic change in refraction after 10 years, compared with a hyperopic change in eyes with only mild nuclear sclerosis.[149] Findings in this study that nuclear cataract was associated with myopia but not with AL provide evidence to support that nuclear sclerosis increases the refractive index and refractive power of the lens. This study also supports findings from most previous studies that cortical cataract is not related to refractive errors[150, 153, 227] but contradicts the Visual Impairment Project[152], where myopia was found to be associated with cortical cataract. The relationship between myopia and PSC is significant in our study. The Blue Mountains Eye Study found that early onset of myopia, defined as a history of wearing spectacles for distance before the age of 20 years may be a risk factor for development of PSC.[150] It is argued that the observed association between myopia and PSC have been confounded by difficulty in grading PSC in the presence of advanced nuclear cataract.[150] Our study now suggests that PSC is related not only to myopia but also longer AL, indicating that the refractive component of myopia is independently associated with PSC since AL is not associated with nuclear cataract. However, AL only accounted for 27.6% of the associations between refractive error and PSC in our study. Other ocular biometric components rather than AL (eg. lens thickness) may be the main biometric constituent that explains the observed association. Our study further demonstrated that only high myopia was significantly associated with nuclear cataract and PSC, indicating that there may be a threshold effect in the refractive association with age-related cataract.

The association of myopia, especially high myopia, with POAG has been confirmed by a systematic review and meta-analysis of 13 population-based studies.[157] Our study now provided additional insights into this association by showing that AL

explained 64.7% of the association between refractive error and POAG. Many hypotheses have attempted to explain the association between myopia or increased AL and glaucoma. One explanation is that increased cup-to-disc ratio found in myopic persons may increase risk for damage to ganglion cell axons.[228] In addition, alterations in connective tissue and sclera rigidity, as well as exaggerated shearing forces across the lamina cribrosa found in myopic eyes, may lead to the greater susceptibility of the optic nerve.[229] It is also possible that shearing forces exerted by scleral tension across the lamina cribrosa may be crucial to the mechanism of glaucomatous damage. Myopic eyes have higher scleral tension across the lamina than eyes with a shorter AL, even when IOP is the same. This difference becomes even more marked in eyes with thinner sclera. Similar connective tissue changes may also occur in glaucoma and myopia.[230] Finding of this study that AL was significantly associated with POAG largely explain the association between myopia and POAG and may support a theory involving connective tissue changes being associated with longer axial dimensions as a potential mechanism for POAG.

5.7 Strengths and Limitations

This study has several strengths. General strengths included its large and representative sample size, standard assessment of a wide range of risk factors, detailed classification of the first and the second generation immigrants, high frequency of gradable retinal photographs, and the use of standardized protocols. In addition, it provides the first population-based data on the patterns of refractive error and ocular biometry in Indians living in Singapore. These data may have relevance to many ethnic

Indian persons outside India. In addition, myopia was assessed by different definitions so that our study could be compared with other studies using different myopia definitions. Pattern of myopia and AL by migration status were assessed so that the impact of environmental exposures on myopia and AL could be teased out from genes. There are also several strengths of the meta-analysis. First, only population-based studies were included, which is likely to minimize the possibility of selection bias. Second, cross-sectional studies and cohort studies were analyzed separately so that heterogeneity due to study design was avoided. Third, we included only data on AMD in which retinal photographs were graded based on standardized classification system.

However, this study has a few limitations. It was a cross-sectional design so that we cannot separate cause from effect when examining risk factors. For example, myopic eyes were found to be more likely to have age-related cataract. It is possible the other way round, that is, eyes with cataract were more likely to develop myopia. Non-participants were older than the participants, so that the prevalence of myopia and other refractive errors could be over-estimated or under-estimated. Excluding an older cohort which contains relatively more AMD, cataract and POAG cases due to its older age distribution might also have caused an imprecision in the estimation of associations due to reduced number of cases. Non-cyclopegic refraction might have possibly overestimated the prevalence of myopia in our study. The IOL Master does not measure other important biometric parameters such as lens thickness and vitreous chamber depth. Baseline refraction was not available for first generation immigrants before they moved to Singapore. Longitudinal studies might be helpful to examine the association between change of refraction and life style related factors. There was no detailed evaluation of

early childhood factors of first generation immigrants from their home country compared with second generation immigrants in Singapore. This study was also limited by the use of interview language as proxy measures of acculturation, which may not fully reflect the complex acculturation processes. Finally, there may be inaccuracies in the diagnosis of eye diseases. For example, diagnosis of glaucoma in high myopic eyes may be difficult. It may also be difficult to grade the myopic fundus for macular RPE changes.[136] DR was graded based on two digital images per eye, which may have underestimated the prevalence of DR, but the underestimation may not be substantial.[231] Limitations of the meta-analysis should also be acknowledged. The application of formal meta-analysis to observational studies has been known to be controversial.[232] The different adjustment strategies among the original studies can influence the precision and magnitude of measure of the association between refractive error and AMD. Another limitation of the current meta-analysis is that only 3 cohort studies are available for the meta-analysis so that the result of meta-analysis for refractive error and incident AMD may be inconclusive. Finally, publication bias could be of concern because studies that report statistically significant results are more likely to get published than studies that report non-significant results, and this could have distorted the findings of our meta-analyses. However, Egger test and Begg's test indicated little evidence of publication bias in the meta-analysis.

5.8 Implications of the Study

This study provides population-based data on the prevalence and patterns of myopia and other refractive errors in this particular ethnic group in Singapore.

Comparisons of our study with data from India may provide important information on the interplay and effects of geographic variation, cultural diversity, environmental differences, and health care systems against a similar background of genetic susceptibility. Furthermore, this population structure provides us a unique opportunity to explore the variation of myopia prevalence between different generations of immigrants. The results of the study emphasize the importance of country-specific environmental impacts such as schooling system and educational pressure on the etiology of myopia. These data would have potential significance for myopia prevention in Singapore, especially for the second or higher generation immigrants.

In addition, currently available data suggest that important ethnic differences exist in the causes and patterns of myopia. The Singapore Indian Eye Study provides the population-based data on the patterns of refractive errors and AL in 3,400 ethnic Indian residents, aged 40–84 years, complementing other population-based eye studies in Singapore and India. Together with the Tanjong Pagar Survey on Singaporean Chinese, the Singapore Malay Eye Study on Singaporean Malays, these combined studies permit the collection of a comprehensive set of data on the distribution and inter-racial variation of refractive errors and ocular biometric parameters. It is also of public health importance across the three major ethnic groups in Asia in a single setting using the same methodology so that the burden of myopia and other refractive errors could be quantified.

Finally, this study provided the data on the refractive associations with major eye diseases. AMD, DR, age-related cataract and POAG are also common eye disorders observed in both clinics and general populations. The impact of myopia, an apparently benign ocular disease, may be larger than it seems. A greater understanding of the

potentially blinding risks of myopia by ophthalmologists and optometrists may facilitate the screening and management of myopia-related ocular complications. Many researches target modifiable risk factors of these eye disorders to relieve the future public health burden. Although myopia seems to have some protective effect on AMD and DR in our study, the association is still inconsistent among different studies and the magnitude of associations is low. In contrast, myopia as risk factor for age-related cataract and POAG is more consistently documented with relatively high magnitude of associations. Findings of our study re-emphasize the importance of the prevention of myopia, especially high myopia, in the general population. The result in this study may provide useful baseline information for future intervention studies and in planning eye care and rehabilitation services, especially for ethnic Indians. First, further well-designed cohort studies are warranted to confirm these associations of both myopia and AL with these major vision-threatening eye diseases. In addition, intervention studies such as health behaviour programs aiming to increase time spent outdoors should be conducted to prevent incident myopia and slow progression.

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Table 1. Prevalence of Myopia in Adults in Population-Based Studies

Author(year)	Country	N	Age	Definition	Refraction Method	Prevalence (%)	95% CI
Cheng (2003)	Taiwan	1361	65+	SE < -0.5 D	Subjective	19.4	16.7, 22.1
Sawada (2007)	Japan	3021	40+	SE <-0.5 D	Subjective	41.8	40.0, 43.6
Saw (2002)	Indonesia	1043	21+	SE <-0.5 D	Objective	48.1	45.0, 51.1
Gupta (2008)	Myanmar	1863	40+	SE < -1.0 D	Objective	42.7	40.4, 44.9
Xu (2005)	China	5324	40+	SE < -0.5 D	Subjective	22.9	21.7, 24.2
Krishnaiah (2009)	India	3642	40+	SE <-0.5 D	Subjective	34.6	33.1, 36.1
Raju (2004)	India	2508	40+	SE <-0.5 D	Subjective	31.0	Not available
Shah (2008)	Pakistan	14490	30+	SE < -0.5 D	Objective	36.5	35.7, 37.3
Bourne (2004)	Bangladesh	11189	30+	SE ⩽-0.5 D	Objective	23.8	23.8, 23.8
Wong (2000)	Singapore	1232	40+	SE < -0.5 D	Subjective	38.7	35.5, 42.1
Saw (2008)	Singapore	2974	40+	SE < -0.5 D	Subjective	26.2	26.0, 26.4
Pan (2011)	Singapore	2805	40+	SE < -0.5 D	Subjective	28.0	25.8, 30.2
Tarczy-Hornoch (2006)	USA	5396	40+	SE ≤ -1.0 D	Subjective	16.8	Not available
Katz (1997)	USA	5028	40+	SE < -0.5 D	Subjective	28.1 (white); 19.4 (black)	Not available

Vitale (2008)	USA	12010	20+	SE < -0.5 D	Objective	33.1	31.5, 34.7
Wu (1999)	USA	4709	40 to 84	SE < -0.5 D	Objective	21.9	20.6, 23.2
Wang (1994)	USA	4926	43 to 84	SE < -0.5 D	Objective	26.2	Not available
Wensor (1999)	Australia	4744	40 to 98	SE < -0.5 D	Subjective	17.0	15.8, 18.0
Attebo (1999)	Australia	3654	49 to 97	SE < -0.5 D	Subjective	15.0	Not available
Rahi (2011)	UK	2487	44 to 45	SE≤-0.75D	Objective	49.0	48.8, 50.8
Midelfart (2002)	Norway	3137	20 to 25	SE < -0.5D	Subjective	35.0	Not available
			40 to 45			30.3	Not available

CI = confidence interval

Table 2. Prevalence of Myopia in Children in Population-Based Studies

Author (Year)	Location	N	Age Range	Myopia Definition	Prevalence (%)	95%CI
Pokharel(2000)	Mechi Zone, Nepal	5067	5-15 years	≤-0.5D	1.2	Not available
Sapkota(2008)	Kathmandu, Nepal	4282	10-15 years	≤-0.5D	19.0	17.8, 20.2
Murthy(2002)	New Delhi, India	6447	5-15 years	≤-0.5D	7.4	5.0, 9.7
Dandona(2002)	Andhra Pradesh, India	4074	7-15 years	≤-0.5D	4.1	3.3, 4.9
Goh(2005)	Gombak district, Malaysia	4634	7-15 years	≤-0.5D	20.7	17.3, 24.1
Zhao(2000)	Shunyi District, Beijing, China	5884	5-15 years	≤-0.5D	21.6	Not available
He(2004)	Guangzhou, China	4364	5-15 years	≤-0.5D	38.1	36.3, 39.8
He(2007)	Yangxi,Guangdong province,China	2454	13 to 17 years	≤-0.5D	42.4	35.8, 49.0
Naidoo(2003)	South Africa	4890	5 to 15 years	≤-0.5D	4.0	3.3, 4.8
Maul(2000)	La Florida, Chile	5303	5 to 15 years	≤-0.5D	7.3	Not available
Saw(2005)	Singapore	1453	7 to 9 years	≤-0.5D	36.7	34.2, 39.2
Dirani(2009)	Singapore	2369	6-72 months	≤-0.5D	11.0	10.9, 11.2
Zadnik(1997)	USA	716	6-14.9 years	≤-0.75D	6 yrs: 2, 12 yrs: 20	Not available
Ip(2008)	Australia	2353	12 years	≤-0.5D	11.9	6.6, 17.2

Rudnicka(2010)	UK	1053	10 to 11 years	≤-0.5D	3.4	Not available
O'Donoghue(2010)	Northern Ireland	1053	6 to 7 years	≤-0.5D	2.8	1.3, 4.3
			12 to 13 years		17.7	13.2, 22.2
Logan(2011)	England	327	6 to 7 years	≤-0.5D	9.4	Not available
			12 to 13 years		29.4	Not available

CI = confidence interval

Table 3. Age-Specific Prevalence of Myopia in Children

Author (Year)	Study Design/ Population (N)	Response rate (%)	Cycloplegic refraction	Myopia Definition	Prevalence (95% confidence interval)
Dirani (2009)	Population-based cross-sectional study, N=2369 Chinese children	72.3%	Cycloplegic autorefraction	≤-0.5D	6-11.9 mths: 15.8% (10.6-22.2) 12-23.9 mths: 14.9% (11.7-18.5) 24-35.9 mths: 20.2% (16.5-24.2) 36-47.9 mths: 8.6% (6.3-11.3) 48-59.9 mths: 7.6% (5.5-10.1) 60-72 mths: 6.4% (4.5-8.8)
Saw (2005)	School-based cross-sectional study, N=1453 Chinese children	66.3%	Cycloplegic autorefraction	≤-0.5D	7 yrs: 29.0% (25.5-32.6) 8 yrs: 34.7% (30.4-39.0) 9 yrs: 53.1% (47.9-58.4)
Sapkota (2008)	Population-based N=4282 children from Kathmandu, Nepal	95.1%	Cycloplegic autorefraction	≤-0.5D	10 yrs: 10.9% (7.00-14.7) 11 yrs: 13.8% (10.5-17.2) 12 yrs: 16.5% (13.2-19.8) 13 yrs: 19.4% (16.7-22.1) 14 yrs: 23.3% (20.0-26.7) 15 yrs: 27.3% (22.6-32.0)
Murthy (2002)	Population-based N=6447	92.0%	Cycloplegic	≤-0.5D	5 yrs: 4.68% (2.54–6.83)

	children from New Delhi, India		retinoscopy		6 yrs: 5.87% (2.59–9.15) 7 yrs: 3.13% (1.17–5.08) 8 yrs: 5.67% (2.50–8.84) 9 yrs: 5.33% (2.61–8.05) 10 yrs: 6.95% (3.44–10.5) 11 yrs: 9.85% (5.91–13.8) 12 yrs: 9.66% (5.64–13.7) 13 yrs: 10.6% (6.02–15.2) 14 yrs: 10.2% (6.85–13.5) 15 yrs: 10.8% (6.71-14.8)
Dandona R (2002)	Population-based N=4074 children from Andhra Pradesh, India	92.3%	Cycloplegic retinoscopy	≤-0.5D	7 yrs: 2.80% (1.28–4.33) 8 yrs: 2.83% (1.50–4.16) 9 yrs: 3.90% (2.05–5.74) 10 yrs: 4.06% (2.09–6.03) 11 yrs: 2.73% (1.38–4.09) 12 yrs: 4.79% (2.91–6.97) 13 yrs: 5.43% (3.25–7.60)

					14 yrs: 6.74% (3.31–10.2) 15 yrs: 6.72% (4.31–9.12)
Goh (2005)	Population-based N=4634 children from Gombak district, Malaysia	32.8%	Cycloplegic autorefraction	≤-0.5D	7 yrs: 10.0% (6.8-13.1) 8 yrs: 14.0% (10.3-17.6) 9 yrs: 16.3% (11.7–20.9) 10 yrs: 16.2% (11.6–20.7) 11 yrs: 22.6% (17.0-28.2) 12 yrs: 24.8% (19.1-30.6) 13 yrs: 25.3% (19.5-31.1) 14 yrs: 32.5% (25.5-39.6) 15 yrs: 32.5% (25.5-39.6)
Zhao (2000)	Population-based N=5884 children from Shunyi District, Beijing, China	95.9%	Cycloplegic autorefraction	≤-0.5D	Males: 5 yrs: 0 15 yrs: 36.7% (29.9-43.4) Females: 5 yrs: 0 15 yrs: 55.0% (49.4-60.6)

He (2004)	Population-based cluster sampling, N=4364 children from Guangzhou, China	86.4%	Cycloplegic autorefraction	≤-0.5D	5 yrs: 5.7% (2.3–9.0) 6 yrs: 5.9% (2.6–9.2) 7 yrs: 7.7% (4.7–10.8) 8 yrs: 14.0% (10.4–17.6) 9 yrs: 25.9% (22.0–29.8) 10 yrs: 30.1% (24.4–35.8) 11 yrs: 41.7% (37.3–46.1) 12 yrs: 49.7% (44.7–54.6) 13 yrs: 57.4% (52.1–62.6) 14 yrs: 65.5% (62.4–68.5) 15 yrs: 78.4% (74.5–82.2)
He (2007)	Population-based N=2454 children from Yangxi, Guangdong province, China	97.6%	Cycloplegic autorefraction	≤-0.5D	13 yrs: 36.8% (29.2-44.3) 14 yrs: 38.8% (30.8-46.7) 15 yrs: 43.0% (34.5-51.4) 16 yrs: 46.8% (37.7-55.9) 17 yrs: 53.9% (39.6-68.1)
Giordano	Population-based cross-sectional	Not stated	Cycloplegic	≤-1.0D	African-American:

(2009)	study, N=1268 African-American and N=1030 White children		autorefraction		6-11 mths: 7.5% 12-23 mths: 10.5% 24-35 mths: 5.9% 36-47 mths: 6.2% 48-59 mths: 6.6% 60-72 mths: 7.4% Whites: 6-11 mths: 0% 12-23 mths: 2.3% 24-35 mths: 1.1% 36-47 mths: 0 % 48-59 mths: 1.5% 60-72 mths: 1.1%
Naidoo (2003)	Population-based N=4890 children from South Africa	87.3%	Cycloplegic autorefraction	≤-0.5D	5 yrs: 3.2% (0.6–5.7) 6 yrs: 4.6% (2.4–6.7) 7 yrs: 2.5% (0.8–4.2) 8 yrs: 2.9% (1.2–4.6)

					9 yrs: 3.1% (1.4–4.8) 10 yrs: 1.9% (0.6–3.2) 11 yrs: 4.4% (2.8–6.1) 12 yrs: 4.4% (2.2–6.6) 13 yrs: 3.4% (1.7–5.2) 14 yrs: 6.3% (3.6–8.9) 15 yrs: 9.6% (6.4–12.7)
Maul (2000)	Population-based N=5303 children from La Florida, Chile	75.8%	Cycloplegic autorefraction	≤-0.5D	Males: 5 yrs: 3.4% (1.87-5.00) 15 yrs: 19.4% (13.6-25.2) Females: 5 yrs: 3.4% (1.72-5.05) 15 yrs: 14.7% (10.1-19.2)
Solang (2008)	Population-based N=2441 children from Brazil	86.4%	Cycloplegic autorefraction	≤-0.5D	11 yrs: 5.4% (3.72-7.08) 12 yrs: 4.52% (2.53-6.65) 13 yrs: 5.83% (4.57-7.08) 14 yrs: 6.05% (4.2-7.89)

Table 4. More Outdoor Time as a Protective Factor for Myopia

Author (Year)	Study design/Population (N)	Cycloplegic	Age	Results (Odds ratio/p-values)
Rose (2008)	1765 six years old (year1) and 2367 twelve years old (year 7) children from the Sydney Myopia Study (SMS)	Yes	Year 1: 5.5-8.4 yrs Year 7: 11.1-14.4 yrs	Year 7 sample: Low near work and high outdoor; OR=1; High near work and low outdoor; OR= 2.6, CI (1.2-6.0), p=0.02. Higher levels of outdoor activity associated with hyperopic refraction and lower myopia prevalence in 12 years old children.
Dirani (2009)	Cross-sectional study, 1249 Singaporean teenagers	Yes	11-20 yrs old	Outdoor activity for all children: OR=0.90(0.84-0.96), p=0.004 Outdoor activity for Chinese children: OR=0.89(0.81-0.97), p=0.02
Jones (2007)	Longitudinal study 514 Orinda 8th grade children initially non-myopes	Yes	Examined at 3rd grade to 8th grade	i) Sports/Outdoor activity: OR=0.91(0.87-1.10), p<0.0001 Statistically significant interaction between number of myopic parents and sports/outdoor activity hours

			(8-13 yrs old)	per week.
Jacobsen (2008)	2-yr longitudinal study on 143 Caucasian Danish medical students from Copenhagen, Denmark	Yes	Mean age = 23 yrs	Studying (h/d): reg. coeff.=-0.063; 95% CI=-0.117—0.008, p=0.024 b) Physical activity (h/d): reg. coeff. = 0.175; 95% CI=0.035-0.315, p=0.015

Table 5. Near Work as a Risk Factor for Myopia

Author (Year)	Study design (N)	Cycloplegic	Age	Results (Odds ratio/p-values)
Saw (2002)	Cross-sectional study 1005 Singapore children	Yes	7-9 yrs	myopia (SE ≤-3D): Reading >2 books/week: OR=3.05(1.80-5.18) Read more than 2hrs/day: OR=1.50(0.87-2.55) Diopter-hrs>8: ORs=1.04(0.61-1.78) AL: books read per week: Reg. Coeff.=0.04mm
Lu (2009)	cross-sectional study, 998 school children from Xichang, China	Yes	13-17 yrs	myopia homework: OR=1.11(0.60-2.05); p=0.74 reading: OR=1.27(0.75-2.143); p=0.38 watching TV: OR=1.41(0.82-2.41); p=0.21
Saw (2002)	Cross-sectional study, 1453 Singapore Chinese children	Yes	7-9 yrs	1. myopia: Reading >2 books/wk (Reg. coeff.=0.17, 95%

				CI=0.07-0.26;p=0.001) 2. SE: Reading >2 books/wk (Reg. coeff.=-0.30, 95% CI=-0.48--0.12;p=0.001)
Tan (2000)	Cross-sectional study, 414 preschool children from Singapore	No	4-6 yrs	>3 hrs/week of near work classes outside vs. <3hrs/week: OR=1.61(1.02-2.53)
Ip (2008)	cross-sectional study, 2339 school children from Sydney	Yes	11.1-14.4 yrs (mean =12.7 yrs)	Myopia: a) Continuous reading>30 min: OR=1.5(1.05-2.1), p=0.02 b) Close reading distance<30 cm, OR=2.5(1.7-4.0), p<0.001
Mutti (2002)	Cross-sectional, 366 8^{th} grade children from OLSM	Yes	Mean:13.7 ±0.5 yrs	Diopter-hrs/wk: OR=1.020(1.008-1.032;p=0.0013
Lim (2009)	cross-sectional, 2788 Malay adults from Singapore	No	40-80 yrs	Myopia: Reading hours/week: Reg. coeff.=0.054, p=0.009

Wong (1993)	Cross-sectional study, adults in Hong Kong	408	No	15-39 yrs	Myopia: 3 or more hours reading/ writing per day vs. none: OR= 3.3(1.3-8.5)

Table 6. Parental Myopia as a Risk Factor for Myopia

Author (Year)	Study design/Population (N)	Cycloplegic	Age	Results (Odds ratio/p-values)
Ip (2007)	Cross-sectional study, 2353 Sydney children	Yes	12 yrs	1 myopic parent: ORs=2.3(1.8-2.9); 2 myopic parent: ORs=7.9(5.0-12.4); Mild myopia: ORs=6.4(1.5-27.8); Moderate myopia: ORs=10.2(2.6-40.1); High myopia: ORs=21.8(5.3-89.4)
Zadnik (1994)	Cohort study, 716 volunteer sample of school children	Yes	6-14 yrs	Children with 2 myopic parents developed myopia more often than (11%) than children with 1 myopic parent (5%) or children with no myopic parents (2%).
Jones (2007)	Longitudinal study 514 Orinda 8th grade children initially non-myopes	Yes	8-13 yrs	No. of myopic parent: a) 1 myopic parent: OR=2.08(1.07-4.05), p=0.03 b) 2. Myopic parents: OR=5.07(2.56-10.05), p<0.0001

Mutti (2002)	Cross-sectional, 366 8th grade children from OLSM (82% response rate)	Yes	13.7±0.5 yrs	1 myopic parent: OR=3.32(1.18-9.37;P=0.023) 2 myopic parents: OR=6.40(2.17-18.87;p=0.0008)
Zadnik (1997)	Cross –sectional and longitudinal study, N=716 children from OLSM	Yes	6.0-14.90 yrs	OR for one myopic parent: 1.32(0.6-2.91) OR for two myopic parents: 5.12(2.37-11.10)

Table 7.The Associations of Refractive Errors with Age-Related Macular Degeneration (Meta-Analysis Table)

Author (year)	Study	Sample Size	Age	AMD Assessment	Definition Hyperopia	Definition Myopia	OR(HR)CI Hyperopia	OR(HR)CI Myopia	OR(HR)CI Per D increase in SE	Adjusted Covariates
Cross-sectional Studies										
Wang et al (1998)	BMES	3654	49+	W	>1.0D	<-1.0D	1.11, 0.86-1.42	0.83, 0.60-1.15	1.05, 1.0-1.11	age, gender, family history and smoking
Ikram et al (2003)	Rotterdam	6209	55+	I	⩾0.5D	⩽-0.5D	1.29, 1.04 -1.61	0.91, 0.49-1.69	1.09, 1.04-1.13	age and gender
Lavanya et al (2010)	SiMES	3070	40+	W	>0.5D	<-0.5D	1.13, 1.11-1.15	0.74, 0.47-1.15	1.08, 1.01-1.16	age, gender, smoking, education, height, and systolic blood pressure
Jonas et al (2012)	CIEMS	4542	30+	W	>0.5D	<-0.5D	1.78, 1.11-2.84	0.91, 0.52-1.72	1.15, 1.06-1.25	age, corneal refractive power
Cheung et al (2011)	SPS	3172	40+	W	>0.5D	<-0.5D	1.07, 0.49-2.38	0.62, 0.30-1.27	-	age, race, chronic kidney disease
Unpublished	SINDI	3337	40+	W	>0.5D	<-0.5D	0.84, 0.56-1.25	0.45, 0.25-0.79	1.14, 1.02-1.28	age, gender, smoking, education, BMI, hypertension and cholesterol level
Cohort Studies										

Ikram et al (2003)	Rotterdam	4822	5-year follow up	I	≥0.5D	≤-0.5D	1.13, 0.91-1.41	0.75, 0.55-1.01	1.05, 1.01-1.10	age, gender and follow-up time
Wang et al (2004)	BMES	2335	5-year follow up	W	≥1.0D	≤-1.0D	0.84, 0.65-1.10	0.71, 0.40-1.25	1.10 0.98-1.15	age, sex, smoking and the correlation between the two eyes
Wong et al (2002)	BDES	3306	10-year follow up	W	≥1.0D	≤-1.0D	0.90, 0.7-1.1	1.0, 0.7-1.3	-	age

W = Wisconsin grading system; I = international AMD classification

OR=odds ratio; HR=hazards ratio; CI=95% confidence interval

BMES = Blue Mountain Eye Study; SiMES = Singapore Malay Eye Study; CIEMS = Central Indian Eye and Medical Study; SPS = Singapore Prospective Study; SINDI = Singapore Indian Eye Study; BDES = Beaver Dam Eye Study.

Table 8.The Association of Myopia with Diabetic Retinopathy

Study Name	Study Design	N	Age	Definition of myopia	Results
Wisconsin Epidemiologic Study of Diabetic Retinopathy	cohort study	Baseline and 4-year follow-up examinations were completed by 891 younger-onset and 987 older-onset diabetes	40+	SE<-2.0	Myopia was not associated with DR incidence or progression in univariate analyses, but showed a protective effect against progression to proliferative DR.
Visual Impairment Project	cross-sectional study	4744	40+	SE<-1.0D	Retinopathy was not significantly associated with age, ethnicity, body mass index, glaucoma, myopia or intake of alcohol, tobacco, or aspirin (all $p > 0.05$).
Singapore Malay Eye Study	cross-sectional study	629	40+	SE<-0.5D	Eyes with myopic SE were less likely to have any DR (OR, 0.90; 95% CI, 0.84–0.96; per diopter decrease), moderate DR (OR, 0.83; 95% CI, 0.73–0.93; per diopter decrease), and vision-threatening DR (OR, 0.77; 95% CI, 0.67–0.88; per diopter decrease).

Table 9. The Association of Myopia with Age-Related Cataract

Author (Year)	Study Design	N	Age	Definition of myopia	OR(HR) of cataract for myopia(95%CI)		
					Nuclear	Cortical	PSC
Lim (1999)	cross-sectional study	7308	49+	SE<-1.0D	1.3(1.0,1.6)	1.2(0.8,1.6)	2.5(1.6,4.7)
McCarty (1999)	cross-sectional study	5147	40+	SE<-1.0D	2.7(1.9,3.9)	1.8(1.3,2.4)	3.6(2.5,5.2)
Wong (2001)	cohort study	4470	43-84	SE<-1.0D	1.7(1.3,2.4)	0.9(0.6,1.2)	1.2(0.8, 2.0)
Leske (2002)	cohort study	2609	40-84	SE<-0.5D	2.8(2.0,4.0)	-	-
Wong (2003)	cross-sectional study	1029	40-79	-3D<SE<-0.5D	2.6(1.5,4.3)	1.1(0.7,1.8)	1.7(0.9,3.3)

OR=odds ratio; HR=hazards ratio; CI= confidence interval

Table 10. The Association of Myopia with Open Angle Glaucoma

Author （year）	Study ethnicity	Study design	Study population(n)	Definition	Result (Odds ratio/p-values)
Daubs and Crick (1981)	White	Case-control study	General ophthalmology patients(n=953)	OAG defined as eyes with open angles and characteristic VFD	OR of OAG 3.1(95% CI 1.6-5.8) for high myopia compared with hyperopia,adjusted for age,IOP,sex,family history,season,blood pressure,astigmatism,urinalysis and health
Ponte et al. (1994)	White	Case-control study	40 years and older(n=264)	Cases: IOP>24mmHg or history of glaucoma or VF suggestive of glaucoma Controls:IOP<20mmHg, CDR 0-0.2 and pink discs	OR of prevalent glaucoma for myopia (SE at least –1.5 D)was 5.56 (95% CI 1.85, 16.67), adjusted for diabetes,hypertension, steroid use and iris texture
Mitchell et al.(1999)	White	cross-sectional study	49 years and older (n=3654)	OAG defined as cup-disc ratio>0.7 or cup-disc asymmetry>0.3	OR of prevalent OAG was 3.3 (95% CI 1.7, 6.4) for moderate to high

					myopia (SE at least –3.0 D) and 2.3 (95% CI 1.3, 4.1)for patients with low myopia (SE < -3.0 D and >1.0 D),adjusted for sex, family history, diabetes, hypertension, migraine, steroid use and pseudoexfoliation
Leske et al. (2001)	African descent	Observational study of families of probands	230 probands and 1056 relatives (from 207 families)	OAG definition includes visual field criteria, optic disc criteria,ophthalmologic criteria.	OR of OAG for refractive error(<-0.5 diopters) is 2.82(95% CI 1.5，5.3）
Wong et al.(2003)	White	cross-sectional study	43-86 years (n=4670)	POAG defined as VFD compatible with glaucoma, IOP>22 mmHg,CDR 0.8 or more,history of glaucoma treatment	The age and gender adjusted ORs of prevalent POAG for myopia (SE at least –1.0 D) was 1.6 (95% CI 1.1, 2.3)
Ramakrishnan et al.(2003)	Indian	cross-sectional study	40 years and older (n=5150)	POAG was defined as angles open on gonioscopy and glaucomatous optic disc changes with matching visual field	OR of POAG for mild myopia was 2.9(95% CI 1.3,6.9);for moderate myopia was 2.1(95% CI 1.0,4.6);for

				defects	severe myopia was 3.9(95% CI 1.6,9.5)
Vijaya et al.（2005）	Indian	cross-sectional study	40 years and more (n=3934)	Cases of glaucoma were defined according to the ISGEO classification	OR of POAG for myopia was 0.68（95% CI 0.40,1.17). There was no associations between POAG and myopia
Suzuki et al.(2006)	Japanese	cross-sectional study	119 POAG patients and 2755 controls	Diagnosis of glaucoma was made based on optic disc appearance, perimetric results, and other ocular findings	OR of POAG for low myopia(SE>-1.0D and SE<-3.0D) was 1.85 (95% CI 1.03-3.31) and for 2.60 [95% CI, 1.56–4.35] for moderate to high myopia(SE>-3D).
Xu et al. (2007)	Chinese	cross-sectional study	40 years and older (n=5324)	Optic Disc Glaucoma with structural optic disc abnormalities Perimetric Glaucoma with optic disc abnormalities plus frequency doubling perimetry defects	In binary logistic regression analysis, presence of glaucoma was significantly associated with the myopic refractive error (P<0.001)
Casson et	Burmese	cross-sectional	40 years and	Primary open-angle glaucoma was	OR of POAG for myopia（SE<0.5D)

al.(2007)		study	more (n=2076)	diagnosed if the criteria for categories 1–3 were met and >90° of posterior TM was visible on static gonioscopy and no secondary cause for glaucoma was present.	was 2.82(95% CI 1.28,6.25) in univariate analysis and 2.74(95% CI 1.0,7.48) in multivariate analysis.
Czudowska et al (2010)	White	cohort study	55 years and more (n=3939)	glaucomatous visual field loss	RR of POAG for myopia（SE<0.5D) was 1.5(95% CI 1.1,2.0) in multivariate analysis.
Perera et al. (2010)	Malays	cross-sectional study	40 years and more (n= 3109)	optic disc abnormalities and glaucomatous visual field loss	OR of POAG for moderate myopia (SE<-4.0D) was 2.8(95% CI 1.1,7.4) in multivariate analysis.
Kuzin et al (2010)	Latinos	cross-sectional study	40 years and more (n=5927)	optic disc abnormalities and glaucomatous visual field loss	OR of OAG for myopia（SE<-1.0D) was 1.8(95% CI 1.2,2.8 in multivariate analysis.

SE = Spherical equivalent, D = Diopters, OR = Odds ratio, CI = Confidence interval, CDR = Cup–disc ratio, POAG = Primary open-angle glaucoma, AL= Axial length, VFD= Visual field defect, IOP = Intraocular pressure

Table 11. Characteristics of the Study Population by Gender and Age

	Total		Men		Women		P
	N	mean or %	N	mean or %	N	mean or %	
Age, years	3400	57.8	1706	58.1	1694	57.5	0.09
Age group, years							0.35
40-49yrs	896	26.4	435	25.5	461	27.2	
50-59yrs	1098	32.3	541	31.7	557	32.9	
60-69yrs	894	26.3	469	27.5	425	25.1	
70-84yrs	512	15.1	261	15.3	251	14.8	
Total	3400	100	1706	50.2	1694	49.8	

Data are presented as numbers and proportions or means and standard deviations.

**p*-value based on chi-square (categorical) and independent sample t test (continuous).

Table 12. Characteristics of the Study Population by Educational Level and Socioeconomic Status

	Total		Men		Women		P*
	N	%	N	%	N	%	
Educational level							<0.001
No formal education	317	9.3	65	3.8	252	14.9	
Primary education	1581	46.6	764	44.9	817	48.3	
high school	819	24.1	417	24.5	402	23.8	
polytechnic	358	10.5	236	13.9	122	7.2	
university	319	9.4	220	12.9	99	5.9	
Monthly Income (SGD)							<0.001
Less than 1000	1092	33.0	328	19.9	764	46.1	
1000 - 2000	539	16.3	170	10.3	369	22.2	
More than 2000	1209	36.5	802	48.5	407	24.5	
Retired	417	14.2	352	21.3	119	7.2	
Housing Status							0.13
1-2 room HDB flat	160	4.7	81	4.8	79	4.7	
3-4 room HDB flat	2021	59.6	985	57.9	1036	61.2	

5 room, executive HDB flat/private housing	1212	35.7	635	37.3	577	34.1	

Data are presented as numbers and proportions; *p-value based on chi-square test.

Table 13. Characteristics of the Study Population with and without Cataract Surgery

	With Cataract Surgery	Without Cataract Surgery	p-value
Age (years)	69.66 (8.06)	55.48 (8.75)	<0.001
Gender, Female	257 (51.2)	1388 (49.5)	0.48
Educational level			<0.001
No formal education	116 (23.2)	180 (6.4)	
Primary education	257 (51.5)	1282 (45.8)	
Secondary education	79 (15.8)	721 (25.7)	
Polytechnic	24 (4.8)	326 (11.6)	
University education	23 (4.6)	293 (10.5)	
Height (cm)	159.64 (9.38)	162.52 (9.13)	<0.001
Weight (kg)	64.57 (12.83)	69.55 (13.51)	<0.001

Data are presented as numbers and proportions or means and standard deviations.

*p-value based on chi-square (categorical) and independent sample t test (continuous).

Table 14. Comparison of Subjects Included in and Excluded from Refraction Data Analyses

	Include(N=2805)	Exclude(N=595)	P*
Age (years)			<0.001
40-49	874(31.2)	22(3.7)	
50-59	1025(36.5)	73(12.3)	
60-69	690(24.6)	204(34.3)	
70+	216(7.7)	296(49.7)	
Gender			0.39
Males	1417(50.5)	289(48.6)	
Females	1388(49.5)	306(51.4)	
Education			<0.001
No formal education	180(6.4)	137(23.1)	
Primary education	1282(45.8)	299(50.5)	
O/N levels	721(25.7)	98(16.6)	
Polytechnic/diploma/ITE/certificate	326(11.6)	32(5.4)	
University education	293(10.5)	26(4.4)	
Occupation			<0.001
Professionals/Office workers	511(18.2)	30(5.0)	
Service workers	139(5.0)	9(1.5)	
Production workers/Cleaners	44(1.6)	5(8.0)	
Homemaker	628(22.4)	202(33.9)	
Retired/Unemployed	376(13.4)	228(38.3)	
Others	1107(39.5)	121(20.3)	
Housing			
1-2 room HDB flat	109(3.9)	51(8.6)	<0.001
3-4 room HDB flat	1662(59.4)	359(60.3)	

5 room, executive HDB flat/private housing	1027(36.7)	185(31.1)	
Individual monthly income			<0.001
Less than S$1000	748(27.3)	344(59.8)	
S$1000-<S$2000	457(16.7)	82(14.3)	
S$2000-<S$3000	726(26.5)	84(14.6)	
More than S$3000	363(13.3)	36(6.3)	
Retired	442(16.2)	29(5.0)	

Data are number of subjects (percentage of total subjects)

* Based on Chi-squared test

Table 15. Prevalence of Myopia and High Myopia in the Singapore Indian Eye Study

		Myopia(SE<-0.5D)	Myopia(SE<-0.75D)	Myopia(SE<-1.0D)	High myopia (SE<-5.0 D)
	N	n (%, 95% CI)	n (%, 95% CI)	n (%, 95% CI)	n (%, 95% CI)
All persons					
Total	2805	733	612	533	108
Crude rate		26.1,24.5-27.8	21.8,20.3-23.3	19.0,17.6-20.5	3.9,3.1-4.6
Age-standard rate*		28.0,25.8-30.2	23.5,21.5-25.6	20.4,18.6-22.4	4.1,3.3-5.0
Men	1417	362	293	251	43
Crude rate		25.6,23.3-27.8	20.7,18.6-22.8	17.7,15.7-19.7	3.0,21.-3.9
Age-standard rate*		26.9,24.0-30.2	21.9,19.3-24.9	18.8,16.3-21.5	3.1,2.2-4.3
Women	1388	371	319	282	65
Crude rate		26.7,24.4-29.1	23.0,20.8-25.2	20.3,18.2-22.4	4.7,3.6-5.8
Age-standard rate*		28.5,25.4-31.9	24.6,21.7-27.8	21.7,19.0-24.7	4.7,3.6-6.3
P-value		0.476	0.139	0.079	0.023
Age group					
40–49 y	874	291	245	214	46
		33.3,30.2-36.4	28.0,25.1-31.0	24.5,21.6-27.3	5.3,3.8-6.8

50–59 y	1025	244	198	179	42
		23.8,21.2-26.4	19.3,16.9-21.7	17.5,15.1-19.8	4.1,2.9-5.3
60–69 y	690	140	119	98	16
		20.3,17.3-23.3	17.3,14.4-20.1	14.2,11.6-16.8	2.3,1.2-3.4
70–80 y	216	58	50	42	4
		26.9,20.9-32.8	23.2,17.5-28.8	19.4,14.1-24.8	1.9,0.004-3.7
P (trend)		<0.001	<0.001	<0.001	0.009

D = diopter; CI = confidence interval. *Age-standardized to the Singapore 2000 census population.

Table 16. Mean Spherical Equivalent by Age and Gender

	N	SE, diopters
All persons	2785	-0.05 ± 2.23
40-49 years	871	-0.70 ± 2.05
50-59 years	1019	-0.03 ± 2.29
60-69 years	682	0.59 ± 2.19
70-83 years	213	0.49 ± 2.06
p		<0.001
Men	1406	-0.02 ± 1.96
40-49 years	427	-0.54 ± 1.69
50-59 years	498	-0.12 ± 2.00
60-69 years	357	0.44 ± 2.04
70-83 years	124	0.36 ± 1.99
p		<0.001
Women	1379	-0.07 ± 2.48
40-49 years	444	-0.85 ± 2.34
50-59 years	521	-0.05 ± 2.54
60-69 years	325	0.76 ± 2.34
70-83 years	89	0.67 ± 2.15
p		<0.001

SE = Spherical Equivalent

Table 17. Nuclear Cataract-Specific Prevalence of Myopia within Each Age Group

		Myopia(SE<-0.5D)		
	N	**n**	**%**	**95%CI**
40–49 y				
NO < 2	526	177	33.7	29.6-37.7
NO 2-4	333	113	33.9	28.8-39.1
NO > 4	0	0	-	-
		P = 0.93		
50–59 y				
NO < 2	468	126	26.9	22.9-31.0
NO 2-4	525	114	21.7	18.2-25.3
NO > 4	7	3	42.7	-
		P = 0.11		
60–69 y				
NO < 2	186	24	12.9	8.0-17.8
NO 2-4	436	90	20.6	16.8-24.5
NO > 4	54	25	46.3	32.6-60.0
		P < 0.001		
70–83 y				
NO < 2	15	1	6.7	-
NO 2-4	124	22	17.7	10.9-24.6
NO > 4	72	33	45.8	34.5-57.6
		P < 0.001		

CI = confidence interval; NO = nuclear opacity score

Table 18. Age-Specific Prevalence of Myopia by Nuclear Opacity Score

		Myopia(SE<-0.5D)		
	N	**n**	**%**	**95%CI**
NO < 2				
40–49 y	526	177	33.7	29.6-37.7
50–59 y	468	126	26.9	22.9-31.0
60–69 y	186	24	12.9	8.0-17.8
70–80 y	15	1	6.7	-
		P<0.001		
NO 2-4				
40–49 y	333	113	33.9	28.8-39.1
50–59 y	525	114	21.7	18.2-25.3
60–69 y	436	90	20.6	16.8-24.5
70–80 y	124	22	17.7	10.9-24.6
		P<0.001		
NO > 4				
40–49 y	0	0	-	-
50–59 y	7	3	42.7	-
60–69 y	54	25	46.3	32.6-60.0
70–80 y	72	33	45.8	34.5-57.6
		P=0.31		

CI = confidence interval; NO = nuclear opacity score

Table 19. Prevalence of Astigmatism, Hyperopia, and Anisometropia in the Singapore Indian Eye Study

	N	Astigmatism (<-0.5cylinder)	Astigmatism (<-1.0cylinder)	Astigmatism (<-1.5cylinder)	Hyperopia (SE>+0.5D)	Hyperopia (SE>+2.0D)	N	Anisometropia (>+1.0D difference)
		n (%, 95% CI)	n (%, 95% CI)	n (%, 95% CI)	n (%, 95% CI)	n (%, 95% CI)		n (%, 95% CI)
All persons								
Total	2805	1585	595	282	1147	277	2762	272
Crude rate		56.5,54.7-58.3	21.2, 19.7-22.7	10.1, 8.9-11.2	40.9,39.1-42.7	9.9, 8.8-11.0		9.9,8.7-11.0
Age-standard rate*		54.9,52.0-57.9	21.3, 19.5-23.2	10.2, 8.9-11.5	35.9,33.7-38.3	8.6, 7.5-9.7		9.8,8.6-11.1
Men	1417	820	310	156	565	121	1391	147
Crude rate		57.9,55.3-60.4	21.9, 19.7-24.0	11.0, 9.4-12.6	39.9,37.3-42.4	8.5, 7.1-10.0		10.6,9.0-12.2
Age-standard rate*		57.1,52.9-61.6	23.0, 20.3-26.0	11.9, 9.9-14.1	35.9,32.7-39.4	7.8, 6.4-9.6		10.7,8.9-12.9
Women	1388	765	285	126	582	156	1371	125
Crude rate		55.1,52.5-57.7	20.5, 18.4-22.7	9.1, 7.6-10.6	41.9,39.3-44.5	11.2, 9.6-12.9		9.1,7.6-10.6
Age-standard rate*		55.6,51.1-60.4	22.0, 19.1-25.3	9.8, 7.9-12.2	38.2,34.7-42.0	11.1, 9.1-13.5		9.9,8.0-12.3
P		0.141	0.38	0.09	0.268	0.02		0.201
Age group								
40–49 y	874	372	122	52	154	10	865	54

		42.6,39.3-45.9	14.0, 11.7-16.3	6.0, 4.4-7.5	17.6,15.1-20.2	1.1, 0.4-1.9		6.2,4.6-7.9
50–59 y	1025	547	177	87	459	79	1010	75
		53.4,50.3-56.4	17.3, 15.0-19.6	8.5, 6.8-10.2	44.8,41.7-47.8	7.7, 6.1-9.3		7.4,5.8-9.1
60–69 y	690	487	192	86	419	140	678	98
		70.6,67.2-74.0	27.8, 24.5-31.2	12.5, 10.0-14.9	60.7,57.1-64.4	20.3, 17.3-23.3		14.5,11.8-17.1
70 -83y	216	179	104	57	115	48	209	45
		82.9,77.8-87.9	48.2, 41.4-54.9	26.4, 20.5-32.3	53.2,46.5-60.0	22.2, 16.6-27.8		21.5,15.9-27.2
P (trend)		<0.001	<0.001	<0.001	<0.001	<0.001		<0.001

D = diopter; CI = confidence interval. *Age-standardized to the Singapore 2000 census population.

Table 20. Mean Spherical Equivalent by Potential Risk Factors for Myopia

	N	Spherical Equivalent (diopters)		
		Mean	Standard Deviation	P
Occupation				<0.001
Professional/office	508	-0.51	2.34	
Service workers	138	0.17	2.08	
Production workers	44	-0.28	2.32	
Homemakers	625	0.19	2.39	
Retired/unemployed	372	0.23	2.07	
Others	1098	-0.08	2.12	
Individual income per month				<0.001
Less than S$1000	745	0.11	2.50	
S$1001-S$2000	450	0.34	1.70	
More than S$2000	1084	-0.07	2.20	
Retired	437	-0.66	2.27	
Education level				<0.001
No formal education	178	0.41	2.33	
Primary education	1274	0.29	2.04	
Secondary education	715	-0.17	2.15	
Polytechnic	324	-0.67	2.53	
University	291	-0.79	2.48	
Hours for Read and Write perday				<0.001
0	347	0.22	2.41	
0.1-1	1084	0.20	1.96	
1-2	931	-0.16	2.17	
2-3	131	-0.45	2.33	
moren than 3	292	-0.75	2.85	
Hours for using computer perday				<0.001

0	1591	0.31	2.07	
0.1-1	319	-0.32	2.12	
1-2	396	-0.24	2.17	
2-3	112	-1.12	2.80	
moren than 3	367	-0.82	2.50	
Height				<0.001
First quartile	709	0.30	2.19	
Second quartile	685	-0.19	2.58	
Third quartile	698	0.00	1.95	
Fourth quartile	688	-0.32	2.14	
Weight				0.004
First quartile	696	0.03	2.29	
Second quartile	702	0.02	2.32	
Third quartile	694	0.06	2.09	
Fourth quartile	687	-0.32	2.22	
BMI				0.95
First quartile	695	-0.06	2.24	
Second quartile	694	-0.04	2.28	
Third quartile	695	-0.01	2.24	
Fourth quartile	694	-0.08	2.18	
Pulse Pressure				<0.001
First quartile	700	-0.38	2.44	
Second quartile	706	-0.15	2.16	
Third quartile	700	0.05	2.20	
Fourth quartile	679	0.29	2.06	
HDL-cholesterol, mmol/L				0.36
First quartile	700	-0.01	1.98	
Second quartile	666	-0.17	2.27	
Third quartile	648	0.01	2.21	

Fourth quartile	671	0.01	2.42	
Smoking Status				0.21
Never Smoked	2038	-0.09	2.33	
Current Smokers	426	0.07	1.74	
Past Smokers	315	0.09	2.20	
Alcohol intake				0.91
Never	2416	-0.05	2.25	
Yes	364	-0.02	2.14	
Diabetes				0.19
No	1887	-0.08	2.23	
Yes	810	0.04	2.22	
Hypertension				0.11
No	1755	-0.12	2.22	
Yes	1030	0.07	2.25	
Any Cataract				<0.001
No	1823	0.24	2.40	
Yes	901	-0.22	2.14	
Any Astigmatism				<0.001
No	1220	0.29	2.16	
Yes	1585	-0.34	2.47	

Table 21. Multiple Logistic Regression Models* of the Risk Factors Associated with Refractive Errors

	Myopia			Astigmatism			Hyperopia			Anisometropia		
	Beta	**Multivariable-OR (95% CI)**	**P**	**Beta**	**Multivariable-OR (95% CI)**	**P**	**Beta**	**Multivariable-OR (95% CI)**	**P**	**Beta**	**Multivariable-OR (95% CI)**	**P**
Age (years)†	-0.001	0.9994 (0.9991-0.9997)	0.001	0.07	1.07(1.05-1.10)	<0.001	0.11	1.12(1.09-1.14)	<0.001	0.04	1.04(1.00-1.08)	0.04
Gender, Female	0.77	2.17(1.30-3.61)	0.003	-0.18	0.84(0.61-1.15)	0.27	0.06	1.07(0.77-1.48)	0.7	0.08	1.08(0.63-1.86)	0.78
Education	—	—	—									
No formal education				0	1.00(referent)		0	1.00(referent)		0	1.00(referent)	
Primary education				-0.42	0.65(0.29-1.50)	0.32	0.31	1.36(0.62-2.98)	0.44	-0.13	0.88(0.27-2.87)	0.84
Secondary education				-0.46	0.63(0.27-1.48)	0.29	0.03	1.03(0.46-2.32)	0.94	0.03	1.03(0.30-3.56)	0.97
Polytechnic				-0.72	0.49(0.20-1.22)	0.13	-0.08	0.92(0.38-2.25)	0.86	0.56	1.76(0.47-6.59)	0.40
University education				-0.55	0.58(0.23-1.48)	0.26	-0.23	0.80(0.32-1.99)	0.63	0.99	2.69(0.72-10.04)	0.14
Time for reading and writing per day(hours)	0.17	1.19(1.06-1.33)	0.003	—	—	—	—	—	—	—	—	—
Height (cm)	0.04	1.04(1.01-1.07)	0.005	—	—	—	—	—	—	—	—	—
Any cataract	-1.55	0.21(0.05-0.91)	0.05	0.15	1.16(0.78-1.74)	0.46	—	—	—	0.42	1.53(0.81-2.89)	0.20
Astigmatism	1.28	3.59(2.52-5.12)	<0.001	—	—	—	-0.67	0.51(0.37-0.72)	<0.001	0.90	2.47(1.36-4.48)	0.003
Myopia	—	—	—	1.28	3.59(2.50-5.15)	<0.001	—	—	—	—	—	—
Diabete mellitus	—	—	—	0.46	1.58(1.10-2.27)	0.01	—	—	—	—	—	—
Cataract*age-squared			0.03									

OR = odds ratio; CI = confidence interval; *Models were run with sampling weights applied for each strata; †Age-square for the model for myopia to examine the U-shape distribution.

Table 22. Prevalence of Myopia (spherical equivalent < -0.5D) Stratified by Lens Opacity Classification System III Grade in Andhra Pradesh Eye Disease Study and Singapore Indian Eye Study

Nuclear cataract (LOCS III grade)	APEDS			SINDI		
	N	Myopia Prevalence		N	Myopia Prevalence	
		n	%(95%CI)		n	%(95%CI)
Grade < 2	1700	229	13.5(11.9-15.1)	1195	328	27.5(24.9-30.0)
Grade 2 to 3.5	1717	998	58.1(55.8-60.4)	1264	301	23.8(21.5-26.2)
Grade > 3.5	158	94	59.5(51.8-67.1)	287	99	34.5(30.0-40.0)

APEDS = Andhra Pradesh Eye Disease Study

SINDI = Singapore Indian Eye Study

LOCS = Lens Opacity Classification System

CI = confidence interval

Table 23. Means of Ocular Biometric Parameters by Age and Gender in the Singapore Indian Eye Study

	N	AL , mm	ACD , mm	CR , mm	AL/CR
All persons	2785	23.45 ± 1.10	3.15 ± 0.36	7.61 ± 0.26	3.08 ± 0.13
Men	1406	23.68 ± 1.06	3.19 ± 0.36	7.68 ± 0.26	3.09 ± 0.12
Women	1379	23.23 ± 1.10	3.10 ± 0.35	7.55 ± 0.25	3.08 ± 0.14
P-value		<0.001	<0.001	<0.001	0.37
All persons					
40-49 years	871	23.53 ± 1.08	3.24 ± 0.35	7.62 ± 0.26	3.09 ± 0.14
50-59 years	1019	23.49 ± 1.15	3.18 ± 0.35	7.61 ± 0.26	3.09 ± 0.14
60-69 years	682	23.35 ± 1.14	3.05 ± 0.35	7.60 ± 0.26	3.07 ± 0.13
70-83 years	213	23.25 ± 0.78	2.92 ± 0.36	7.61 ± 0.26	3.06 ± 0.10
p (trend)		<0.001	<0.001	0.22	0.11
Men					
40-49 years	427	23.71 ± 1.01	3.27 ± 0.36	7.68 ± 0.26	3.09 ± 0.13
50-59 years	498	23.72 ± 1.07	3.23 ± 0.34	7.68 ± 0.25	3.09 ± 0.12
60-69 years	357	23.68 ± 1.19	3.11 ± 0.36	7.68 ± 0.26	3.08 ± 0.13
70-83 years	124	23.36 ± 0.70	2.97 ± 0.34	7.64 ± 0.27	3.06 ± 0.09
p (trend)		0.02	<0.001	0.44	0.09
Women					
40-49 years	444	23.36 ± 1.12	3.20 ± 0.33	7.57 ± 0.26	3.09 ± 0.15
50-59 years	521	23.28 ± 1.18	3.13 ± 0.34	7.55 ± 0.25	3.09 ± 0.15
60-69 years	325	22.99 ± 0.96	2.98 ± 0.33	7.51 ± 0.24	3.06 ± 0.13
70-83 years	89	23.09 ± 1.25	2.85 ± 0.32	7.58 ± 0.25	3.05 ± 0.11
p (trend)		<0.001	<0.001	0.06	0.12

AL = axial length; ACD = anterior chamber depth; CR = corneal radius of curvature

Table 24. Median and Distribution of Ocular Biometric Parameters in the Singapore Indian Eye Study

	Median	Range	IQR	Kurtosis	Skewness	K-S test
AL						
all	23.31	13.62	1.22	6.1	1.43	<0.001
men	23.52	11.54	1.19	8.72	1.17	<0.001
women	23.06	11.98	1.13	4.74	1.4	<0.001
40-49y	23.39	10.21	1.28	3.57	1.23	<0.001
50-59y	23.32	13.59	1.31	6.07	1.42	<0.001
60-69y	23.23	11.9	1.24	8.72	1.75	<0.001
70-84y	23.18	5.83	0.91	1.30	0.05	0.68
ACD						
all	3.15	2.56	0.48	0	-0.01	0.44
men	3.2	2.35	0.46	0.03	-0.06	0.62
women	3.11	2.56	0.48	0	0.01	0.74
40-49y	3.24	2.34	0.48	0.04	-0.03	0.95
50-59y	3.18	2.34	0.46	0.14	-0.06	0.78
60-69y	3.06	2.31	0.49	0.09	0.08	0.7
70-84y	2.89	1.99	0.48	-0.06	0.16	0.63
CR						
all	7.61	2.73	0.34	0.63	0.02	0.1

men	7.67	2.63	0.35	1.36	-0.16	0.58
women	7.54	1.81	0.31	0.32	0.16	0.37
40-49y	7.62	2.73	0.33	1.72	-0.1	0.25
50-59y	7.6	1.71	0.33	0.28	0.13	0.58
60-69y	7.61	1.55	0.37	-0.09	-0.01	0.97
70-84y	7.63	1.45	0.34	0.13	0.10	0.77

AL = axial length; ACD = anterior chamber depth; CR = corneal radius of curvature

IQR = inter quartile range

Table 25. Mean Ocular Biometric Parameters by Potential Determinants

	N	AL(mm)	ACD(mm)	CR(mm)
Occupation				
Professional/office	508	23.71, 1.19	3.24, 0.35	7.65, 0.25
Service workers	138	23.25, 1.00	3.10, 0.37	7.55, 0.26
Production workers	44	23.28, 0.84	3.17, 0.31	7.57, 0.26
Homemakers	625	23.16, 1.06	3.07, 0.35	7.54, 0.24
Retired/unemployed	372	23.43, 1.05	3.08, 0.37	7.62, 0.28
Others	1098	23.54, 1.08	3.18, 0.35	7.64, 0.27
P		<0.001	<0.001	<0.001
Individual income per month				
Less than S$1000	745	23.26, 1.05	3.06, 0.35	7.56, 0.25
S$1001-S$2000	450	23.18, 0.95	3.12, 0.37	7.58, 0.26
More than S$2000	1084	23.51, 1.08	3.18, 0.35	7.63, 0.26
Retired	437	23.87, 1.87	3.23, 0.36	7.68, 0.27
P		<0.001	<0.001	<0.001
Education level				
No formal education	178	23.03, 0.96	3.00, 0.37	7.54, 0.27
Primary education	1274	23.28, 1.00	3.13, 0.35	7.59, 0.25
Secondary education	715	23.52, 1.06	3.17, 0.37	7.62, 0.27

Polytechnic	324	23.80, 1.14	3.21, 0.33	7.67, 0.25
University	291	23.88, 1.31	3.21, 0.39	7.67, 0.26
P		<0.001	<0.001	<0.001
Hours for Read and Write per day				
0	347	23.25, 1.27	3.08, 0.37	7.58, 0.26
0.1-1	1084	23.29, 0.97	3.12, 0.35	7.60, 0.26
1-2	931	23.57, 1.08	3.17, 0.35	7.63, 0.27
2-3	131	23.76, 1.19	3.22, 0.37	7.65, 0.26
more than 3	292	23.79, 1.25	3.23, 0.36	7.65, 0.25
P		<0.001	<0.001	0.001
Hours for using computer per day				
0	1591	23.27, 1.01	3.10, 0.36	7.59, 0.25
0.1-1	319	23.53, 1.03	3.20, 0.36	7.62, 0.26
1-2	396	23.59, 1.13	3.17, 0.37	7.64, 0.26
2-3	112	24.02, 1.35	3.27, 0.33	7.70, 0.27
more than 3	367	23.87, 1.22	3.24, 0.35	7.66, 0.28
P		<0.001	<0.001	<0.001
Height				
First quartile	709	22.99, 1.01	3.05, 0.34	7.51, 0.24
Second quartile	685	23.38, 1.13	3.13, 0.37	7.59, 0.26

Third quartile	698	23.53, 0.97	3.17, 0.35	7.63, 0.25
Fourth quartile	688	23.92, 1.10	3.24, 0.36	7.73, 0.26
P		<0.001	<0.001	<0.001
Weight				
First quartile	696	23.22, 1.09	3.06, 0.34	7.56, 0.25
Second quartile	702	23.38, 1.08	3.13, 0.37	7.59, 0.27
Third quartile	694	23.46, 1.07	3.17, 0.35	7.63, 0.25
Fourth quartile	687	23.76, 1.11	3.22, 0.36	7.67, 0.27
P		<0.001	<0.001	<0.001
BMI				
First quartile	695	23.44, 1.08	3.12, 0.35	7.61, 0.26
Second quartile	694	23.48, 1.15	3.15, 0.36	7.63, 0.26
Third quartile	695	23.48, 1.10	3.16, 0.36	7.63, 0.26
Fourth quartile	694	23.42, 1.09	3.15, 0.36	7.59, 0.26
P		0.63	0.26	0.005
Pulse Pressure				
First quartile	700	23.58, 1.18	3.22, 0.37	7.63, 0.26
Second quartile	706	23.53, 1.08	3.17, 0.33	7.63, 0.27
Third quartile	700	23.43, 1.13	3.14, 0.36	7.61, 0.25
Fourth quartile	679	23.26, 0.99	3.06, 0.36	7.58, 0.26

P		<0.001	<0.001	0.002
HDL-cholesterol, mmol/L				
First quartile	700	23.59, 1.05	3.19, 0.37	7.65, 0.25
Second quartile	666	23.49, 1.04	3.18, 0.34	7.61, 0.27
Third quartile	648	23.37, 1.12	3.12, 0.36	7.61, 0.26
Fourth quartile	671	23.34, 1.20	3.10, 0.37	7.59, 0.26
P		<0.001	<0.001	<0.001
Smoking Status				
Never Smoked	2038	23.41, 1.14	3.14, 0.36	7.59, 0.26
Current Smokers	426	23.48, 0.89	3.19, 0.35	7.64, 0.26
Past Smokers	315	23.66, 0.96	3.15, 0.37	7.70, 0.25
P		0.001	0.01	<0.001
Alcohol intake				
Never	2416	23.42, 1.10	3.14, 0.36	7.60, 0.26
Yes	364	23.63, 1.02	3.19, 0.36	7.67, 0.25
P		0.001	0.008	<0.001
Diabetes				
No	1887	23.49, 1.11	3.16, 0.36	7.62, 0.27
Yes	810	23.35, 1.04	3.11, 0.36	7.60, 0.25
P		0.003	0.001	0.10

Hypertension				
No	1755	23.48, 1.12	3.16, 0.36	7.62, 0.26
Yes	1030	23.40, 1.07	3.13, 0.36	7.60, 0.26
P		0.23	0.06	0.11
Nuclear Cataract				
No	1823	23.53, 1.09	3.20, 0.34	7.63, 0.26
Yes	901	23.33, 1.07	3.08, 0.37	7.58, 0.27
P		<0.001	<0.001	<0.001

AL = axial length; ACD = anterior chamber depth; CR = corneal radius of curvature

Values are means and standard deviations

Table 26. Multivariate Analysis on the Determinants of Ocular Biometric Parameters

	AL (mm)			ACD (mm)			CR (mm)		
	Beta	**95% CI**	**P**	**Beta**	**95% CI**	**P**	**Beta**	**95% CI**	**P**
Age (years)	-0.001	-0.007,0.004	0.61	-0.011	-0.018,-0.004	<0.001	0.001	-0.004,0.006	0.67
Female	0.098	-0.018,0.215	0.10	-0.028	-0.061,0.005	0.16	-0.009	-0.125,0.107	0.88
Reading hours per day	0.064	0.034,0.094	<0.001	0.013	0.004,0.022	0.02	-		-
Education level				-		-	-		-
No formal education	0		-						
Primary education	0.065	-0.104,0.235	0.45						
Secondary education	0.166	-0.020,0.351	0.08						
Polytechnic	0.350	0.142,0.558	0.001						
University	0.408	0.192,0.624	<0.001						
Height (cm)	0.034	0.0034,0.028	<0.001	0.004	0.0008,0.007	<0.001	0.009	0.002,0.015	0.008
Diabetes	-0.078	-0.164,0.007	0.07	-		-	-		-
Nuclear Cataract	0.001	-0.142,0.143	0.99	-		-			

AL = axial length; ACD = anterior chamber depth; CR = corneal radius of curvature

Beta = regression coefficient

CI = confidence interval

Table 27. Correlation of Ocular Biometric Parameters and Spherical Equivalent by Refractive Status

	ALL	Hyperopia	Emmetropia	Myopia
AL vs. CR	0.48*	0.75*	0.72*	0.43
AL vs. SE	-0.65*	-0.28*	-0.15*	-0.68
SE vs. CR	0.08	-0.03	-0.03	0.07
SE vs. AL/CR	-0.78*	-0.36*	-0.17*	-0.77
ACD vs. SE	-0.31*	-0.17*	-0.03	-0.17
ACD vs. AL	0.47*	0.39*	0.36*	0.43*

*indicate $P < 0.05$

AL = axial length; ACD = anterior chamber depth; CR = corneal radius of curvature; SE = spherical equivalent

Table 28. Multivariable Linear Regression Models for Spherical Equivalent Refraction, by Axial Length, Corneal Curvature, Axial Length / Corneal Curvature ratio and Nuclear Opacity (LOCS III) Stratified by Age

	Unstandardized Regression Coefficient	Standardized Regression Coefficient	p value
All persons			
Model 1			
AL	-1.88	-0.91	<0.001
CR	4.39	0.53	<0.001
NO (LOCS III)	-0.009	-0.005	0.73
Model 2			
AL/CR	-13.5	-0.8	<0.001
NO (LOCS III)	0.02	0.01	0.47
40-49 years			
Model 1			
AL	-1.81	-0.95	<0.001
CR	4.2	0.54	<0.001
NO (LOCS III)	0.18	0.005	0.76
Model 2			
AL/CR	-12.8	-0.84	<0.001
NO (LOCS III)	-0.03	-0.01	0.57

	50-59 years		
	Model 1		
AL	-1.94	-0.97	<0.001
CR	4.62	0.52	<0.001
NO (LOCS III)	-0.44	-0.04	0.02
	Model 2		
AL/CR	-14.1	-0.84	<0.001
NO (LOCS III)	0.004	0.002	0.93
	60-69 years		
	Model 1		
AL	-1.81	-0.87	<0.001
CR	4.36	0.52	<0.001
NO (LOCS III)	-0.8	-0.14	<0.001
AL/CR	-13.1	-0.74	<0.001
NO (LOCS III)	-0.28	-0.15	<0.001
	70-83 years		
	Model 1		
AL	-1.5	-0.57	<0.001
CR	4.42	0.57	<0.001
NO (LOCS III)	-1.12	-0.27	<0.001

Model 2			
AL/CR	-11.5	-0.55	<0.001
NO (LOCS III)	-0.54	-0.31	<0.001

In each regression model, noncycloplegic refraction is the dependent variable. In model 1, AL, CR and NO (LOCS III) are the independent variable. In model 2, AL/CR ratio and NO (LOCS III) are the independent variable. AL = axial length; ACD = anterior chamber depth; CR = corneal radius of curvature.

Table 29. Mean Axial Length and Spherical Equivalent in Adults 40-49 Years of Age in Different Population-Based Studies

Study	Ethnicity	Measurement of AL	Mean SE (Diopters)		Mean AL (mm)	
			Men	Women	Men	Women
The Los Angeles Latino Eye Study[18]	Latinos	ultrasound	-0.3	-0.3	23.7	23.2
The Mongolian Study[20]	Mongolians	ultrasound	0.1	-0.3	23.4	23.0
The Tanjong Pagar Survey[17]	Chinese	ultrasound	-1.4	-2.1	23.8	23.4
The Meiktila Eye Study[19]	Burmese	ultrasound	-0.4	-0.6	23.2	22.6
The Singapore Malay Eye Study[118]	Malay	IOL Master	-0.6	-1.1	23.8	23.6
The Singapore Indian Eye Study	Indians	IOL Master	-0.5	-0.8	23.7	23.2

AL = axial length; SE = spherical equivalent

Table 30. Characteristics of the First and Second (or Higher) Generation Indian Immigrants Living in Singapore

	First Generation (N=1,109)	Second (or Higher) Generation (N=1,877)	P value*
Age	59.1 (10.1)	54.2 (7.8)	<0.001
Female gender	525 (47.3)	959 (51.1)	0.05
Height (cm)	161.9 (9.4)	162.7 (9.1)	0.03
BMI (kg/m^2)	25.8 (4.2)	26.5 (4.9)	<0.001
Education (no formal education)	109 (9.8)	107 (5.7)	<0.001
Monthly income (<SGD$1000)	394 (36.5)	439 (24.0)	<0.001
Housing type (1-2 room flat)	60 (5.4)	63 (3.4)	0.002
Time spent reading and writing per day (h)	1.8 (1.4)	1.9 (1.5)	0.05
Lens Nuclear Opacity (LOCS III)	2.4 (1.4)	2.0 (1.1)	<0.001

BMI=body mass index; SGD=Singapore dollar; LOCS= Lens Opacities Classification System; Data presented are means (standard deviations) or number (%), as appropriate for variable. *P value, comparing the differences between the 2 generation immigrants, based on chi-square test or t test, as appropriate.

Table 31. Prevalence of Myopia, High Myopia, Mean Spherical Equivalent, Axial Length, Anterior Chamber Depth and Corneal Radius of Curvature between Different Generation Immigrants

	1st Generation Immigrants	2nd (or higher) Generation	P value
Prevalence of myopia (SE<-0.5D) (%)			
Age and gender standardized	23.4; 20.6,26.1	30.2, 28.1,33.0	
Prevalence of high myopia (SE<-5.0D) (%)			
Age and gender standardized	2.5; 1.3,3.7	4.8; 4.0,5.7	
Spherical Equivalent (Diopter)			
Age and gender adjusted	-0.05; -0.19, 0.10	-0.37; -0.49,-0.24	<0.001
Multivariate adjusted*	0.01; -0.12, 0.15	-0.13; -0.23,-0.02	0.11
Axial Length (mm)			
Age and gender adjusted	23.40; 23.33, 23.46	23.59; 23.53, 23.65	<0.001
Multivariate adjusted*	23.37; 23.31, 23.44	23.50; 23.45, 23.55	0.004
Anterior Chamber Depth (mm)			
Age and gender adjusted	3.15; 3.12,3.17	3.15; 3.14,3.17	0.64
Multivariate adjusted*	3.15; 3.12,3.17	3.15; 3.13,3.17	0.53
Corneal Radius of Curvature (mm)			
Age and gender adjusted	7.61;7.59,7.63	7.61;7.60,7.62	0.75
Multivariate adjusted*	7.61;7.60,7.63	7.61;7.60,7.63	0.94

Data are presented as value and 95% confidence interval; * adjusted for age, gender, educational level, height and lens nuclear opacity.

Table 32. Effect of Potential Explanatory Factors on the Excess Prevalence of Myopia and High Myopia in Second (or higher) Generation Immigrants Compared with First Generation Immigrants

Model	Myopia (SE<-0.5D)				High Myopia (SE<-5.0D)			
	OR*	**95% CI**	**P value**	**% Reduction Excess Prevalence†**	**OR***	**95% CI**	**P value**	**% Reduction Excess Prevalence†**
1	1.40	1.14,1.71	0.001	Reference	2.54	1.56,4.15	<0.001	Reference
2	1.37	1.13,1.67	0.002	7.5	2.57	1.58,4.19	<0.001	-1.0
3	1.25	1.05,1.49	0.02	37.5	1.70	1.08,2.66	0.02	33.1
4	1.42	1.16,1.73	0.001	-5.0	2.46	1.51,4.01	<0.001	3.1
5	1.25	1.04,1.50	0.01	37.5	1.70	1.09,2.66	0.02	33.1

*Odds ratio (95% confidence interval) of myopia (SE<-0.5D) and high myopia (SE<-5.0D), comparing the 1st generation immigrants and the new immigrants, adjusted for the following variables:

Model 1: age and gender; Model 2: age, gender and height; Model 3: age, gender and educational level; Model 4: age, gender and lens nuclear opacity score; Model 5: age, gender, height, educational level and lens nuclear opacity score.

†% reduction in excess prevalence defined by the formula: (Ra-Rb)/(Ra-1), where Ra is the OR of myopia in 2nd (or higher) generation immigrants vs the 1st generation immigrants adjusted for age and gender only (Model 1, reference) and Rb is the OR after additional adjustment for the variables in Models 2 to 5.

Table 33. Prevalence of Myopia, Mean Axial Length and Spherical Equivalent by Age at Migration among the First Generation Immigrants

Migration Age	<12 years		12-15.9 years		16-20.9 years		>21 years	
	% or mean	95%CI	% or mean	95%CI	% or mean	95%CI	% or mean	95%CI
Myopia	26.8	21.7,31.9	15.8	7.4,24.2	22.9	16.8,28.9	22.9	19.2, 22.6
SE	-0.01	-0.25,0.24	0.70	0.24, 1.16	0.51	0.24,0.79	0.08	-0.09,0.25
AL	23.51	23.39,23.63	23.18	22.98,23.38	23.10	22.97,23.23	23.36	23.27,23.46

AL = axial length; SE = spherical equivalent; CI = confidence interval

Table 34. Associations of Age at Migration with the Prevalence of Myopia (Spherical Equivalent <-0.5D), Spherical Equivalent and Axial Length in First Generation Immigrants

Migration Age	SE(diopter)			AL(mm)			Myopia		
	Beta	**95%CI**	**P value**	**Beta**	**95%CI**	**P value**	**Odds Ratio**	**95%CI**	**P value**
Model 1*									
per year earlier	-0.014	-0.02,-0.01	<0.001	0.009	0.003,0.014	0.002	1.02	1.00,1.03	0.03
Model 2*									
⩾21years		**Reference**			**Reference**			**Reference**	
16 to 20.9 years	0.08	-0.11,0.27	0.41	-0.06	-0.24,0.13	0.56	1.23	0.77,1.96	0.39
12 to 15.9 years	0.12	-0.15,0.38	0.38	0.02	-0.24,0.28	0.87	0.91	0.45,1.85	0.79
<12 years	-0.33	-0.49,-0.17	<0.001	0.27	0.11,0.43	0.001	1.58	1.07,2.35	0.02

Beta = regression coefficient; AL = axial length; SE = spherical equivalent

Table 35. Associations of Age at Migration with the Prevalence of Myopia (Spherical Equivalent <-0.5D), Spherical Equivalent and Axial Length for the Whole Study Participants

Migration Age	Spherical Equivalent (D)			Axial Length (mm)			Myopia (SE<-0.5D)		
	Beta	**95%CI**	**P value**	**Beta**	**95%CI**	**P value**	**Odds Ratio**	**95%CI**	**P value**
Model 1*									
per year earlier	-0.02	-0.03,-0.01	<0.001	0.01	0.007,0.014	<0.001	1.02	1.01,1.03	<0.001
Model 2*									
First Generation (Born outside Singapore): Migration Age≥21years (Educated outside Singapore)		**Reference**			**Reference**			**Reference**	
First Generation (Born outside Singapore): Migration Age: < 21 years (Educated in Singapore)	-0.40	-0.69,-0.11	0.006	0.19	0.06,0.33	0.005	1.85	1.32,2.59	<0.001
Second (or higher) generation (Born in Singapore)	-0.55	-0.80,-0.31	<0.001	0.30	0.19,0.42	<0.001	1.99	1.49,2.65	<0.001

Table 36. Associations of Interview Language with Myopia (Spherical Equivalent <-0.5D), Spherical Equivalent and Axial Length in Migrant Indians Living in Singapore

	Interview language	Myopia (SE<-0.5D)			SE (Diopters)			AL (mm)		
		Odds Ratio	95%CI	P value	Beta	95%CI	P value	Beta	95%CI	P value
1st generation immigrants	English	1.48	1.01,2.17	0.04	-0.33	-0.63,-0.03	0.03	0.17	0.01,0.32	0.03
	Non-English		Reference			Reference			Reference	
2nd generation immigrants	English	0.92	0.69,1.25	0.61	0.10	-0.02,0.22	0.10	0.05	-0.07,0.17	0.42
	Non-English		Reference			Reference			Reference	

SE = spherical equivalent; AL = axial length; Beta = regression coefficient; CI = Confidence interval

* Multivariate models adjusted for age, gender, educational level and height

Table 37. Risk Factors for Myopia among the First and Second (higher) Generation Immigrants

	1st generation			2nd or higher generation		
	OR	**95%CI**	**P**	**OR**	**95%CI**	**P**
Age (years)	0.975	0.955,0.996	0.02	0.959	0.942,0.976	<0.001
Gender						
Male		Reference			Reference	
Female	1.20	0.77,1.88	0.43	2.04	1.45,2.85	<0.001
Height (cm)	1.02	1.00,1.05	0.07	1.03	1.01,1.05	0.004
Educational level						
No formal education		Reference			Reference	
Primary education	0.92	0.52,1.63	0.77	0.90	0.51,1.58	0.71
Secondary education	1.02	0.52,2.01	0.95	1.90	1.05,3.43	0.03
Polytechnic	1.65	0.77,3.55	0.20	2.89	1.53,5.43	0.001
University	3.02	1.41,6.49	0.005	6.04	2.87,12.07	<0.001
Lens Opcaity (LOCS III)	1.51	1.30,1.75	P<0.001	1.19	1.06,1.34	0.003
Language for interview						
Non-English		Reference			Reference	
English	1.46	1.00,2.17	0.05	1.06	0.78,1.43	0.73
Age at migration	0.983	0.969,0.997	0.02			

OR = odds ratio; CI =confidence interval

Table 38. Characteristics of Included Participants with and without any Age-Related Macular Degeneration

	Any Age-Related Macular Degeneration		P*
	Present	**Absent**	
Age (years)	65.3(10.4)	57.1(9.8)	<0.001
Sex，Female	89(44.1)	1574(50.2)	0.09
Income, <S$1000	85(43.6)	974(31.8)	0.001
Education, elementary or less	124(62.0)	1733(55.3)	0.16
HbA1c, mmol/L	6.6(1.3)	6.4(1.4)	0.06
Diabetes	79(40.1)	1026(33.7)	0.07
Hypertension	152(75.2)	1729(55.3)	<0.001
Total cholesterol, mmol/L	4.9(1.1)	5.2(1.1)	<0.001
Triglycerides, mmol/L	1.9(1.3)	2.0(1.2)	0.83
Body mass index, kg/m2	26.2(4.8)	26.2(4.8)	0.87
Never smoked	142(70.3)	2307(73.7)	0.008

Data are expressed as the mean (SD) or *n* (%), as appropriate for the variable.

*Difference in characteristics by AMD status, based on chi-square test or t-test, as appropriate

Table 39. Associations of Refractive Error and Axial Length with Age-Related Macular Degeneration or Specific Age-Related Macular Degeneration Signs

	N	Any AMD					Any Drusen					Any Pigmentary Abnormality				
		n	%	OR*	95%CI	p	n	%	OR*	95%CI	p	n	%	OR*	95%CI	p
Refractive error																
Myopia(SE < -0.5D)	1428	23	1.6	0.45	0.25,0.79	0.005	68	4.8	0.61	0.43,0.86	0.004	61	4.3	0.5	0.35,0.70	<0.001
Emmetropia(-0.5D≤SE≤0.5D)	1870	61	3.3		Reference		135	7.2		Reference		139	7.4		Reference	
Hyperopia(SE > 0.5D)	2315	92	4	0.84	0.56,1.25	0.38	254	11.0	1.06	0.81,1.37	0.68	182	7.9	0.88	0.67,1.16	0.37
SE (per diopter increase)	5613	176	3.1	1.14	1.02，1.28	0.02	457	8.1	1.13	1.06,1.21	<0.001	382	6.8	1.14	1.07,1.23	<0.001
AL (per mm increase)	6460	264	4.1	0.76	0.65,0.89	0.001	616	9.5	0.77	0.69, 0.86	<0.001	496	7.7	0.79	0.70.0.89	<0.001

* Adjusted for age, gender, smoking, education, body mass index, hypertension and total cholesterol level in generalized estimating equation models.

OR = Odds Ratio; CI = Confidence Interval; SE = Spherical Equivalent; AL = Axial Length

Table 40. Associations of Severity of Myopia with AMD or Specific AMD Signs

	N	Age-Related Macular Degeneration†					Drusen					Retinal Pigmentary Abnormality				
		n	%	OR*	95%CI	P	n	%	OR*	95%CI	P	n	%	OR*	95%CI	P
Refractive error																
High Myopia	143	1	0.7	0.24	0.03,1.81	0.17	4	3.0	0.46	0.17,1.27	0.13	3	2.2	0.29	0.09,0.91	0.03
Moderate Myopia	307	6	2.0	0.55	0.20,1.51	0.24	6	2.0	0.26	0.10,0.69	0.01	10	3.3	0.32	0.14,0.72	0.006
Mild Myopia	987	16	1.6	0.44	0.23,0.83	0.01	58	5.9	0.75	0.53,1.06	0.10	48	4.9	0.58	0.40,0.84	0.004
Emmetropia	1870	61	3.3		Ref		135	7.2		Ref		139	7.4		Ref	
Hyperopia	2315	92	4.0	0.84	0.56,1.25	0.38	254	11.0	1.06	0.81,1.37	0.68	182	7.9	0.88	0.67,1.16	0.37

* Adjusted for age, gender, smoking, education, body mass index, hypertension and total cholesterol level in generalized estimating equation models. †Age-related macular degeneration refers to either early or late AMD.

Emmetropia: -0.5D≤SE≤0.5D; Hyperopia: SE > 0.5D; High Myopia: SE<-6.0D; Moderate Myopia: -6.0D≤SE<-3.0D; Mild Myopia: -3.0D≤SE<-0.5D

OR = Odds Ratio; CI = Confidence Interval; D = Diopter; AMD = Age-Related Macular Degeneration

Table 41. Characteristics of Included Diabetic Participants with and without any Retinopathy

	Any Diabetic Retinopathy		P*
	Present	Absent	
Age (years)	61.3(9.4)	60.6(10.2)	0.29
Sex，Female	181(44.9)	346(49.8)	0.12
Income, <S$1000	182(46.1)	260(38.2)	0.06
Education, elementary or less	267(66.4)	417(60.0)	0.11
HbA1c, mmol/L	8.0(1.6)	7.5(1.8)	<0.001
Hypertension	223(55.3)	307(44.2)	<0.001
Total cholesterol, mmol/L	4.9(1.1)	4.8(1.3)	0.21
Triglycerides, mmol/L	2.1(1.2)	2.1(1.3)	0.73
Body mass index, kg/m2	26.3(5.0)	27.1(4.8)	0.004
Never smoked	288(71.5)	516(74.2)	0.32

Data are expressed as the mean (SD) or *n* (%), as appropriate for the variable.

*Difference in characteristics by DR status, based on chi-square test or t-test, as appropriate

Table 42. Associations of Refractive Error and Axial Length with Diabetic Retinopathy or Vision-threatening Diabetic Retinopathy

	N	Any Diabetic Retinopathy					Any Vision-threatening Diabetic Retinopathy				
		n	%	OR*	95%CI	p	n	%	OR*	95%CI	p
Refractive error											
Myopia(SE < -0.5D)	411	89	21.7	0.68	0.46,0.98	0.04	19	4.6	0.96	0.46,2.01	0.79
Emmetropia(-0.5D≤SE≤0.5D)	512	155	30.3		Reference		31	6.1		Reference	
Hyperopia(SE > 0.5D)	756	222	29.4	1.13	0.82,1.56	0.44	58	7.7	1.58	0.87,2.87	0.13
SE (per diopter increase)	1679	466	27.8	1.14	1.05,1.23	0.001	108	6.4	1.15	0.94,1.39	0.18
AL (per mm increase)	1701	474	27.9	0.73	0.63,0.86	<0.001	109	6.4	0.73	0.49,1.09	0.13

*Adjusted for age, gender, education, body mass index, hemoglobin A1c, hypertension and total cholesterol level in generalized estimating equation models.

OR = Odds Ratio; CI = Confidence Interval; SE = Spherical Equivalent; AL = Axial Length

Table 43. Associations of Severity of Myopia with Diabetic Retinopathy or Vision-threatening Diabetic Retinopathy

	N	Diabetic Retinopathy					Vision-threatening Diabetic Retinopathy				
		n	%	OR*	95%CI	P	n	%	OR*	95%CI	P
Refractive error											
High Myopia	43	6	14.0	0.39	0.12,1.24	0.11	3	7.0	1.36	0.25,7.43	0.72
Moderate Myopia	80	18	22.5	0.57	0.27,1.20	0.14	3	3.8	0.82	0.20,3.32	0.78
Mild Myopia	288	65	22.6	0.75	0.50,1.13	0.17	13	4.5	0.93	0.40,2.14	0.86
Emmetropia	512	155	30.3		Reference		31	6.1		Reference	
Hyperopia	756	222	29.4	1.13	0.82,1.56	0.44	58	7.7	1.58	0.87,2.87	0.13

*Adjusted for age, gender, education, body mass index, hemoglobin A1c, hypertension and total cholesterol level in generalized estimating equation models.

Emmetropia: -0.5D≤SE≤0.5D; Hyperopia: SE > 0.5D; High Myopia: SE<-6.0D; Moderate Myopia: -6.0D≤SE<-3.0D; Mild Myopia: -3.0D≤SE<-0.5D

OR = Odds Ratio; CI = Confidence Interval; SE = Spherical Equivalent; D = Diopter

Table 44. Characteristics of Included Participants with and without any Age-Related Cataract

	Any Age-Related Cataract		P*
	Present	Absent	
Age (years)	64.5(9.3)	52.4(6.9)	<0.001
Sex，Female	737(50.2)	915(49.2)	0.56
Income, <S$1000	694(48.3)	373(20.7)	<0.001
Education, elementary or less	1001(68.4)	855(46.0)	<0.001
HbA1c, mmol/L	6.6(1.4)	6.3(1.3)	<0.001
Diabetes	657(46.1)	431(24.0)	<0.001
Hypertension	714(48.6)	627(33.7)	<0.001
Total cholesterol, mmol/L	5.0(1.2)	5.3(1.0)	<0.001
Triglycerides, mmol/L	1.9(1.1)	2.0(1.2)	0.37
Body mass index, kg/m2	25.8(4.8)	26.5(4.7)	<0.001
Never smoked	1064(72.5)	1376(74.0)	0.32

Data are expressed as the mean (SD) or *n* (%), as appropriate for the variable.

*Difference in characteristics by cataract status, based on chi-square test or t-test, as appropriate

Table 45. Associations of Refractive Error and Axial Length with Age-Related Cataract

	N	Nuclear Cataract					Cortical Cataract					Posterior Subcapsular Cataract				
		n	**%**	**OR**	**95% CI**	**P**	**n**	**%**	**OR**	**95% CI**	**P**	**n**	**%**	**OR**	**95% CI**	**P**
Refractive error																
Myopia(SE < -0.5D)	1498	199	13.4	1.57	1.13, 2.20	0.007	339	22.9	1.06	0.84,1.33	0.64	72	4.9	1.73	1.10,2.72	0.02
Emmetropia(-0.5D≤SE≤0.5D)	1909	150	8		Reference		380	20.4		Reference		45	2.4		Reference	
Hyperopia(SE > 0.5D)	2361	271	11.8	0.63	0.46,0.87	0.005	767	33.5	1.08	0.88,1.32	0.45	56	2.4	0.63	0.40,1.02	0.06
SE (per diopter increase)	5768	620	11	0.85	0.80,0.89	<0.001	1486	26.4	0.99	0.95,1.03	0.56	173	3.1	0.83	0.77,0.88	<0.001
AL (per mm increase)	6656	707	11	1.02	0.88,1.19	0.77	1610	24.2	0.96	0.87,1.05	0.39	240	4	1.29	1.07,1.55	0.007

*Adjusted for age, gender, education, diabetes and smoking in generalized estimating equation models.

OR = Odds Ratio; CI = Confidence Interval; SE = Spherical Equivalent; AL = Axial Length

Table 46. Associations of Severity of Myopia with Age-Related Cataract

	N	Nuclear Cataract					Cortical Cataract					Posterior Subcapsular Cataract				
		n	%	OR*	95% CI	P	n	%	OR*	95% CI	P	n	%	OR*	95% CI	P
Refractive error																
High Myopia	145	18	12.4	3.42	1.67,7.00	<0.001	34	23.4	0.65	0.37,1.14	0.13	14	9.7	5.90	2.68,12.97	<0.001
Moderate Myopia	324	37	11.4	1.38	0.78,2.45	0.27	71	21.9	0.87	0.58,1.30	0.49	15	4.6	1.72	0.83,3.57	0.14
Mild Myopia	1029	144	14.0	1.46	1.02,2.07	0.04	234	22.7	1.01	0.79,1.29	0.94	43	4.2	1.39	0.87,2.22	0.17
Emmetropia	1909	150	8.0		Reference		380	20.4		Reference		45	2.4		Reference	
Hyperopia	2361	271	11.8	0.63	0.46,0.87	0.005	767	33.5	1.08	0.88,1.32	0.45	56	2.4	0.63	0.40,1.02	0.06

*Adjusted for age, gender, education, diabetes and smoking in generalized estimating equation models.

Emmetropia: -0.5D≤SE≤0.5D; Hyperopia: SE > 0.5D; High Myopia: SE<-6.0D; Moderate Myopia: -6.0D≤SE<-3.0D; Mild Myopia: -3.0D≤SE<-0.5D

OR = Odds Ratio; CI = Confidence Interval; SE = Spherical Equivalent; D = Diopter

Table 47. Characteristics of Participants With and Without any Primary Open Angle Glaucoma

	Any Primary Open Angle Glaucoma		P *
	Present	Absent	
Age, y	60.7(10.9)	57.7(10.1)	0.05
Female	18(39.1)	1676(50.0)	0.14
Education, no formal education	9(19.6)	308(9.2)	0.29
Hypertension	20(43.5)	1348(40.2)	0.65
Diabetes mellitus	18(40.9)	1092(33.6)	0.31
SBP (mmHg)	138.2(18.3)	135.4(19.6)	0.33
HbA1c (%)	6.4(1.1)	6.4(1.4)	0.86
Total cholesterol level, mean (SD), mg/dL	4.9(1.0)	5.2(1.1)	0.08
Triglyceride level, mean (SD), mg/dL	2.2(1.5)	2.0(1.2)	0.11
Height (mm)	162.7(11.1)	162.0(9.3)	0.60
BMI	25.9(4.2)	26.2(4.8)	0.68
Never smoked	38(84.4)	2452(73.2)	0.24

Data are expressed as the mean (SD) or *n* (%), as appropriate for the variable.

*Difference in characteristics by POAG status, based on chi-square test or t-test, as appropriate

Table 48. Age and Gender adjusted Mean Spherical Equivalent, Axial Length, Corneal Curvature, Anterior Chamber Depth, Central Corneal Thickness and Intraocular Pressure in Eyes With and Without Any Primary Open Angle Glaucoma

	Eyes with POAG (n=55)		Eyes without POAG (n=5934)		P Value
	mean	95%CI	mean	95%CI	
Spherical equivalent, D	-1.12	-2.15;-0.10	-0.03	-0.10,0.05	0.04
Axial length, mm	23.98	23.51;24.46	23.42	23.38;23.45	0.02
Anterior chamber depth, mm	3.23	3.12;3.34	3.13	3.12;3.14	0.07
Corneal curvature, mm	7.63	7.56;7.69	7.61	7.60;7.62	0.70
Central corneal thickness, µm	533.9	525.3;542.6	541.4	540.2;542.6	0.10
Intraocular pressure, mm/Hg	17.5	16.1;19.0	15.8	15.7;15.9	0.02

POAG = Primary Open Angle Glaucoma; CI = confidence interval

Table 49. Age and Gender Adjusted Associations of Central Corneal Thickness and Intraocular Pressure with Myopia or Axial Length

	Intraocular Pressure			Central Corneal Thickness		
	Beta	**95%CI**	**p**	**Beta**	**95%CI**	**p**
myopia (SE<-0.5D)	0.28	0.06;0.50	0.01	-1.35	-4.00;1.29	0.32
myopia (SE<-1.0D)	0.32	0.07;0.57	0.01	-1.35	-4.29;1.58	0.37
myopia (SE<-2.0D)	0.24	-0.08;0.57	0.15	-0.94	-4.58;2.70	0.61
SE (per D increase)	-0.05	-0.10;-0.01	0.02	0.26	-0.28;0.79	0.35
AL(per mm increase)	-0.04	-0.13;0.06	0.45	1.68	0.52;2.85	0.005

Beta = Regression coefficient; CI = Confidence Interval; SE = Spherical Equivalent; AL = Axial Length

Table 50. Associations of Refractive Error and Axial Length with Primary Open Angle Glaucoma

	N	Primary Open Angle Glaucoma				
		n	%	OR*	95%CI	P
Refractive error						
Myopia(SE < -0.5D)	1403	17	1.2	1.20	0.50,2.89	0.68
Emmetropia(-0.5D≤SE≤0.5D)	1826	19	1.0		Reference	
Hyperopia(SE > 0.5D)	2249	18	0.8	0.64	0.30,1.36	0.24
SE (per diopter increase)	5478	54	1.0	0.84	0.75,0.93	0.001
AL (per mm increase)	6167	61	1.0	1.43	1.13,1.80	0.003

*Adjusted for age, gender, education, hemoglobin A1c, total cholesterol level, intraocular pressure and central corneal thickness in generalized estimating equation models.

OR = Odds Ratio; CI = Confidence Interval; SE = Spherical Equivalent; AL = Axial Length

Table 51. Associations of Severity of Myopia with Primary Open Angle Glaucoma

	N	Primary Open Angle Glaucoma				
		n	%	OR*	95%CI	P
Refractive error						
High Myopia	132	7	5.3	6.97	2.20,22.16	<0.001
Moderate Myopia	287	3	1.0	1.10	0.23,5.36	0.90
Mild Myopia	984	7	0.7	0.62	0.27,1.45	0.27
Emmetropia	1826	19	1.0		Reference	
Hyperopia	2249	18	0.8	0.64	0.30,1.36	0.24

*Adjusted for age, gender, education, hemoglobin A1c, total cholesterol level, intraocular pressure and central corneal thickness in generalized estimating equation models.

Emmetropia: -0.5D≤SE≤0.5D; Hyperopia: SE > 0.5D; High Myopia: SE<-6.0D; Moderate Myopia: -6.0D≤SE<-3.0D; Mild Myopia: -3.0D≤SE<-0.5D

OR = Odds Ratio; CI = Confidence Interval; SE = Spherical Equivalent; D = Diopter

Table 52. Association of Spherical Equivalent and Axial Length with Primary Open Angle Glaucoma in High Intraocular Pressure and Normal Intraocular Pressure Groups

	Axial Length		Spherical Equivalent	
	OR	**95%CI**	**OR**	**95%CI**
IOP≤21mmHg	1.37	1.07,1.77	0.86	0.76,0.96
IOP>21mmHg	1.53	1.19,1.97	0.64	0.42,0.98

OR = odds ratio; CI = confidence interval; IOP = Intraocular Pressure

Table 53. Combined Effect of Myopia and Intraocular Pressure on Primary Open Angle Glaucoma

	SE<-1D		SE<-2D		SE<-3D	
	OR	**95%CI**	**OR**	**95%CI**	**OR**	**95%CI**
IOP≤21mmHg and non-myopia	Reference		Reference		Reference	
IOP≤21mmHg and myopia	1.8	0.7, 4.4	2.5	1.0, 6.3	3.5	1.3, 9.1
IOP>21mmHg and non-myopia	7.0	1.9, 25.5	11.0	3.8, 31.8	10.7	3.7, 30.9
IOP>21mmHg and myopia	39.3	10.0, 154.7	35.3	4.6, 273.1	43.3	5.49, 341.1

SE = Spherical Equivalent; IOP = intraocular pressure

Table 54. Difference in Mean Refraction between Eyes with and without Ocular Disease, Adjusted for Axial Length

Models	Mean Refraction (D)				
	Present	Absent	Difference in Means	P†	Relative Proportion (%)
Age-Related Macular Degeneration					
(reference)*	0.28	-0.14	0.42	0.02	Reference
(reference+AL)	-0.02	-0.12	0.10	0.55	76.2
Diabetic Retinopathy					
(reference)*	0.27	-0.20	0.47	<0.001	Reference
(reference+AL)	0.11	0	0.11	0.32	76.6
Nuclear Cataract					
(reference)*	-1.08	-0.06	-1.02	<0.001	Reference
(reference+AL)	-1.08	-0.08	-1.00	<0.001	2.0
Posterior Subcapsular Cataract					
(reference)*	-1.47	-0.13	-1.34	<0.001	Reference
(reference+AL)	-1.13	-0.16	-0.97	<0.001	27.6
Primary Open Angle Glaucoma					
(reference)*	-1.31	-0.15	-1.16	0.04	Reference

(reference+AL)	-0.50	-0.09	-0.41	0.17	64.7

AL = axial length

*For age-related macular degeneration, reference model was adjusted for age, gender, smoking, education, body mass index, hypertension and total cholesterol level. For diabetic retinopathy, reference model was adjusted for age, gender, education, body mass index, hemoglobin A1c, hypertension and cholesterol level. For nuclear cataract or posterior subcapsular cataract, reference model was adjusted for age, gender, education, diabetes and smoking. For primary open angle glaucoma, reference model was adjusted for age, gender, education, hemoglobin A1c, total cholesterol level, intraocular pressure and central corneal thickness.

†Probability represents the difference in mean refraction between eyes with and without a specific eye disease, adjusted for other covariates.

Relative proportion defined as (difference in mean refraction in reference model - difference in mean refraction in models with AL added /difference in mean refraction in reference model).

Table 55. Pooled Estimates on the Associations of Refractive Error and Age-related Macular Degeneration

	Number of studies available	Pooled OR(HR)	95%CI	P value
Cross-sectional studies				
Hyperopia versus Emmetropia	6	1.16	1.04-1.29	0.01
Myopia versus Emmetropia	6	0.75	0.61-0.92	0.005
Per diopter increase in SE	5	1.09	1.06-1.12	<0.001
Per mm increase in AL	3	0.76	0.69-0.85	<0.001
Cohort studies				
Hyperopia versus Emmetropia	3	0.96	0.80-1.14	0.63
Myopia versus Emmetropia	3	0.84	0.68-1.04	0.10
Per diopter increase in SE	2	1.06	1.02-1.10	0.002
Per mm increase in AL	0	-	-	-

OR = odds ratio; HR = hazards ratio; CI = confidence interval

Figure 1. Formation of Myopia and Correction by Spectacles

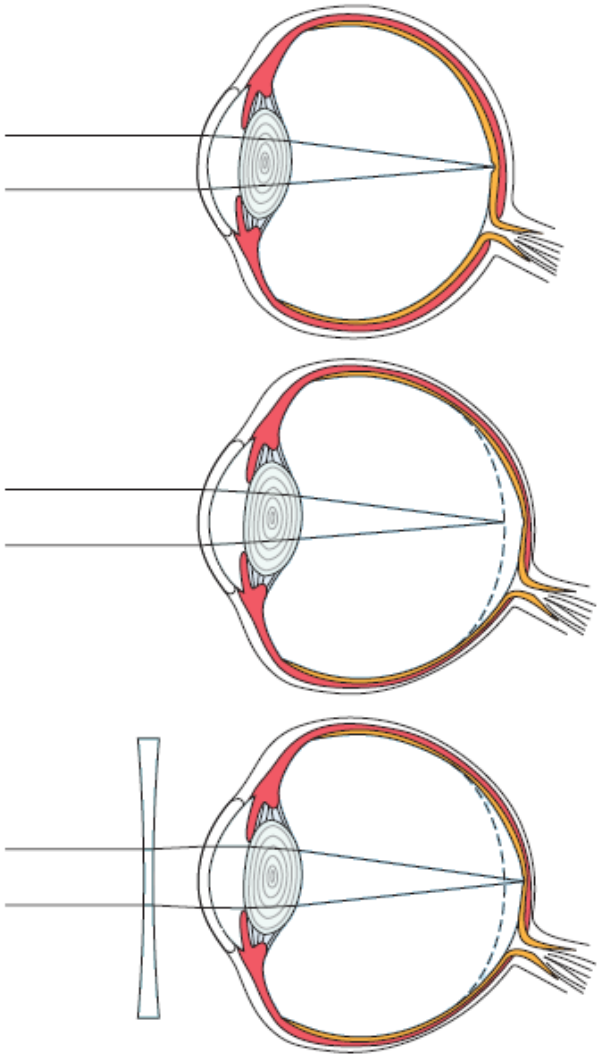


Figure 2. Urban versus Rural Differences in Myopia Prevalence in the Refractive Error Study in Children

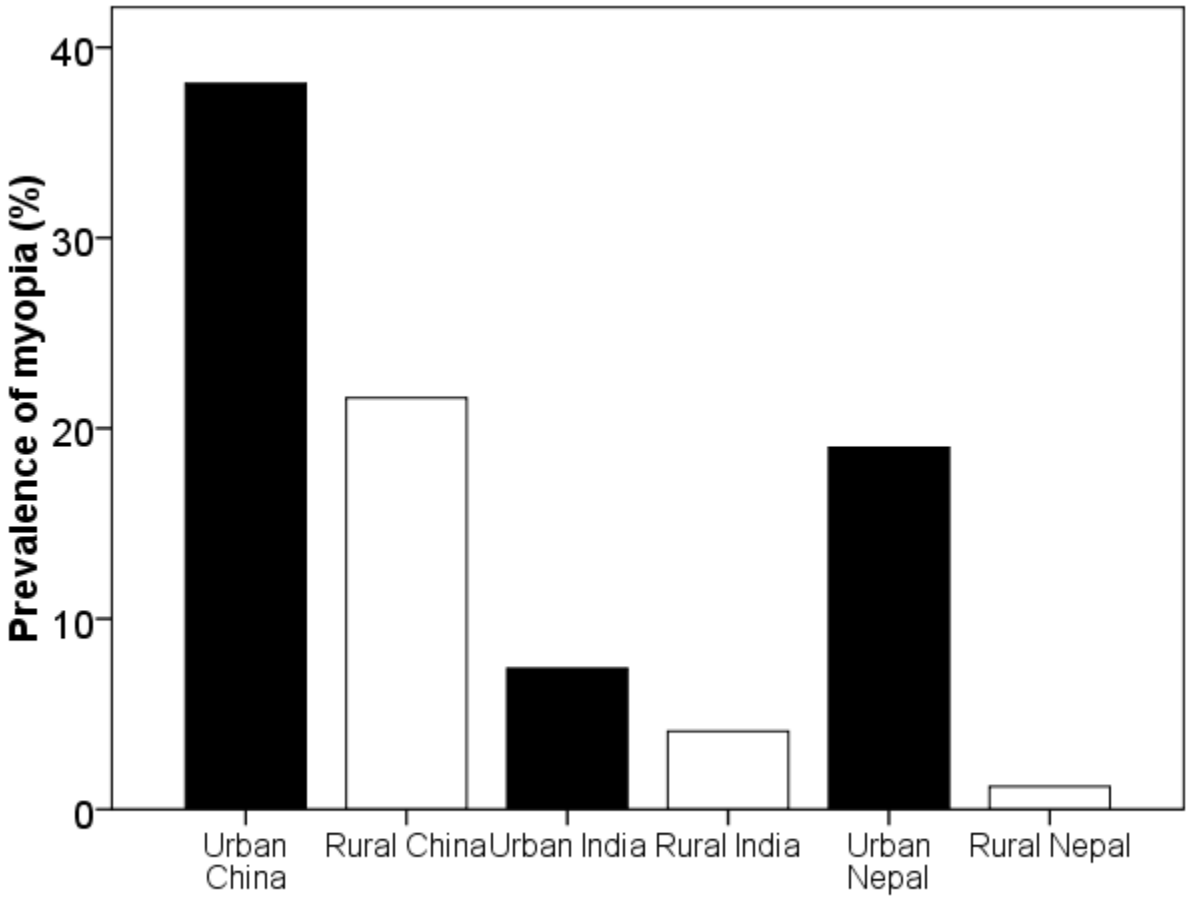
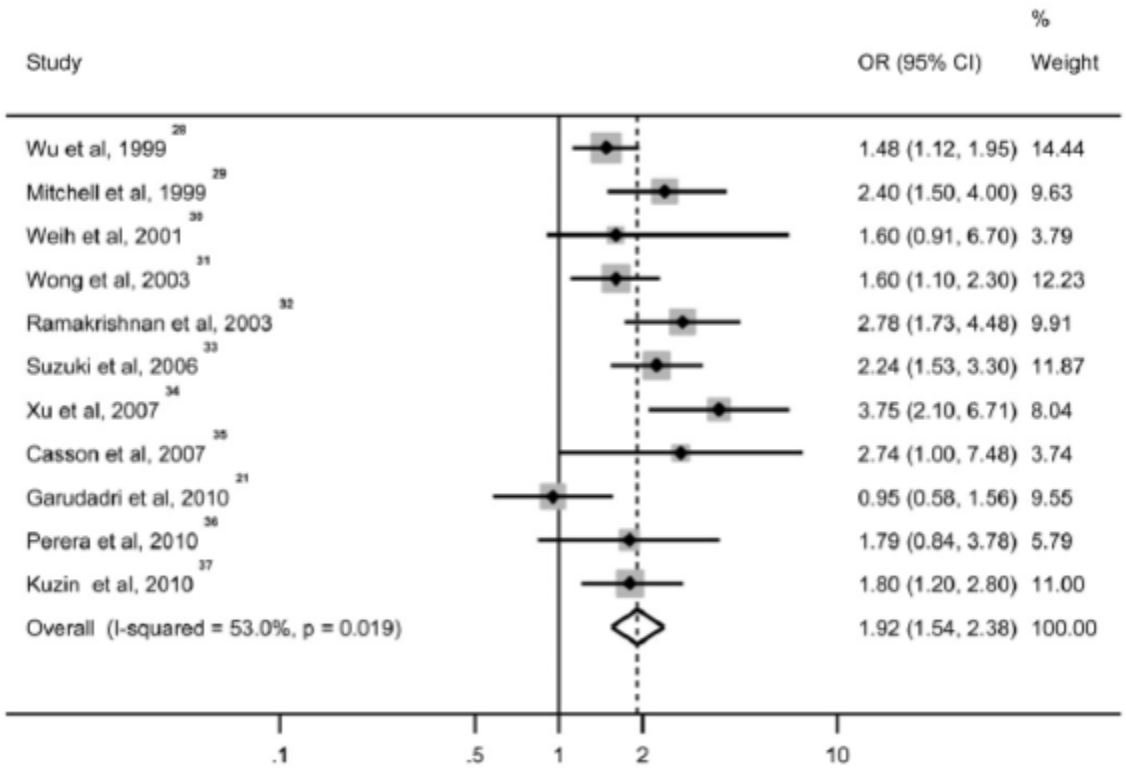
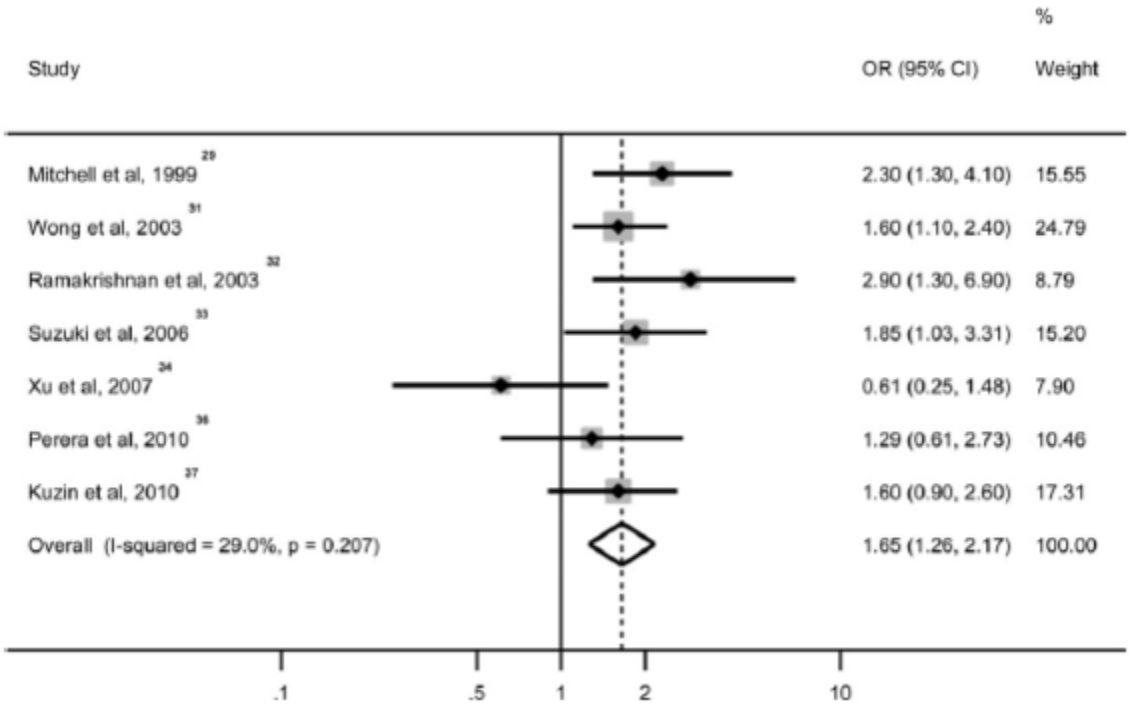


Figure 3. Forest Plot of Risk Estimates of the Association between any Myopia and Open-Angle Glaucoma. CI = confidence interval; OR = odds ratio.*



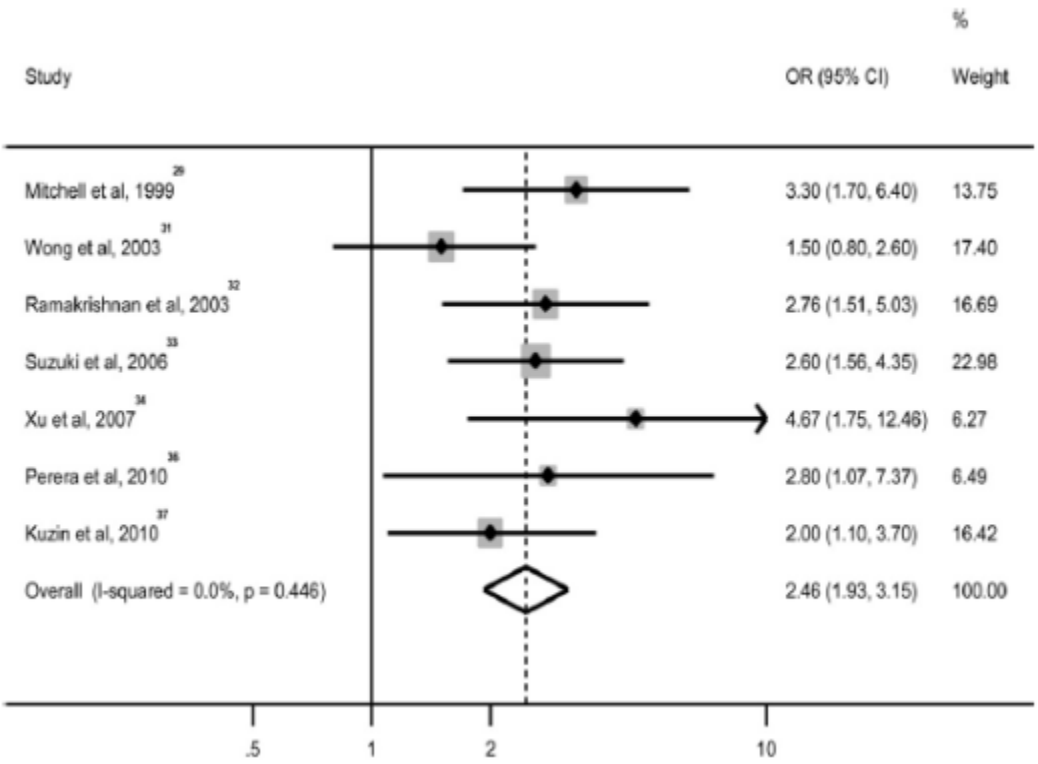
*Data taken from Reference 157

Figure 4. Forest Plot of Risk Estimates of the Association between Low Myopia and Open-Angle Glaucoma. CI = confidence interval; OR = odds ratio.*



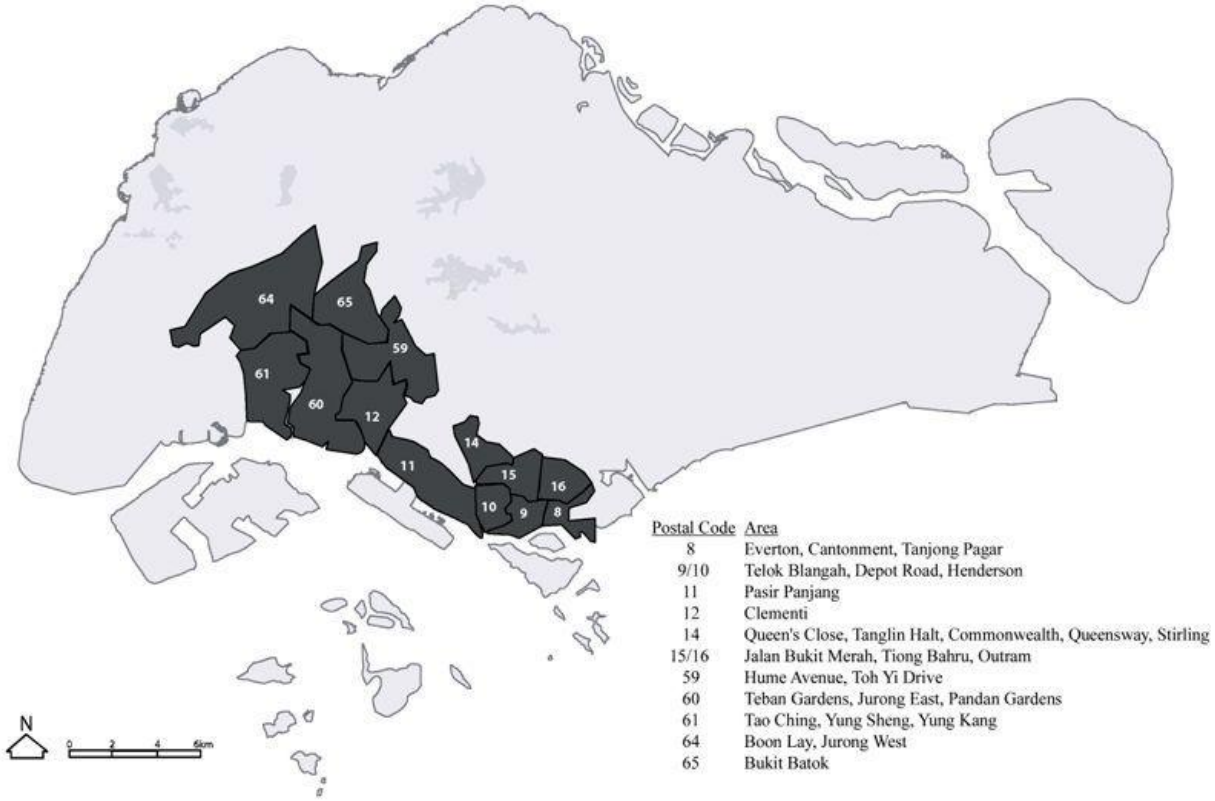
*Data taken from Reference 157

Figure 5. Forest Plot of Risk Estimates of the Association between High Myopia and Open-Angle Glaucoma. CI = confidence interval; OR = odds ratio.*



*Data taken from Reference 157

Figure 6. Study Area for the Singapore Indian Eye Study



Postal Code	Area
8	Everton, Cantonment, Tanjong Pagar
9/10	Telok Blangah, Depot Road, Henderson
11	Pasir Panjang
12	Clementi
14	Queen's Close, Tanglin Halt, Commonwealth, Queensway, Stirling
15/16	Jalan Bukit Merah, Tiong Bahru, Outram
59	Hume Avenue, Toh Yi Drive
60	Teban Gardens, Jurong East, Pandan Gardens
61	Tao Ching, Yung Sheng, Yung Kang
64	Boon Lay, Jurong West
65	Bukit Batok

Figure 7. Sampling Frame of the Singapore Indian Eye Study

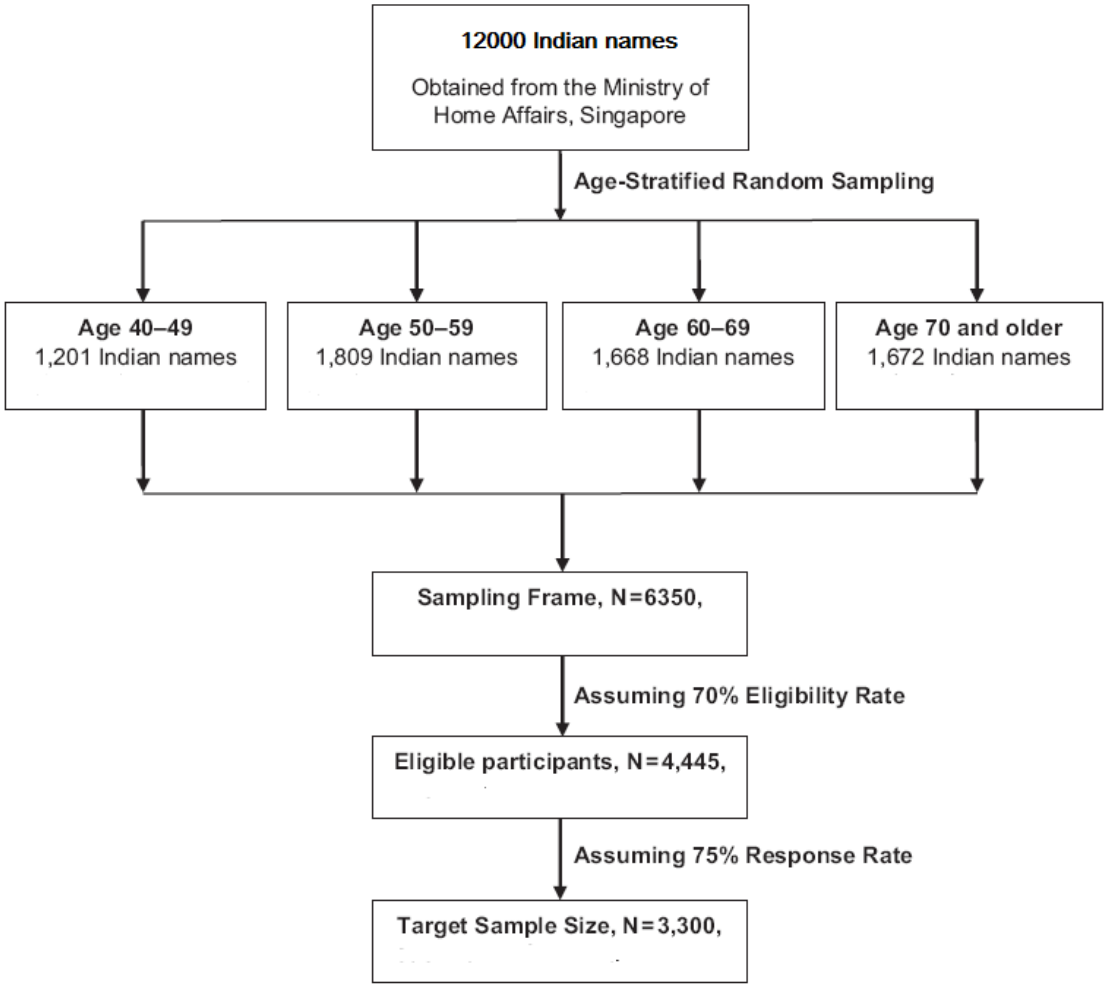


Figure 8. Examination Flowchart for the Singapore Indian Eye Study

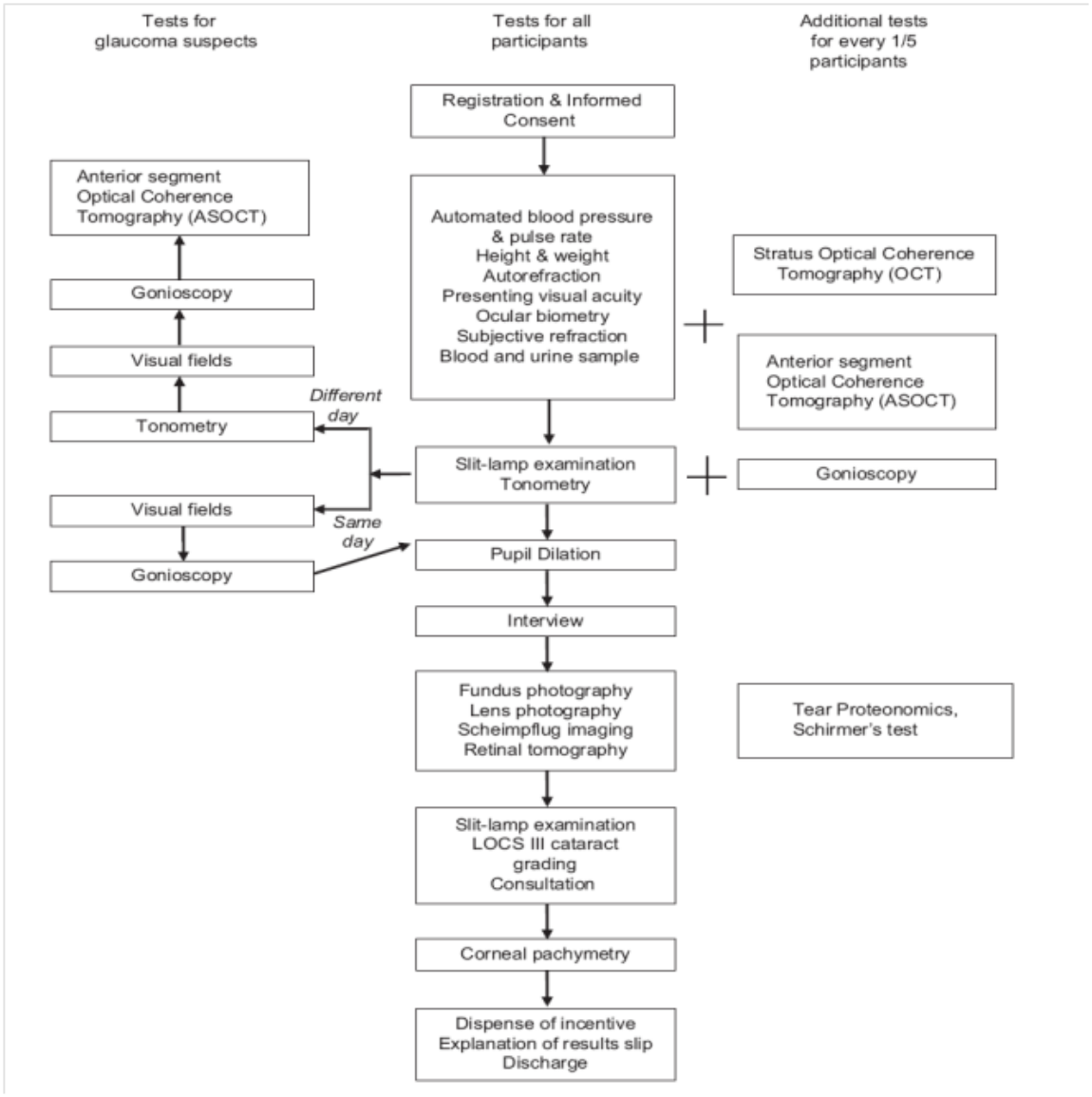


Figure 9. Final Response for the Singapore Indian Eye Study

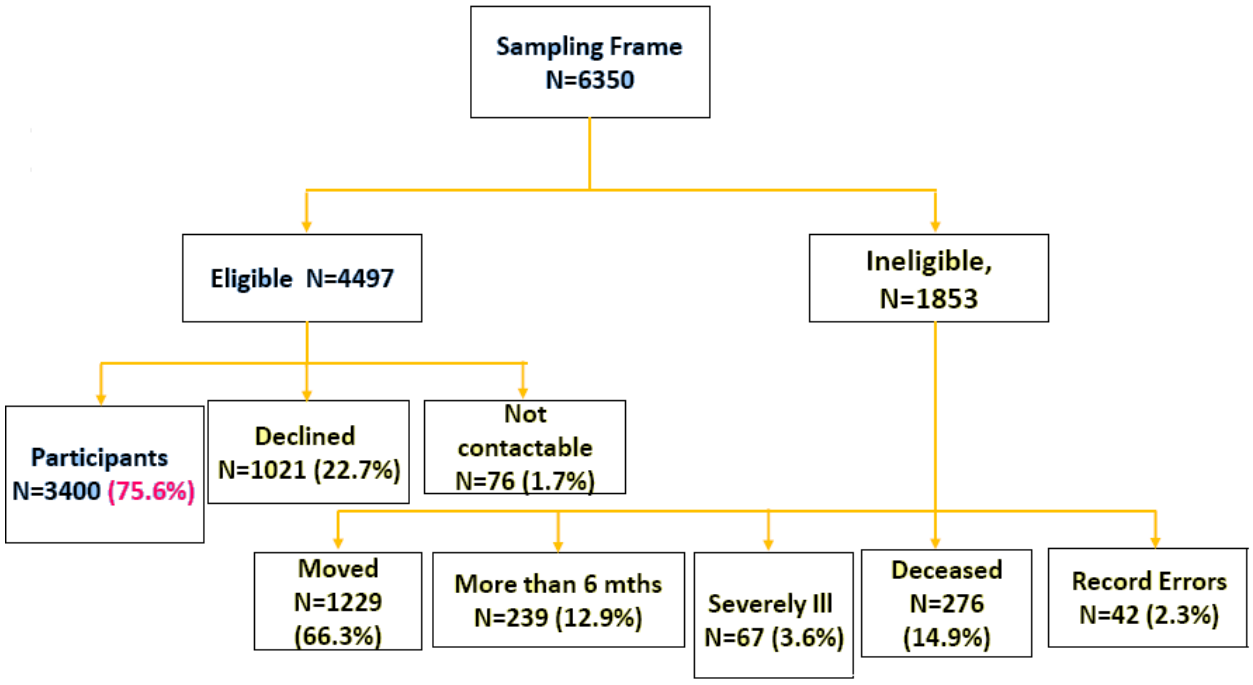


Figure 10. Age and Gender Distribution of the Singapore Indian Eye Study

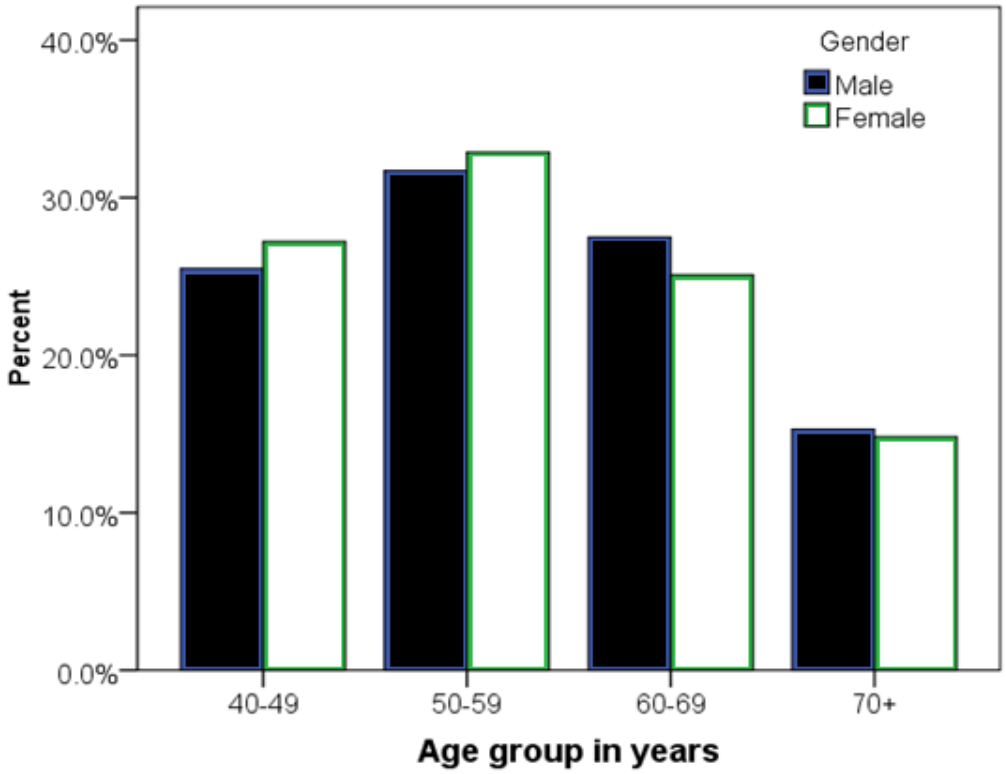


Figure 11. Educational Level in the Singapore Indian Eye Study

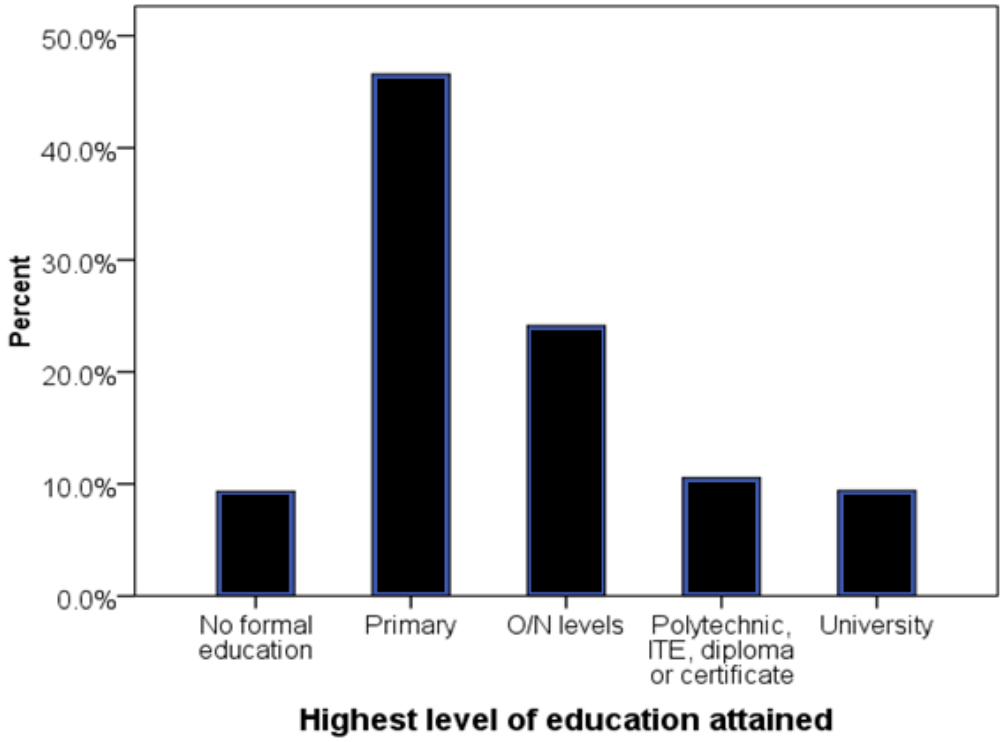


Figure 12. Housing Type in the Singapore Indian Eye Study

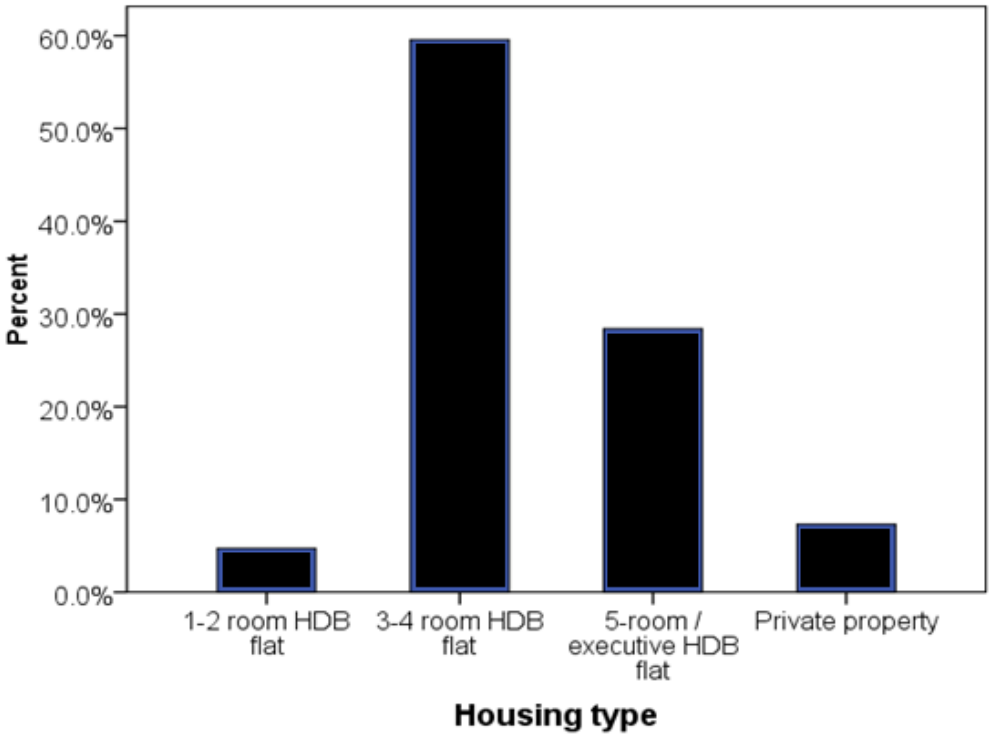


Figure 13. Individual Monthly Income in the Singapore Indian Eye Study

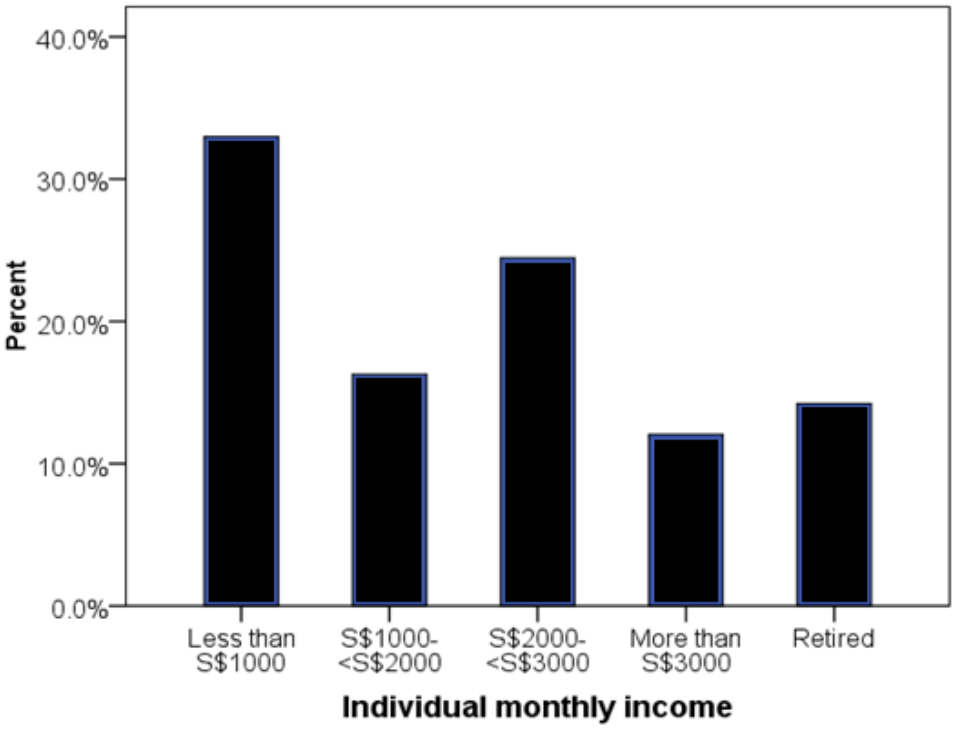


Figure 14. Smoking Categories in the Singapore Indian Eye Study

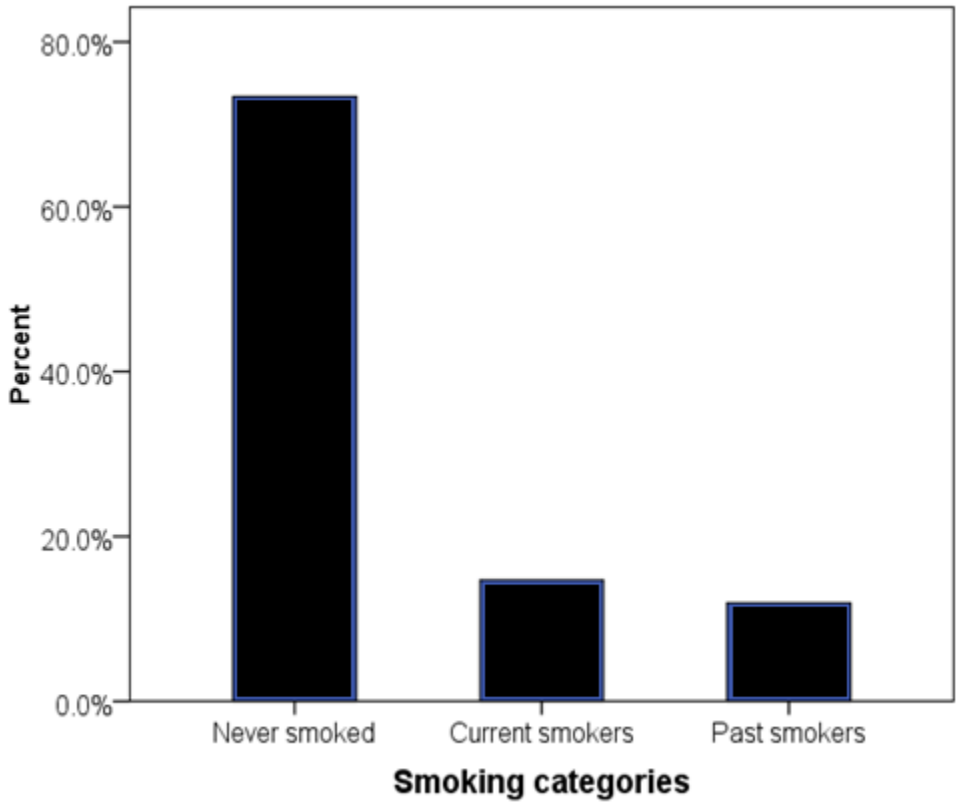


Figure 15. Distribution of Height and Weight in the Singapore Indian Eye Study

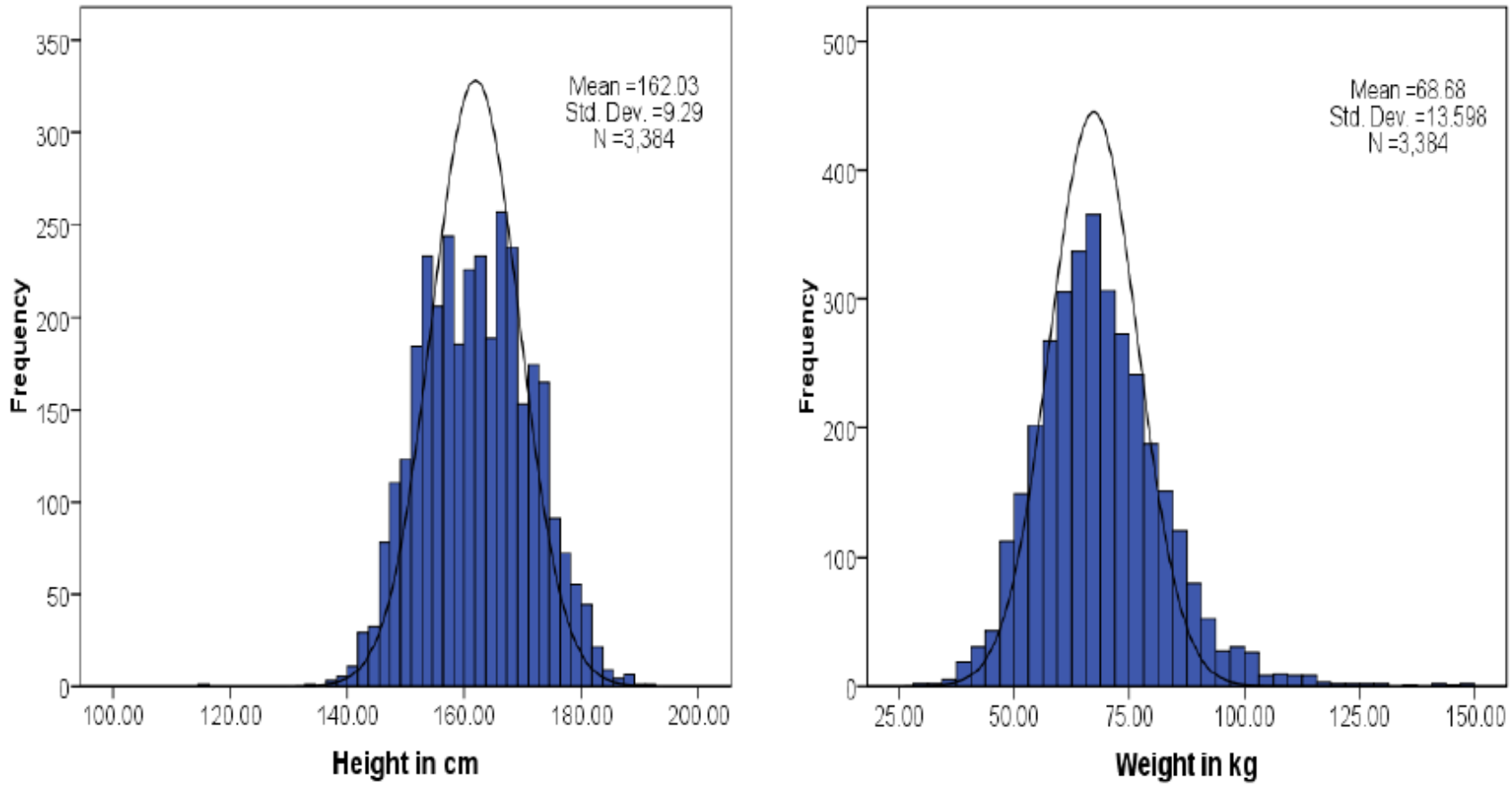


Figure 16. Distribution of Blood Pressure in the Singapore Indian Eye Study

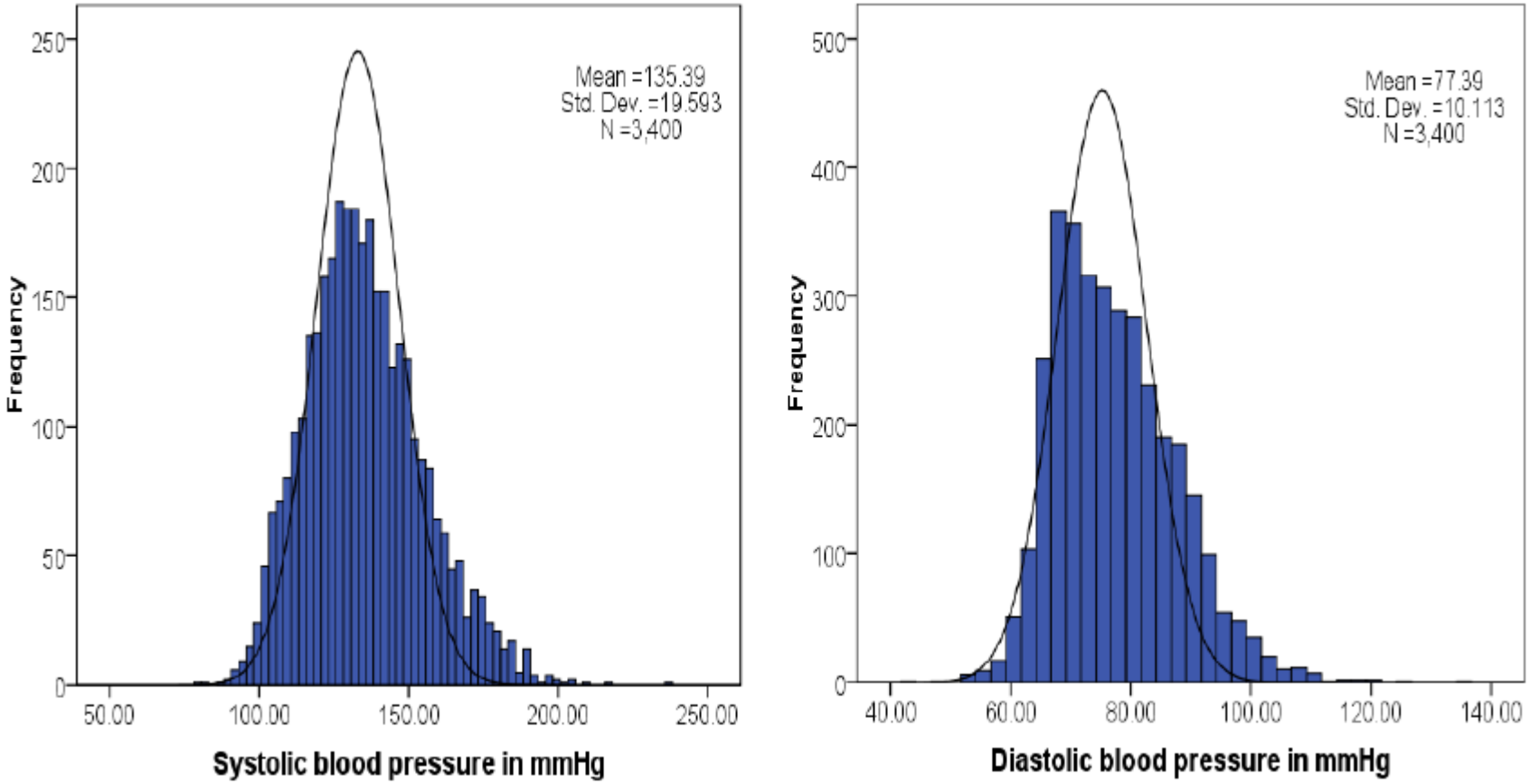


Figure 17. Distribution of Intraocular Pressure in the Singapore Indian Eye Study

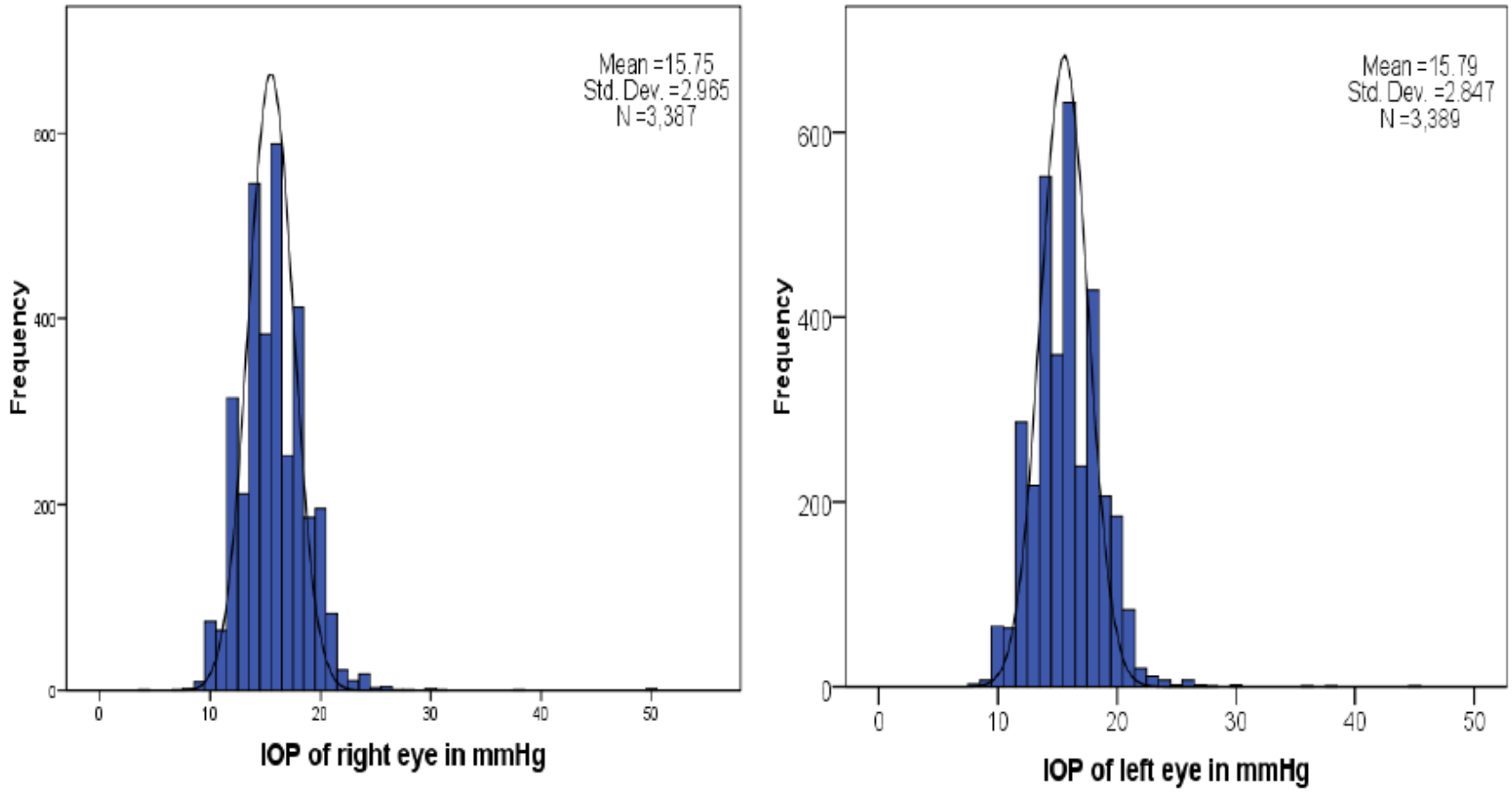


Figure 18. Distribution of Cup Disc Ratio in the Singapore Indian Eye Study

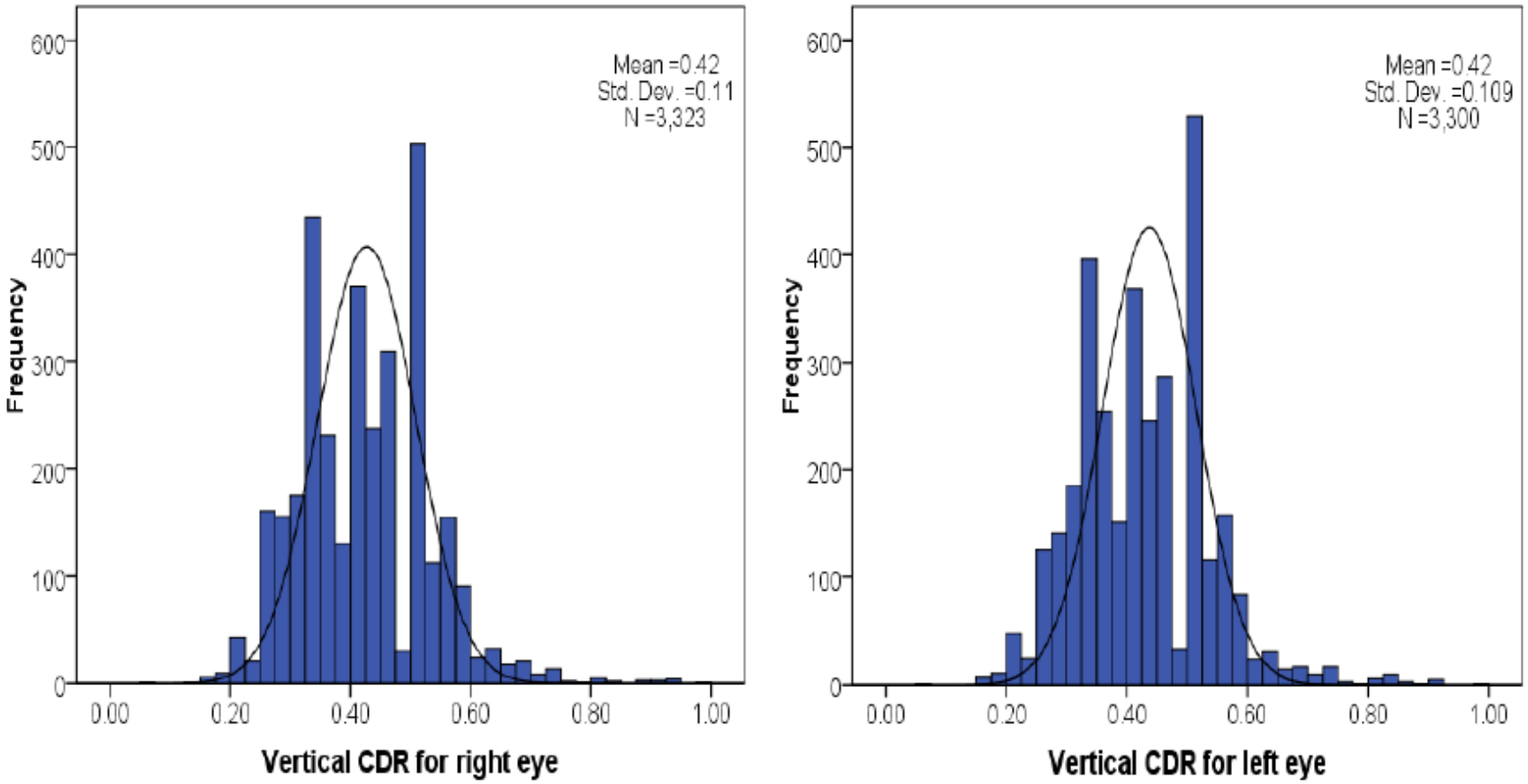


Figure 19. Distribution of Central Cornea Thickness in the Singapore Indian Eye Study

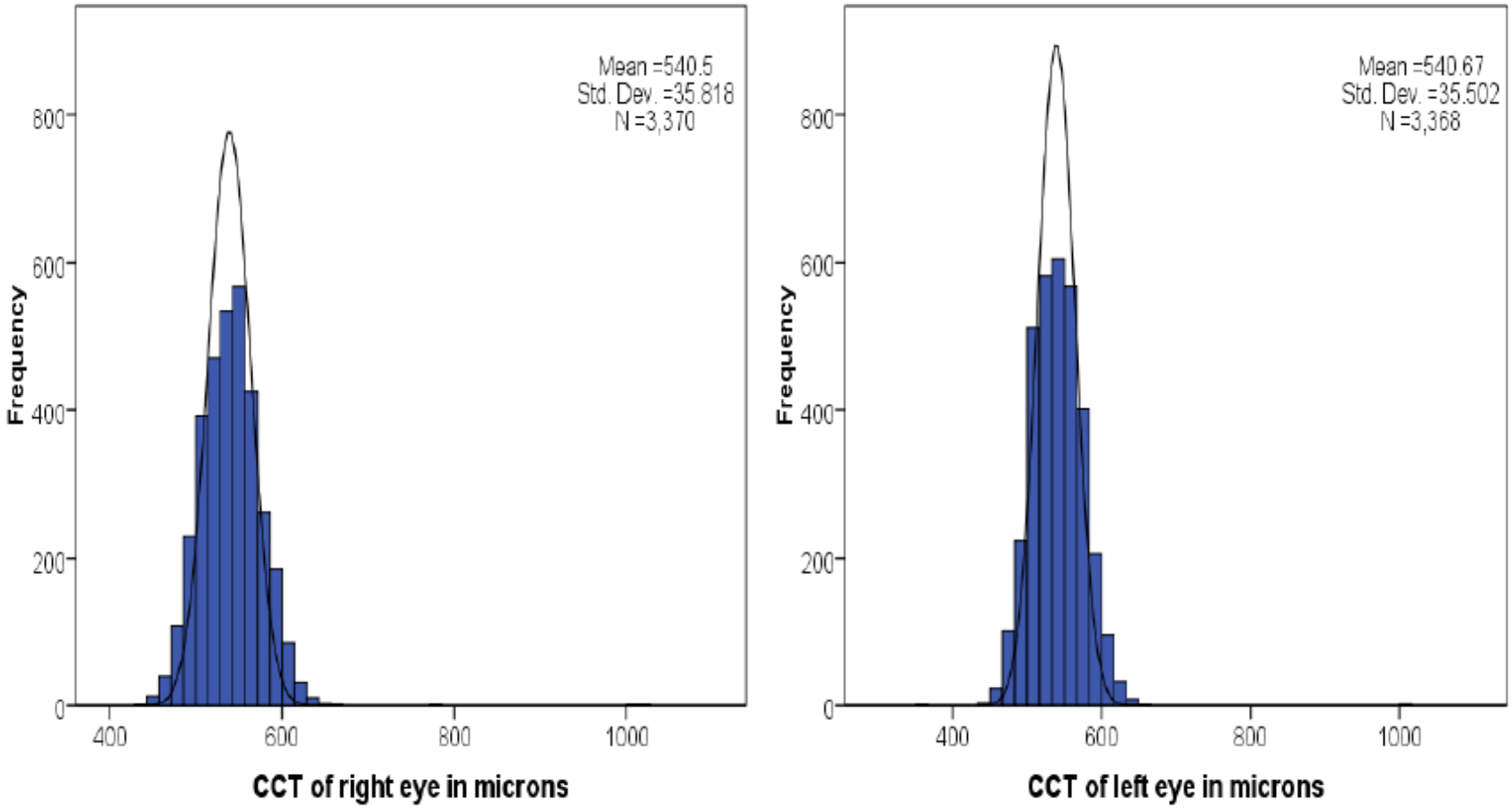


Figure 20. Distribution of Hypertension in the Singapore Indian Eye Study

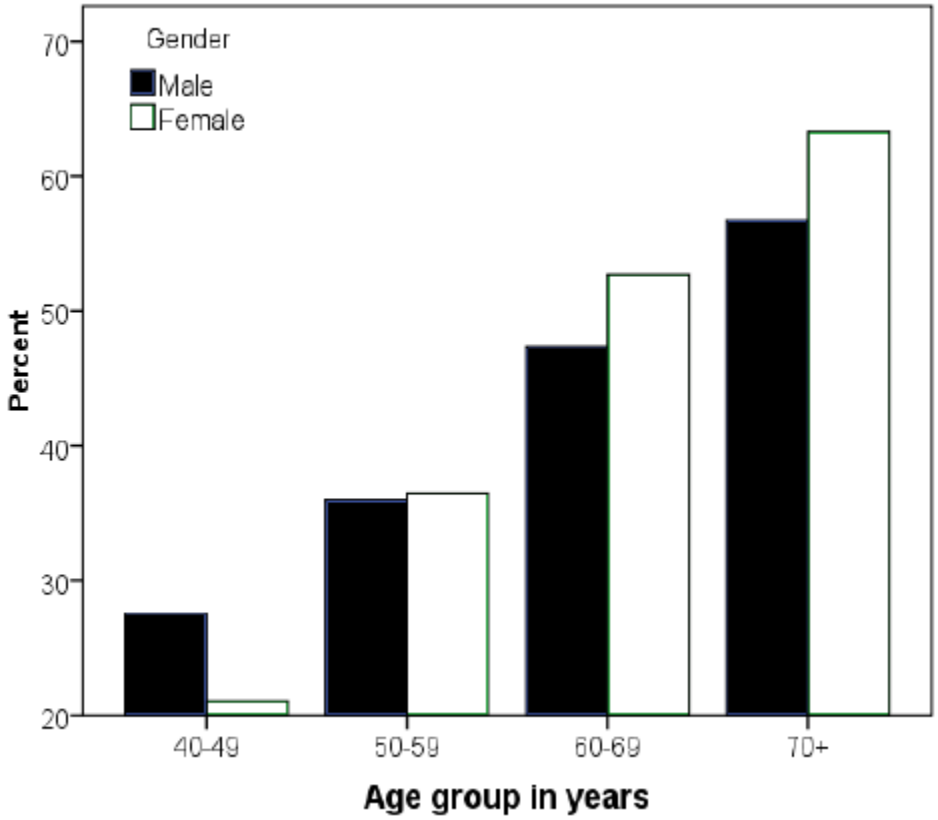


Figure 21. Distribution of Diabetes in the Singapore Indian Eye Study

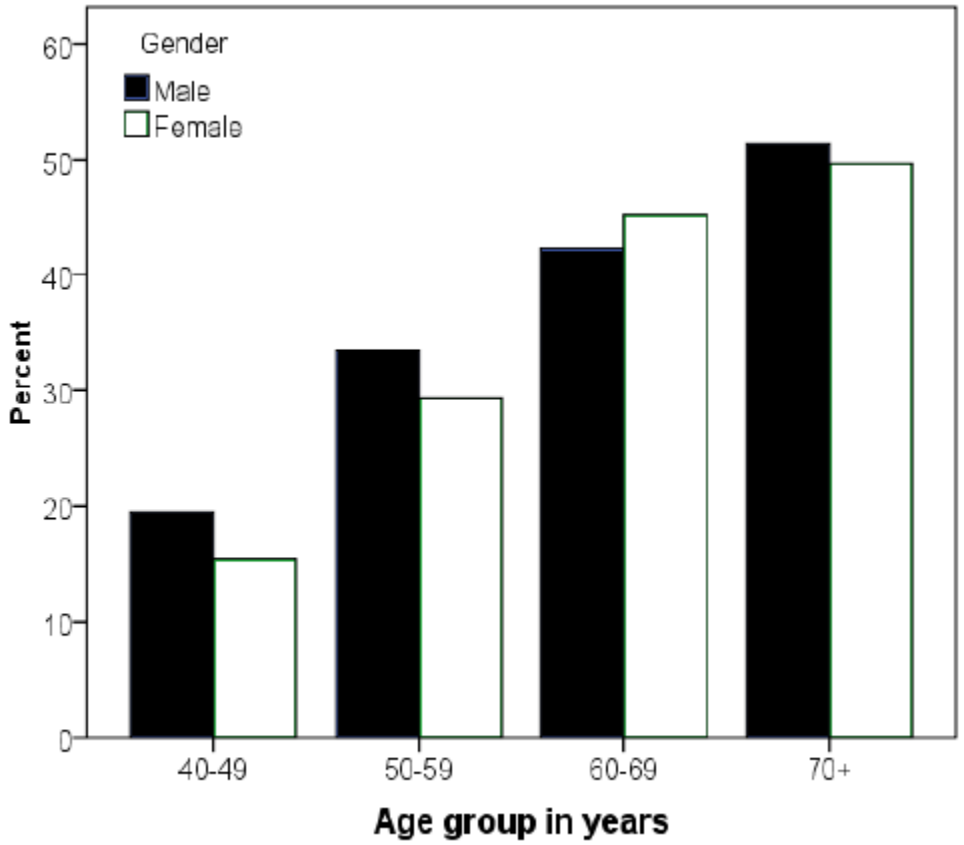


Figure 22. Distribution of Spherical Equivalents in the Right Eye by Age Group in Indian Residents in Singapore.

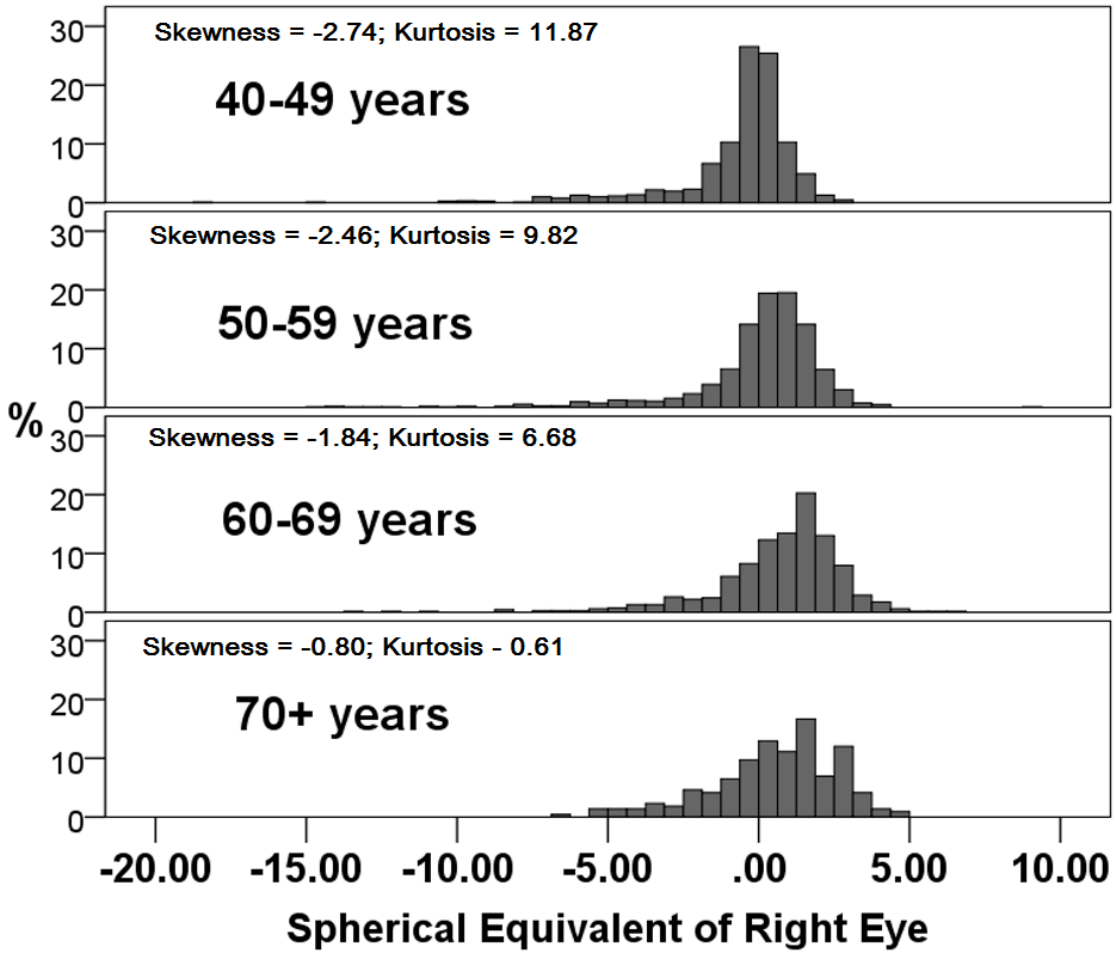


Figure 23. Box Plot of Spherical Equivalent by Age Groups

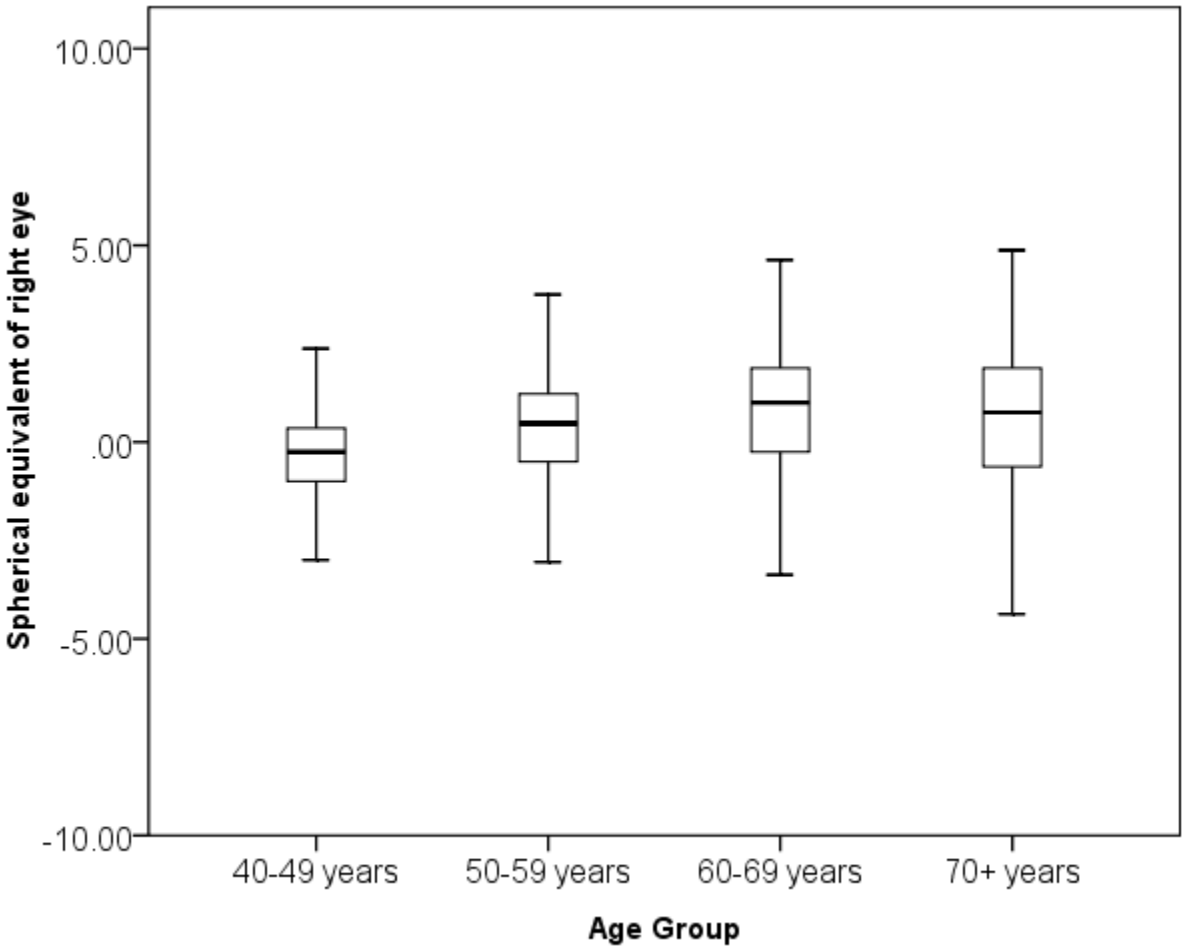


Figure 24. Prevalence of Myopia by Educational Level

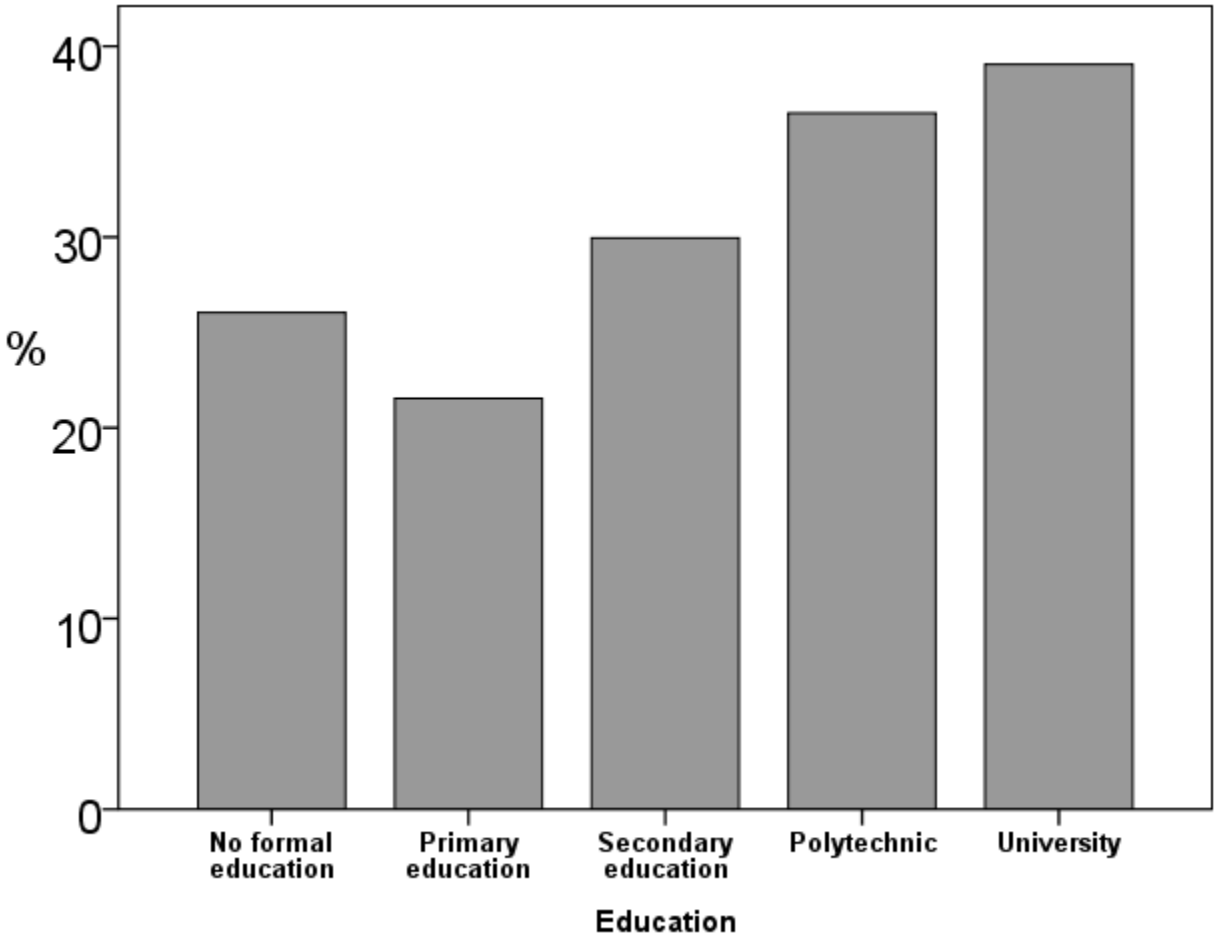


Figure 25. Line Graphs of Prevalence of Myopia by Age for Those with (n = 323), without Nuclear Cataract, and All Adults.

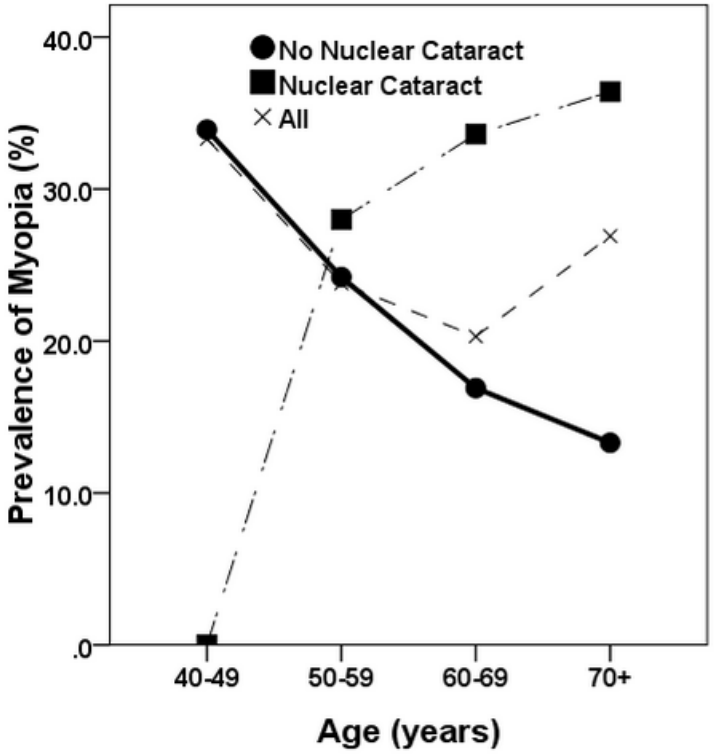


Figure 26. Line Graphs of Prevalence of Myopia by Age in Andhra Pradesh Eye Disease Study, Chennai Glaucoma Study and Singapore Indian Eye Study.

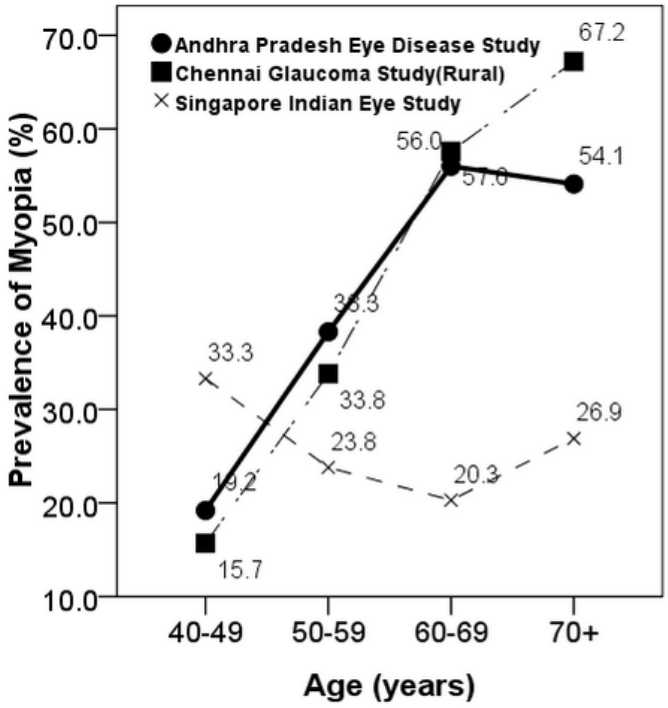


Figure 27. Prevalence of Myopia in the Tanjong Pagar Survey, Singapore Malay Eye Study and Singapore Indian Eye Study in Men

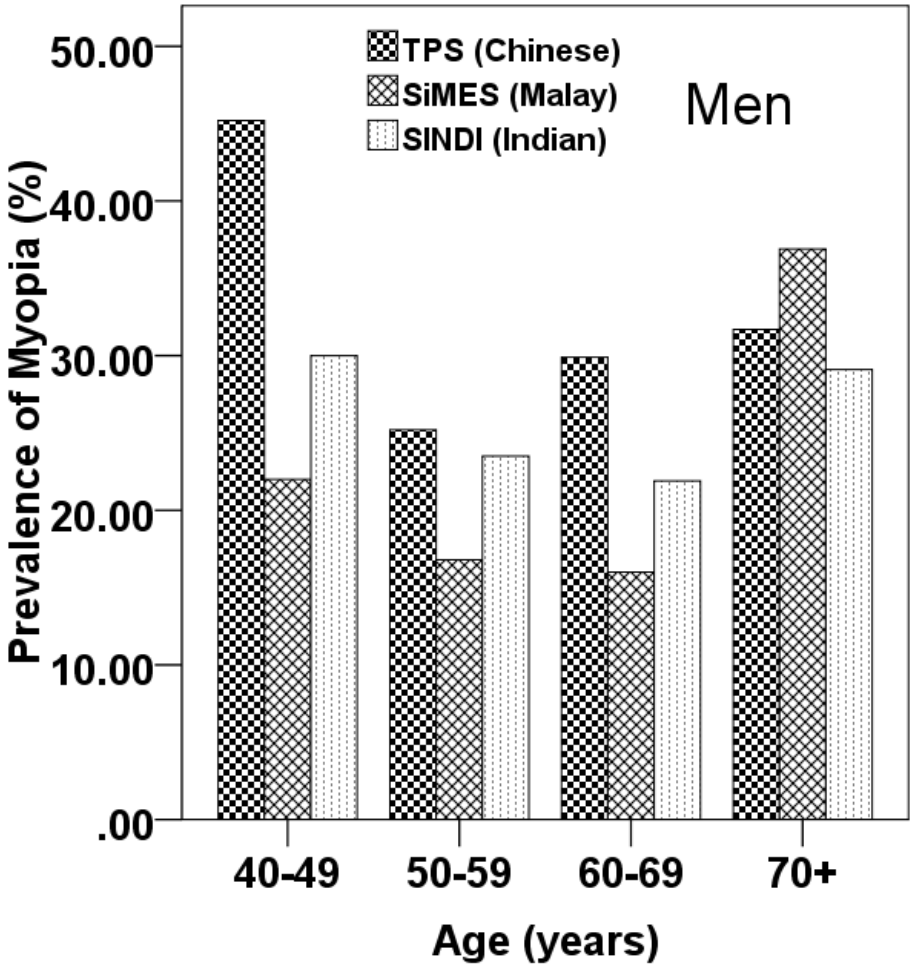


Figure 28. Prevalence of Myopia in the Tanjong Pagar Survey, Singapore Malay Eye Study and Singapore Indian Eye Study in Women

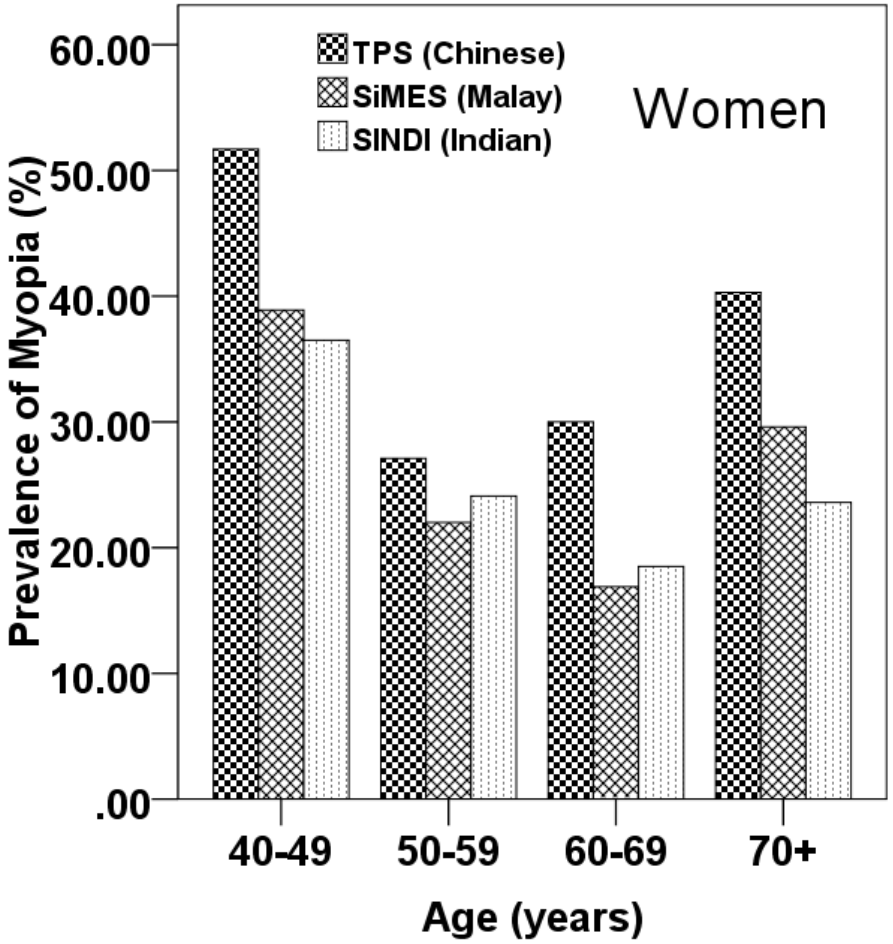


Figure 29. Distribution of Axial Length in the Singapore Indian Eye Study

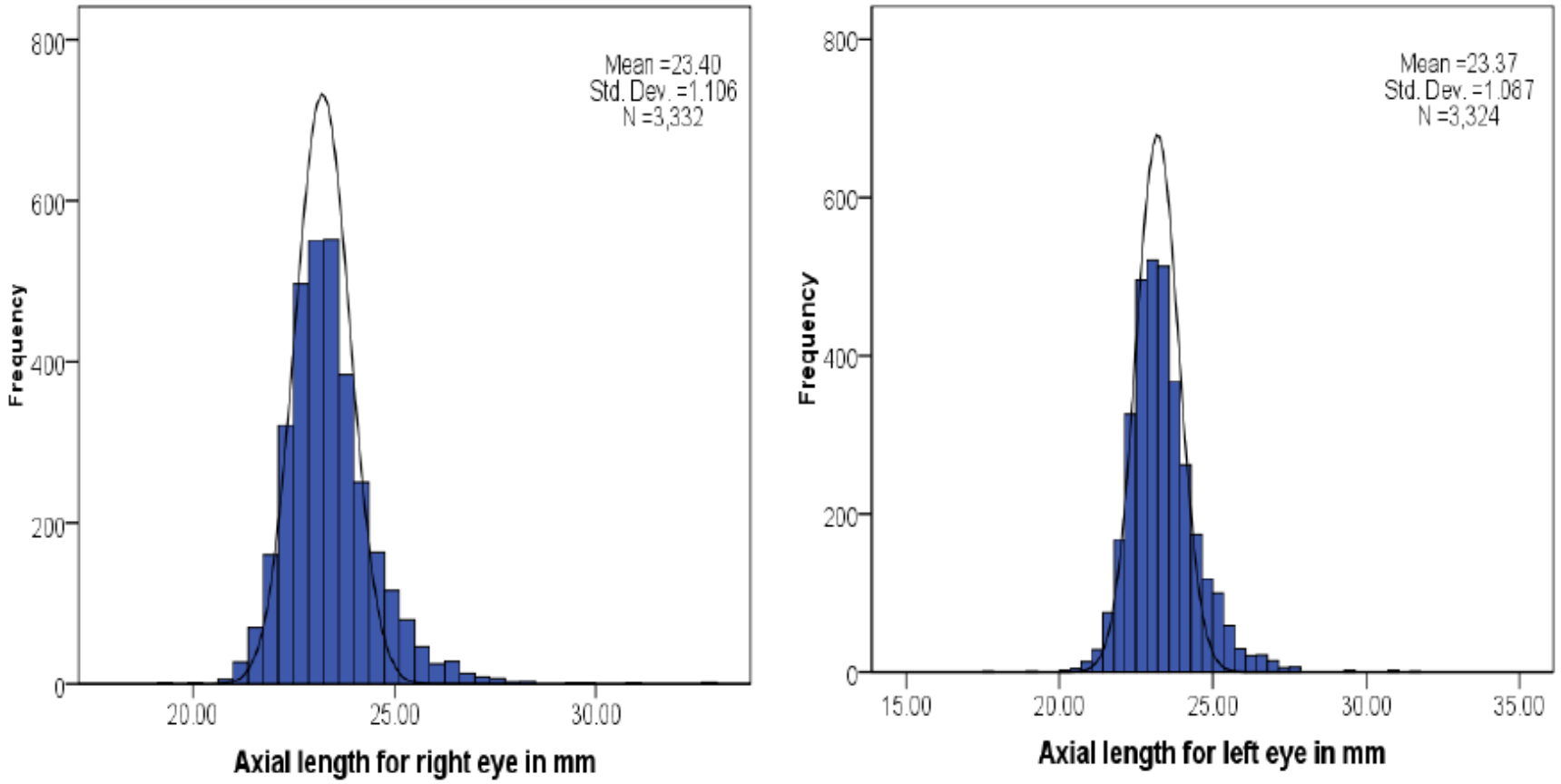


Figure 30. Distribution of Axial Lengths by Age Groups

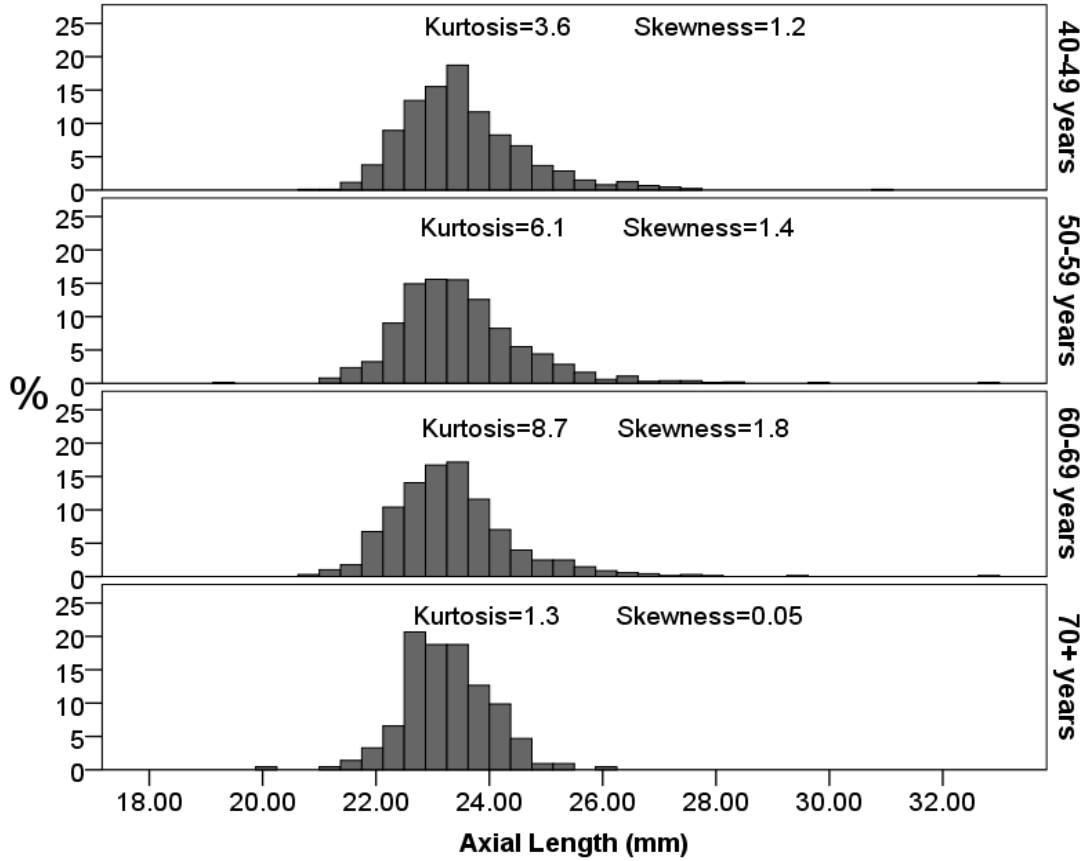


Figure 31. Distribution of Anterior Chamber Depth in the Singapore Indian Eye Study

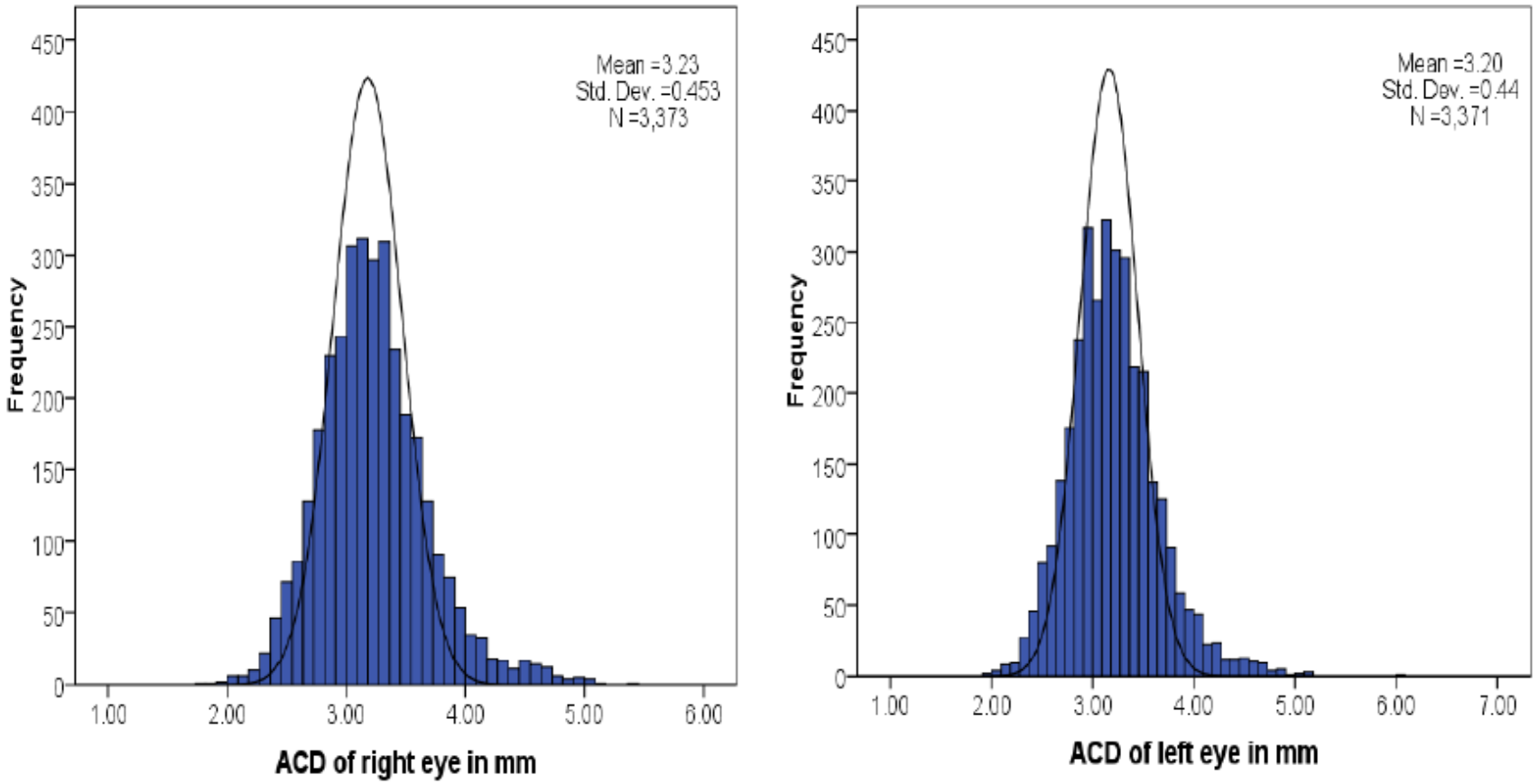


Figure 32. Distribution of Corneal Curvature in the Singapore Indian Eye Study

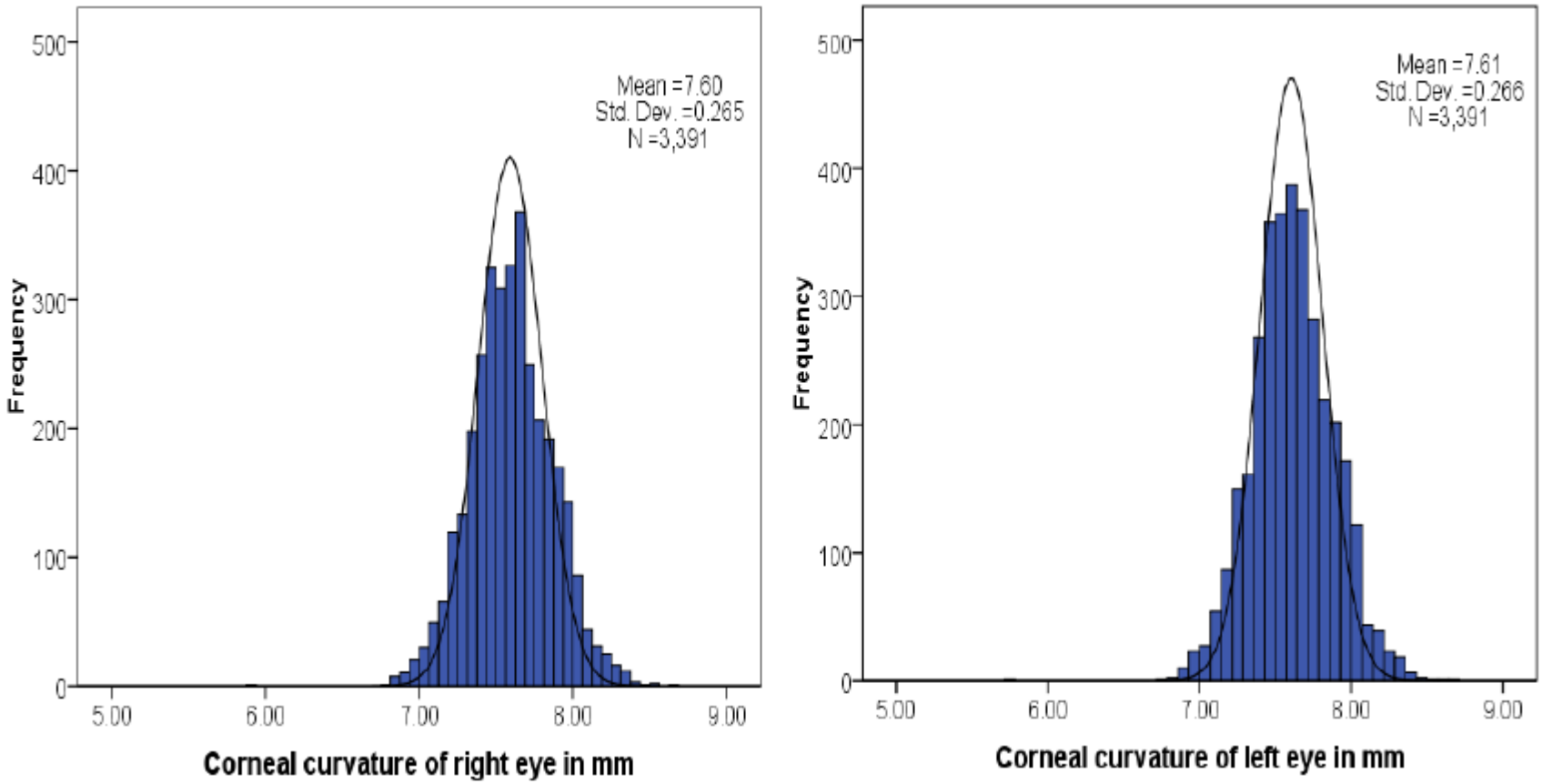


Figure 33. LOWESS Plot on the Association between Axial Length and Spherical Equivalent

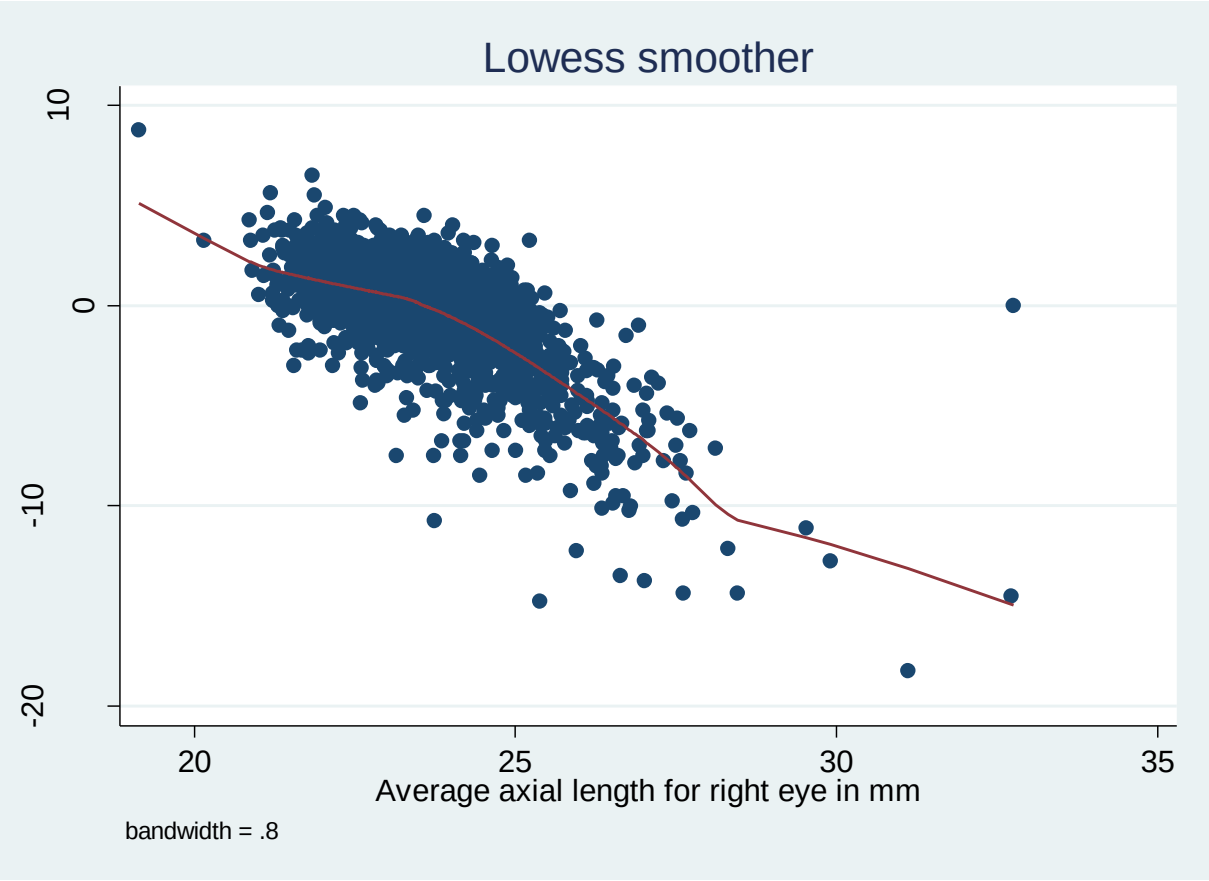


Figure 34. LOWESS Plot on the Association between Axial Length/ Corneal Curvature Ratio and Spherical Equivalent

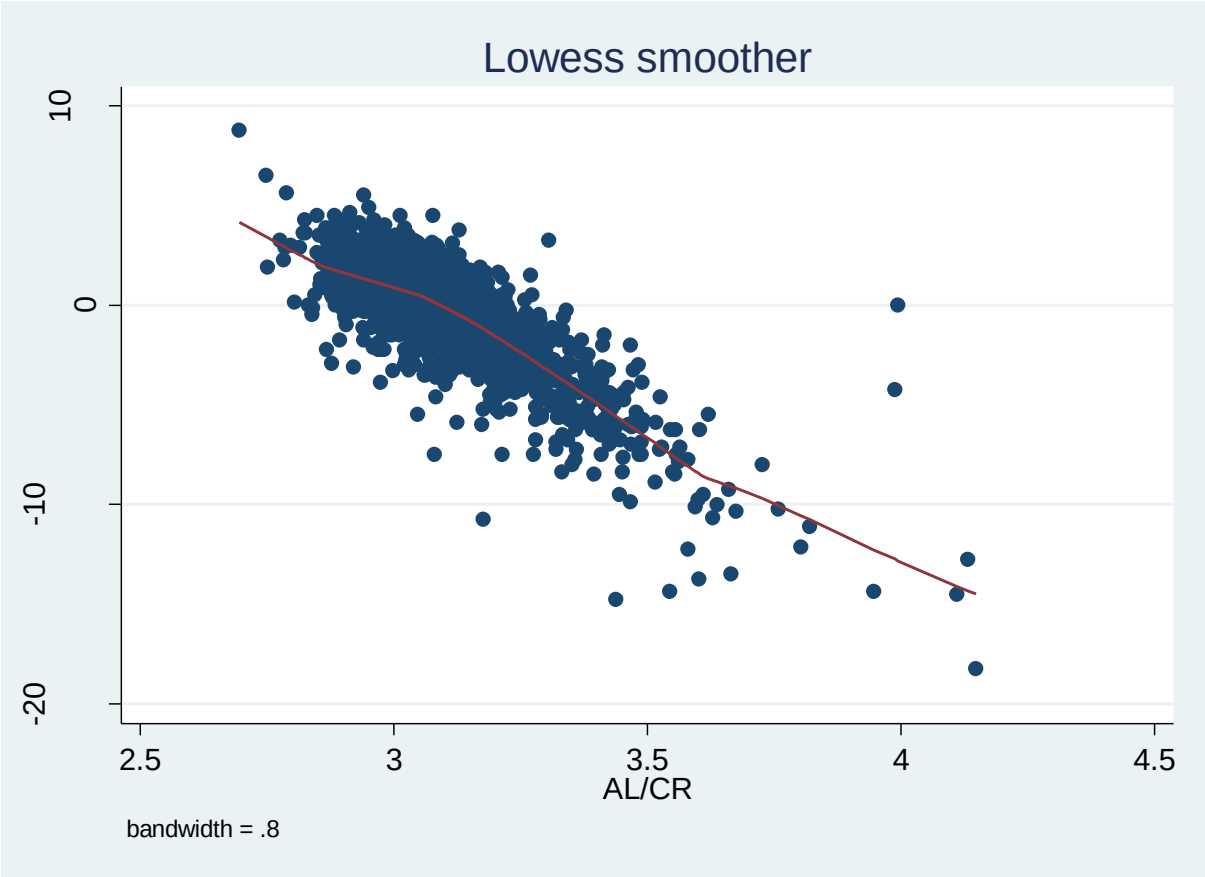


Figure 35. LOWESS Plot on the Association between Anterior Chamber Depth and Spherical Equivalent

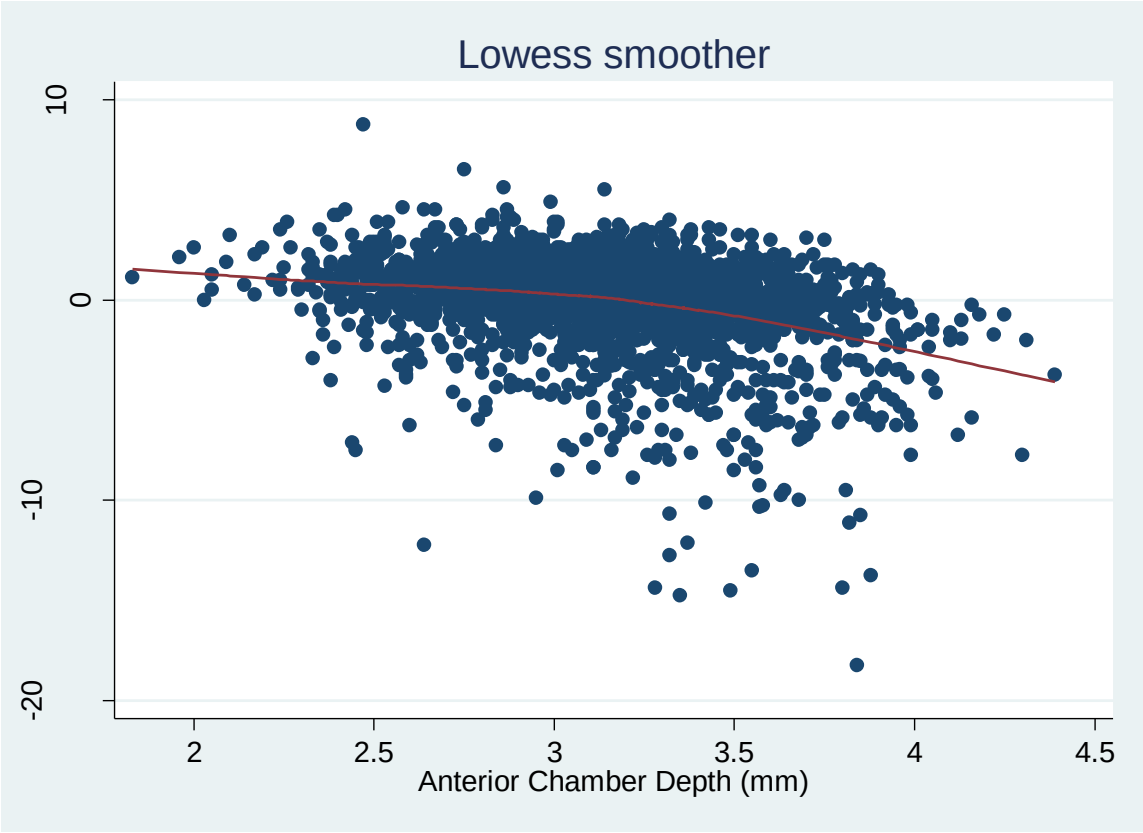


Figure 36. LOWESS Plot on the Association between Corneal Curvature and Spherical Equivalent

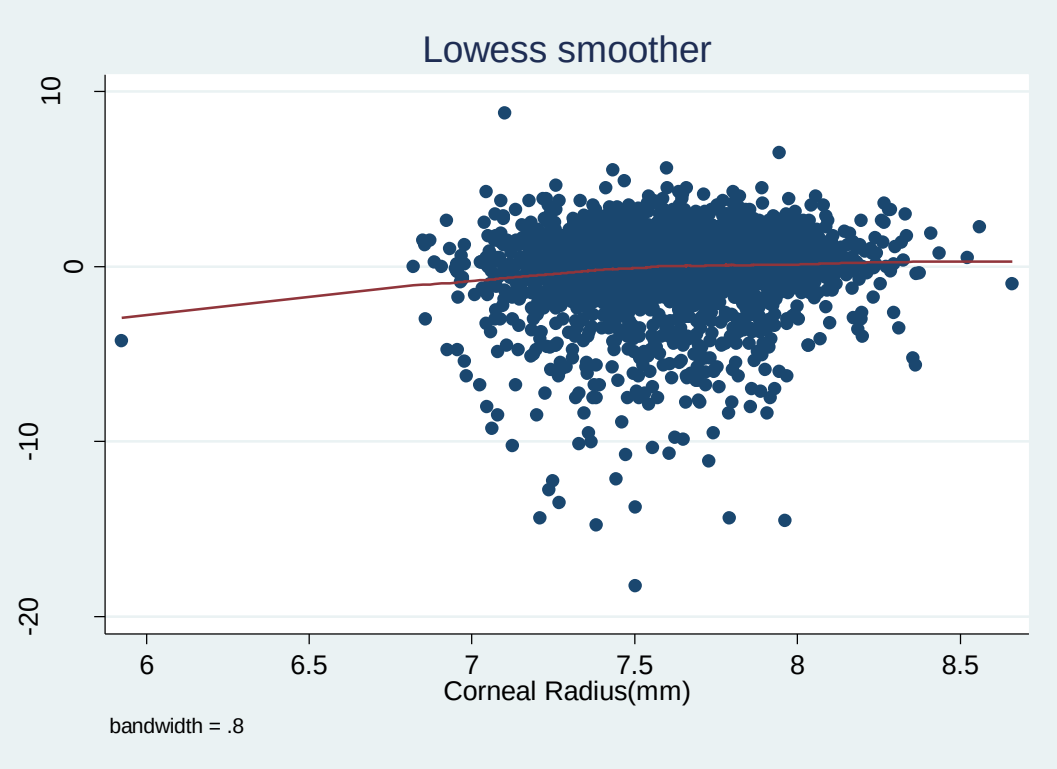


Figure 37. Box Plot of Axial Length by Spherical Equivalent Groups

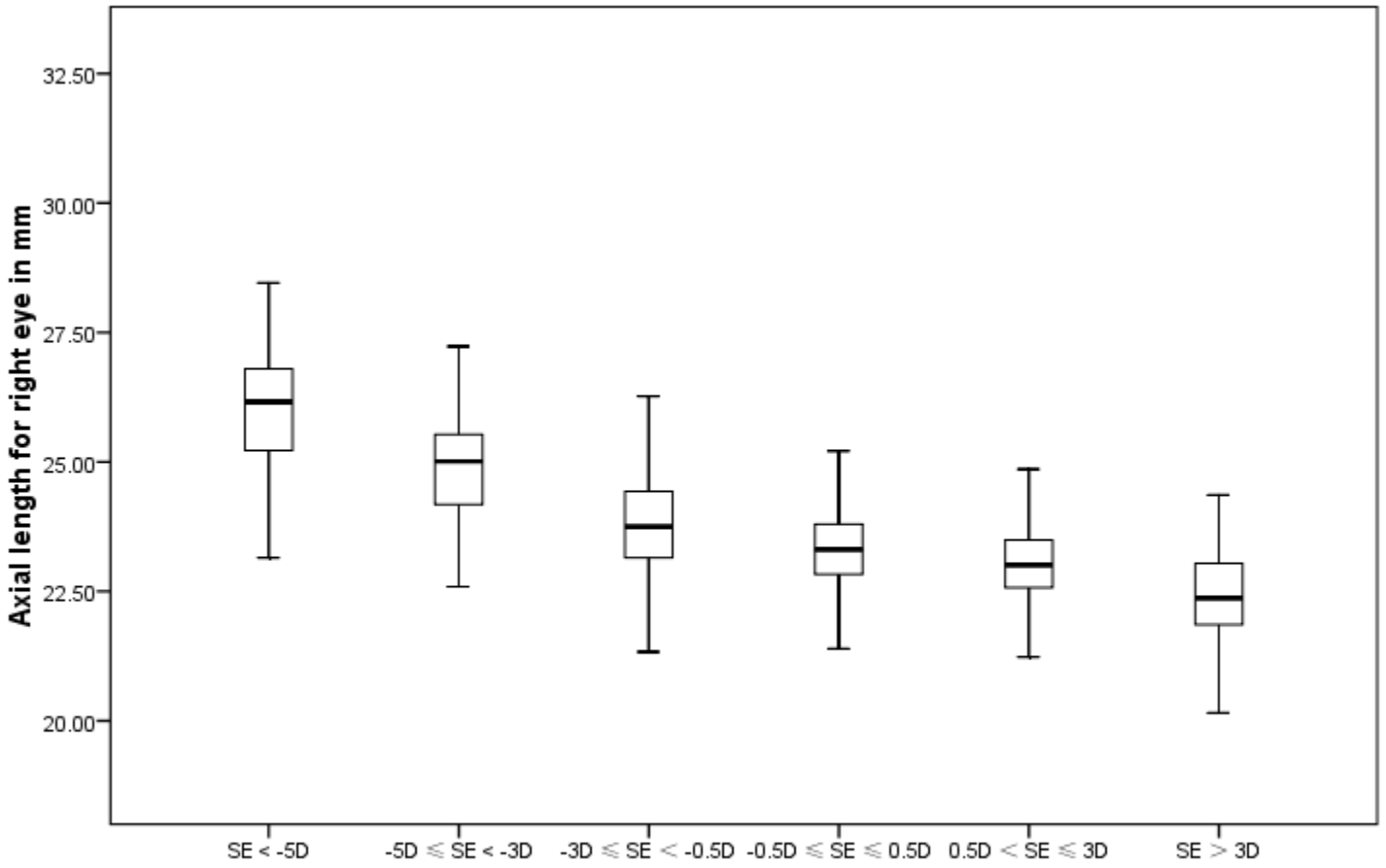


Figure 38. Box Plot of Anterior Chamber Depth by Spherical Equivalent Groups

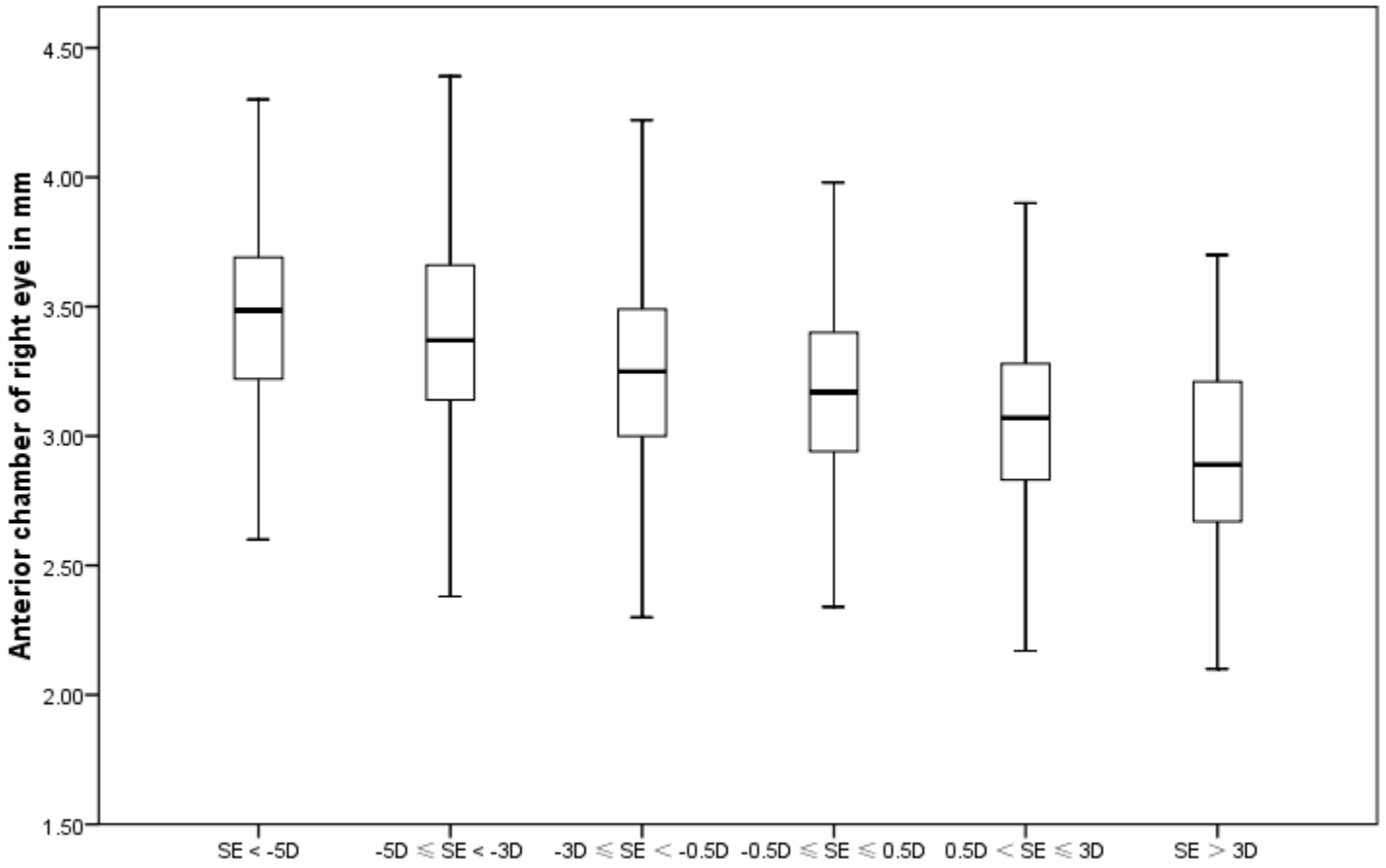


Figure 39. Box Plot of Corneal Curvature by Spherical Equivalent Groups

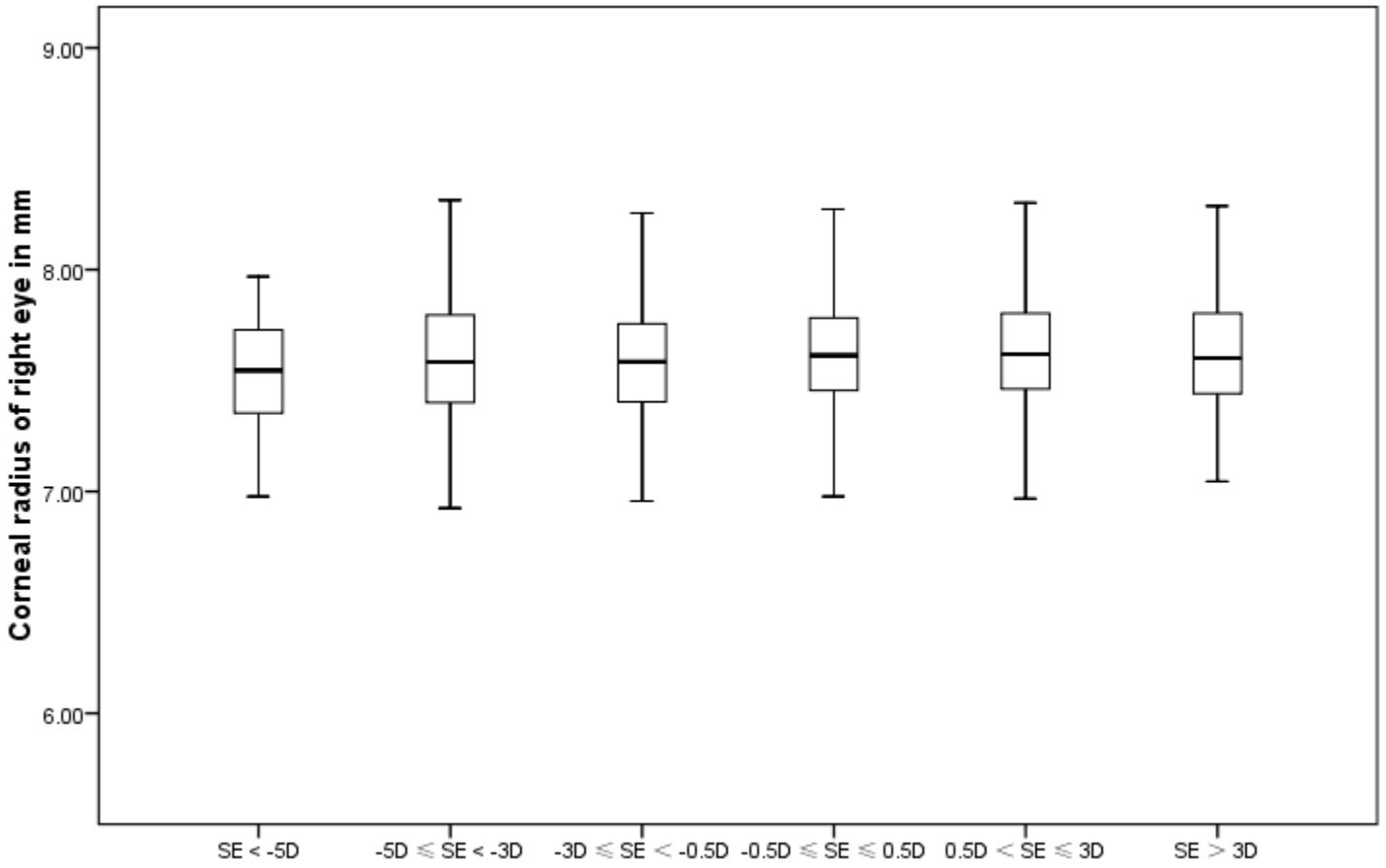


Figure 40. Box Plot of Axial Length/ Corneal Curvature Ratio by Spherical Equivalent Groups

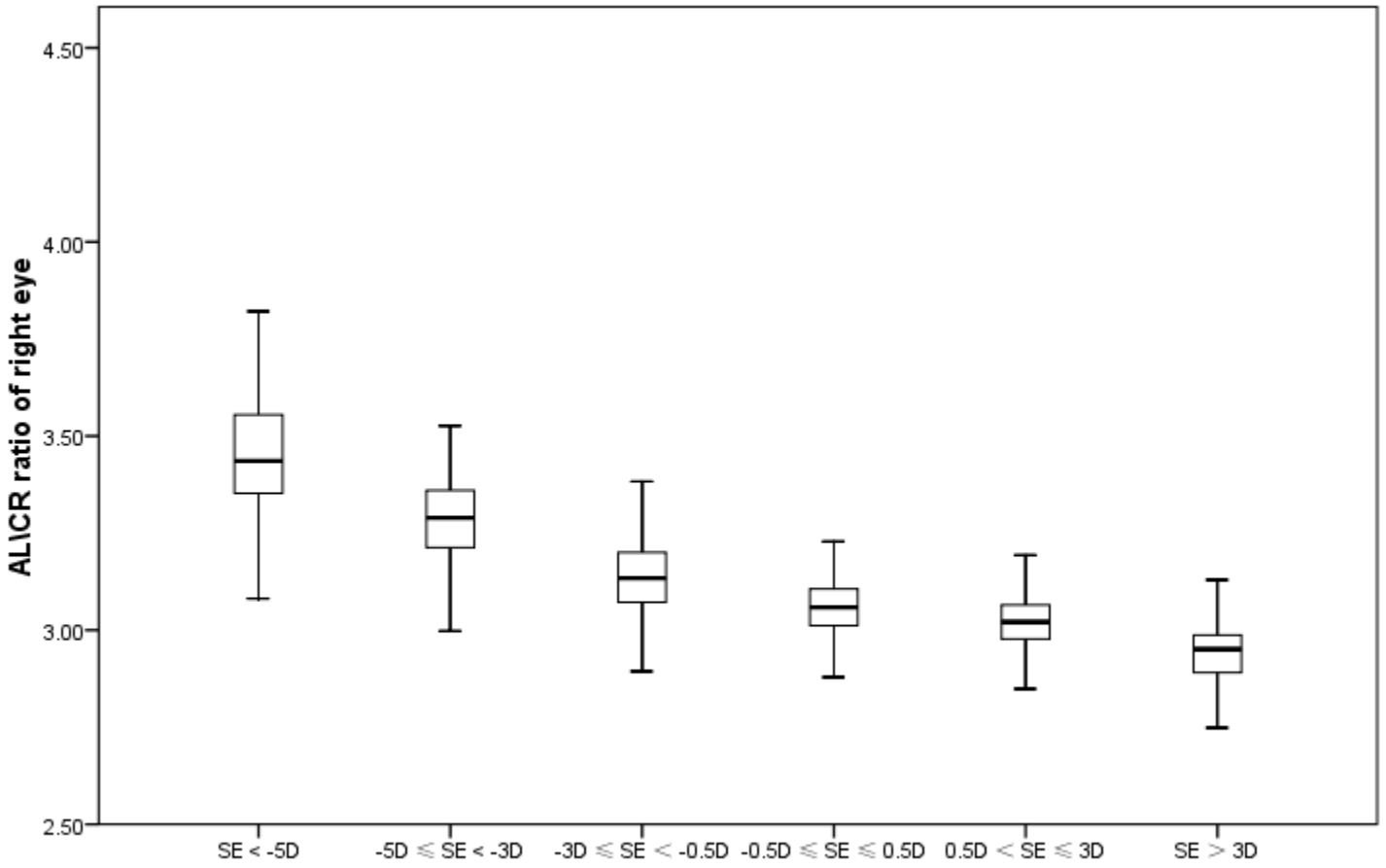


Figure 41. Height-Adjusted Axial Length by Age and Gender

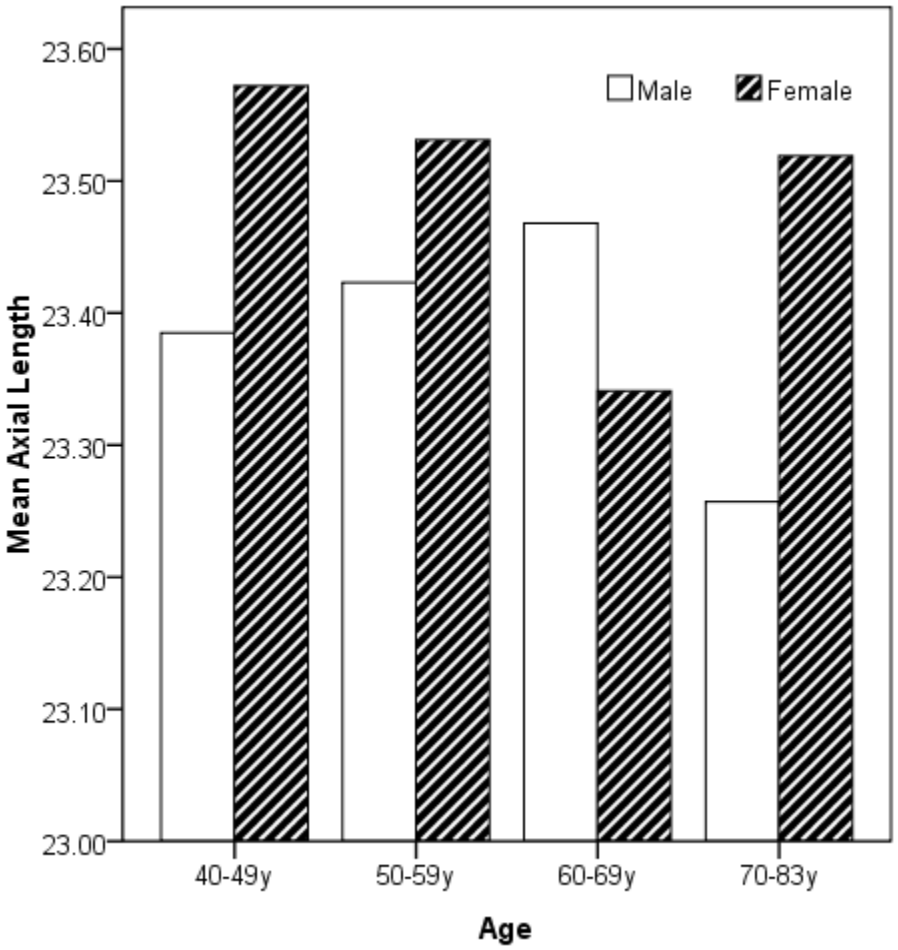


Figure 42. Association between Axial Length and Spherical Equivalent in Adults with and without Nuclear Cataract

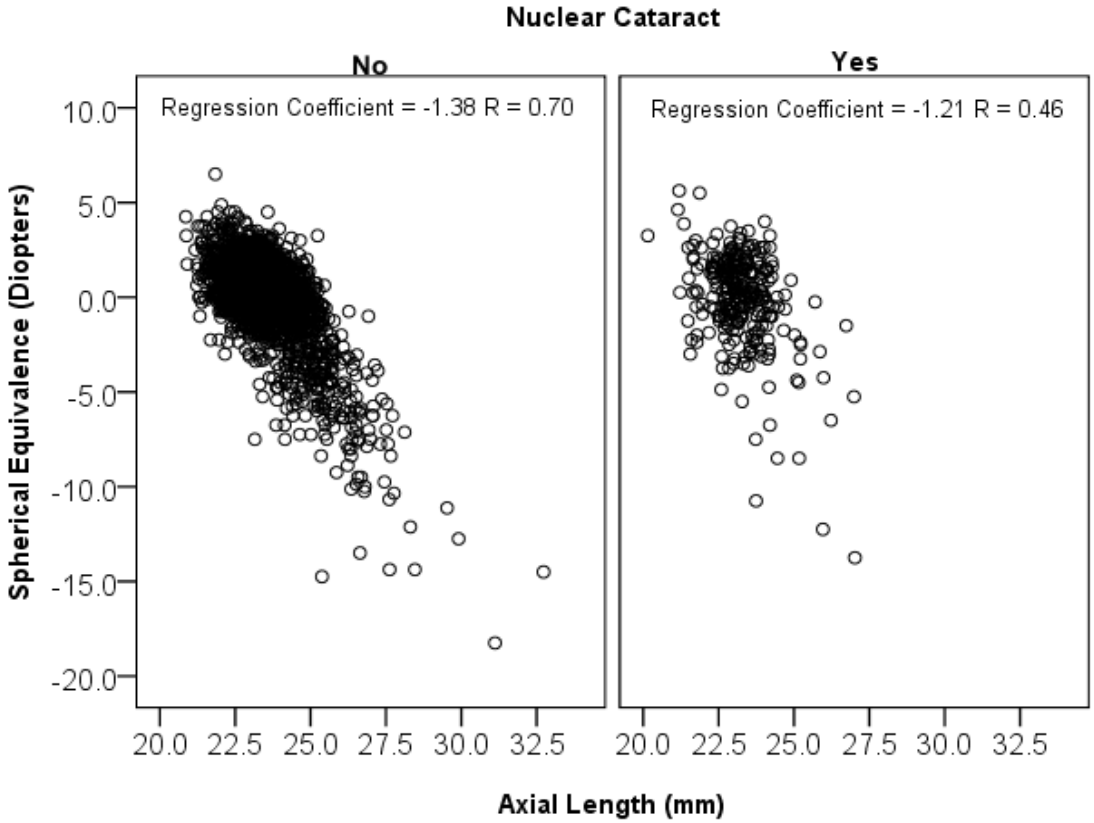


Figure 43. Correlations between Axial Length and Corneal Radius by Refractive Status

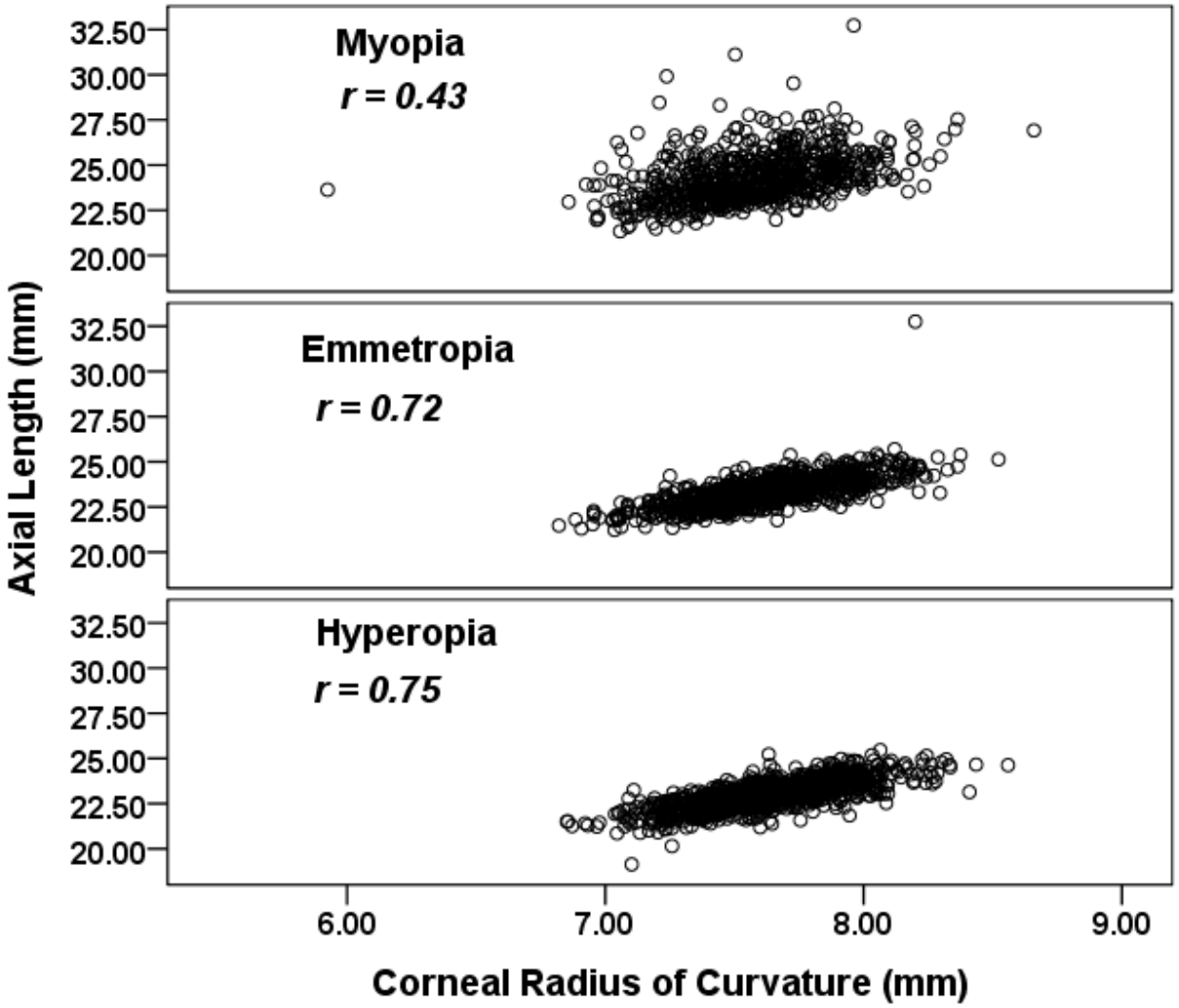


Figure 44. Distribution of Birth Place

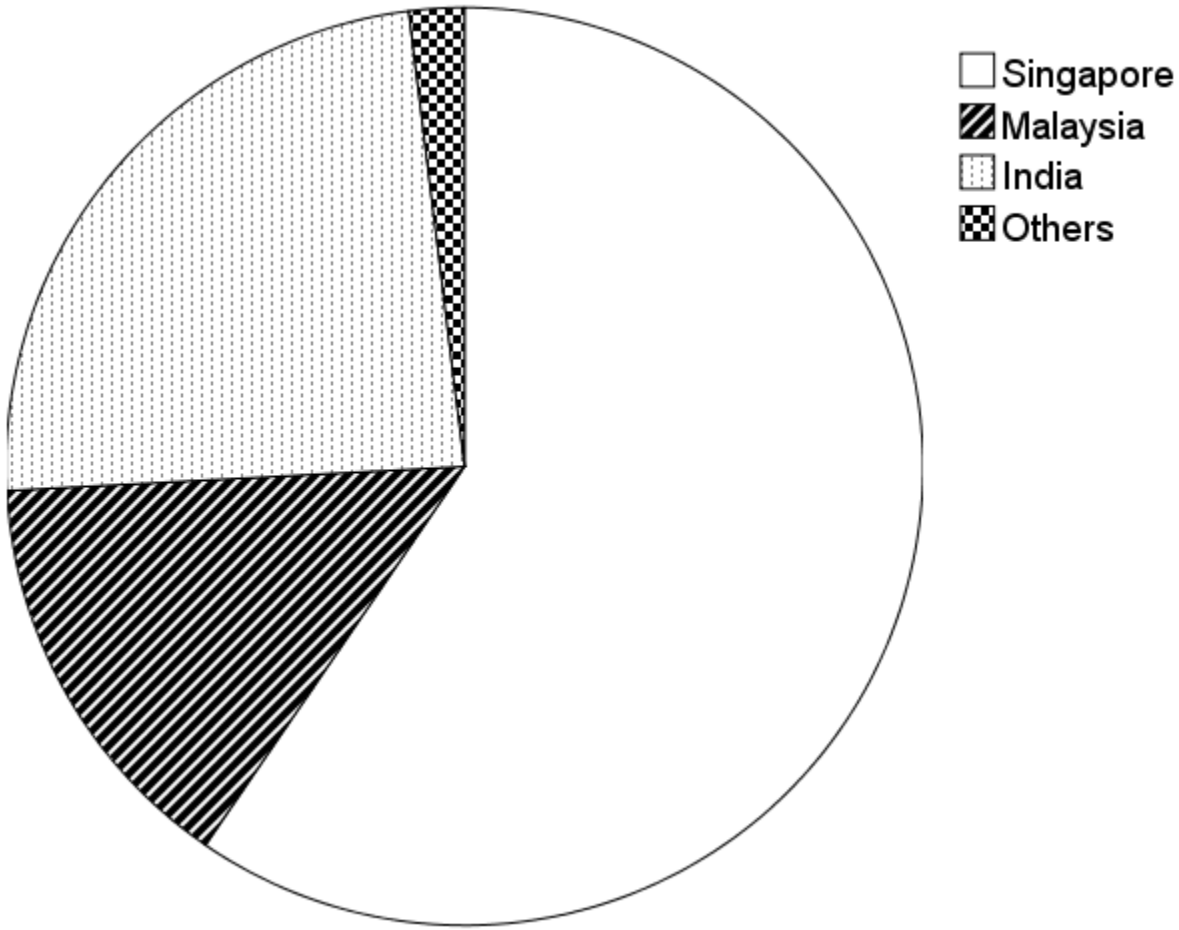


Figure 45. Distribution of Age at Migration among the First Generation Immigrants

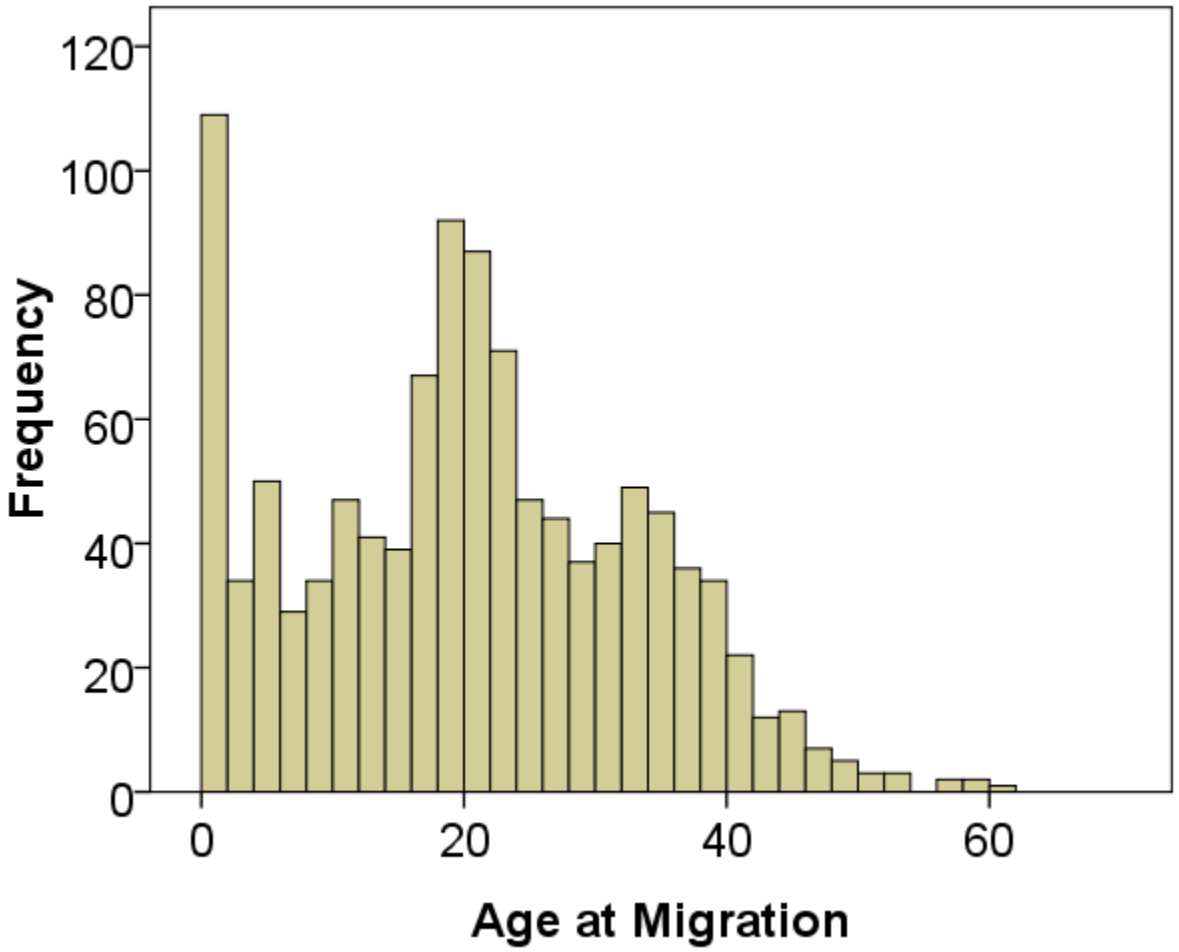


Figure 46. Association of Axial Length and Age at Migration

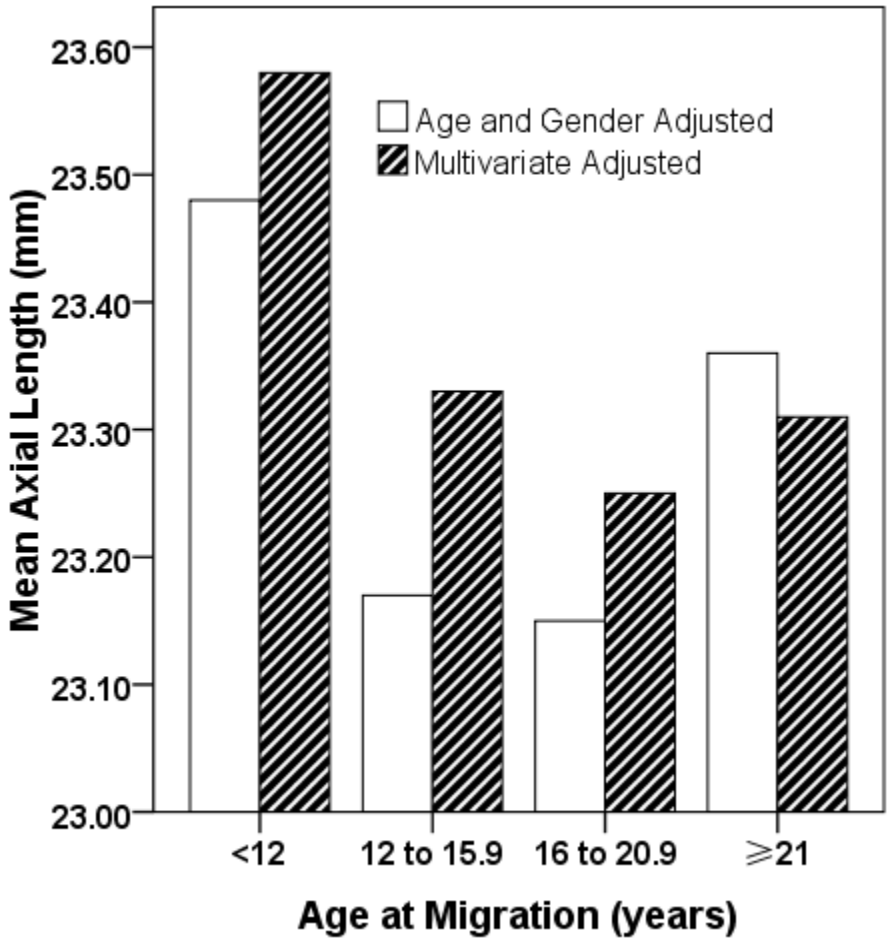


Figure 47. Distribution of Age-Related Macular Degeneration

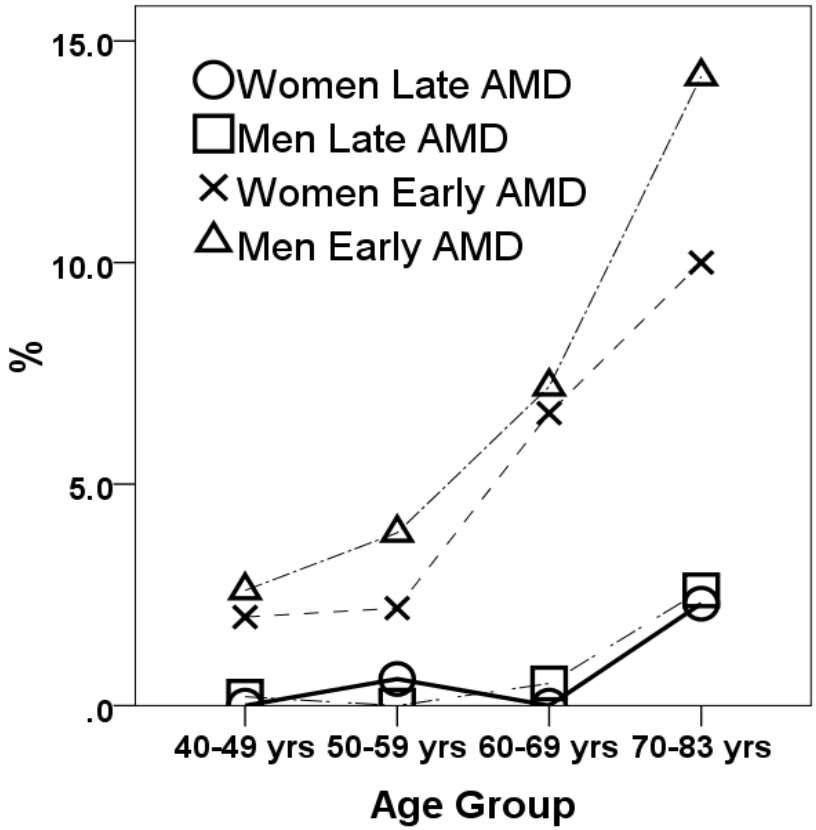


Figure 48. Distribution of Diabetic Retinopathy

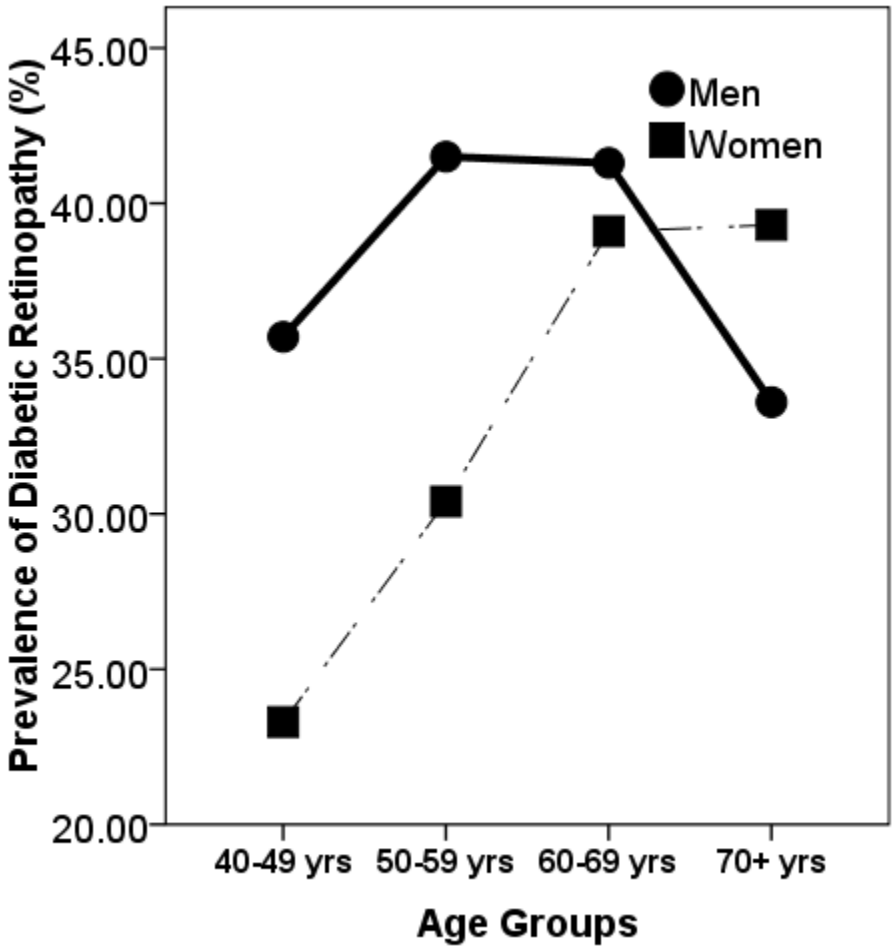


Figure 49. Distribution of Nuclear Cataract

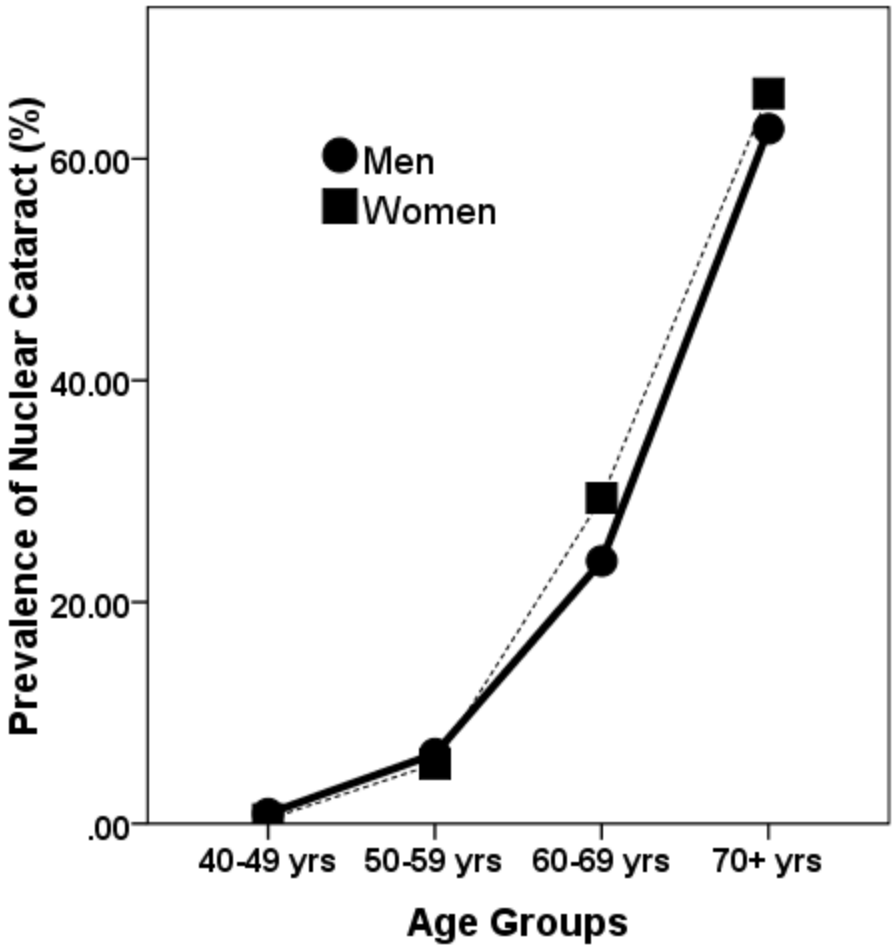


Figure 50. Distribution of Cortical Cataract

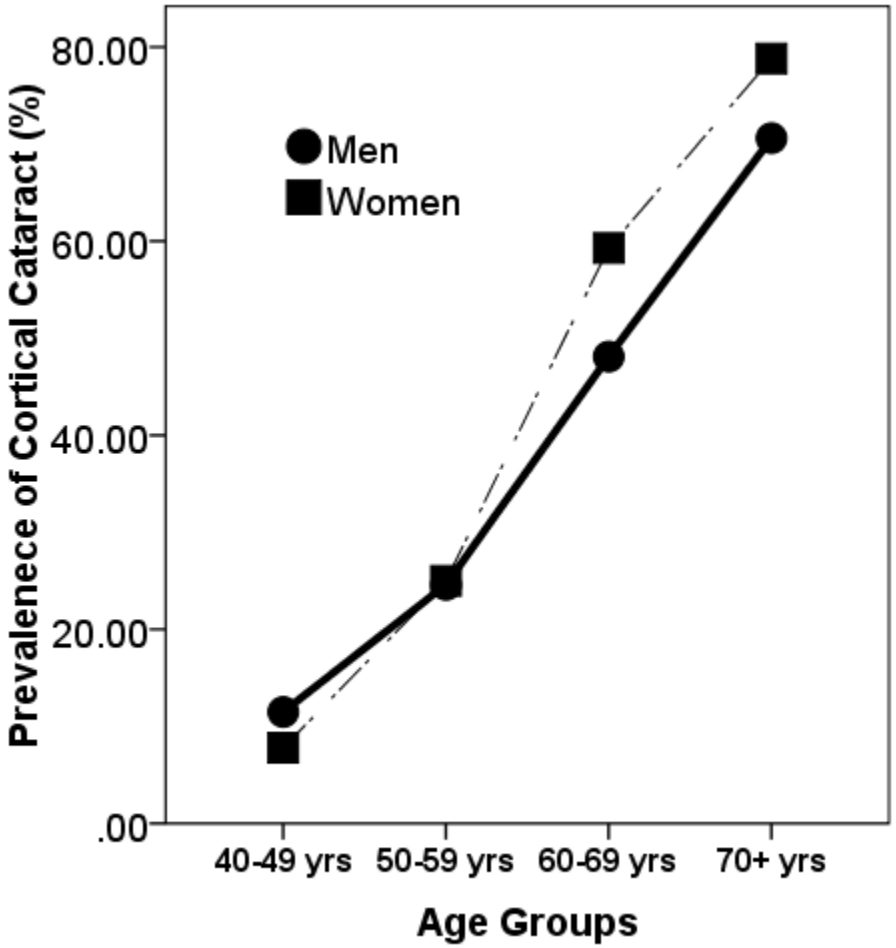


Figure 51. Distribution of Posterior Subcapsular Cataract

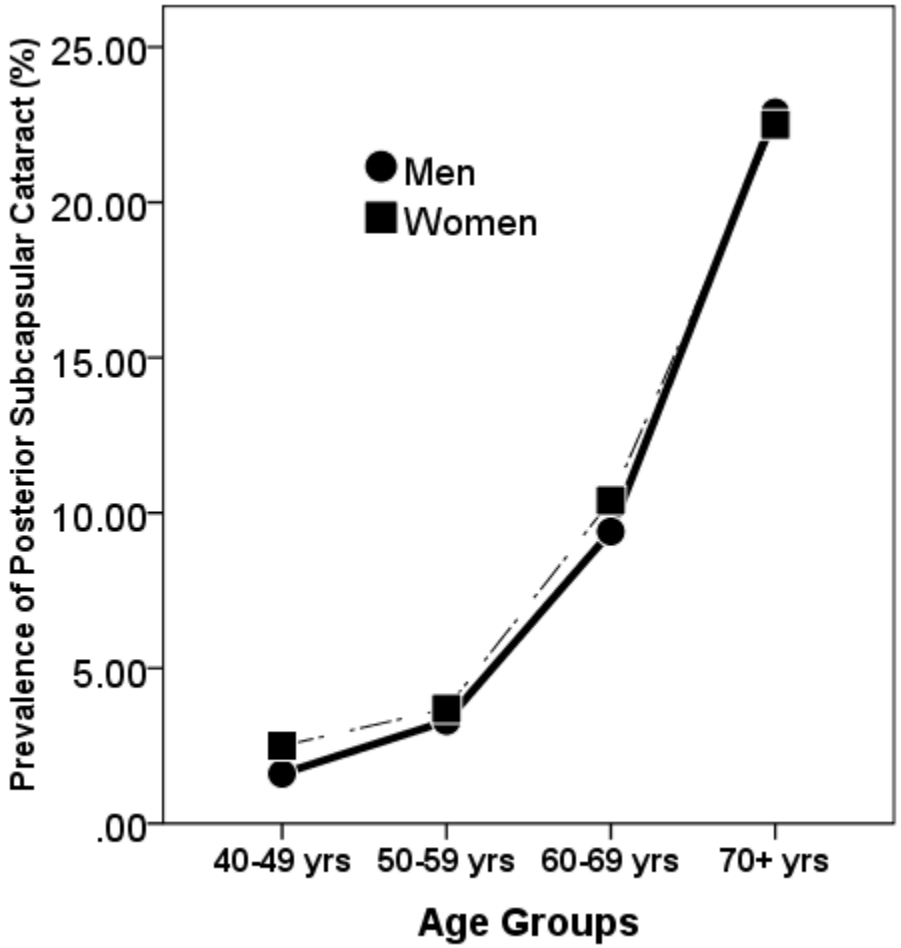


Figure 52. Distribution of Primary Open Angle Glaucoma

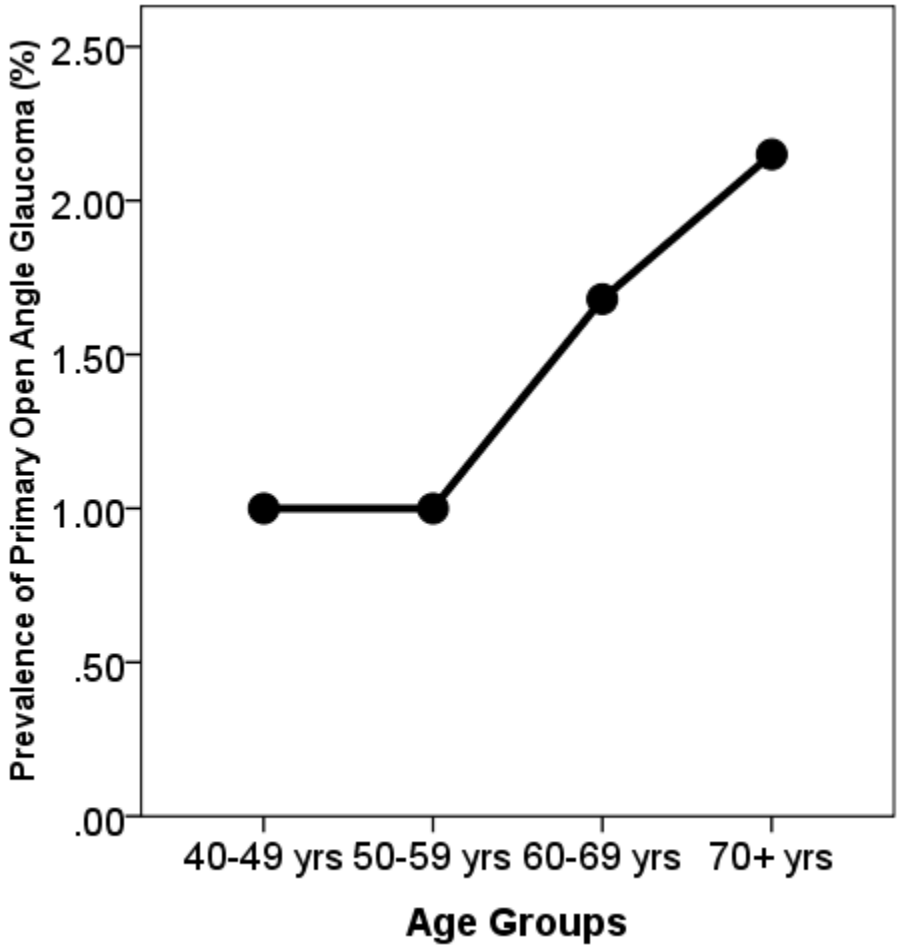


Figure 53. LOWESS Plot of the Relationship between Spherical Equivalent and Prevalence of Primary Open Angle Glaucoma

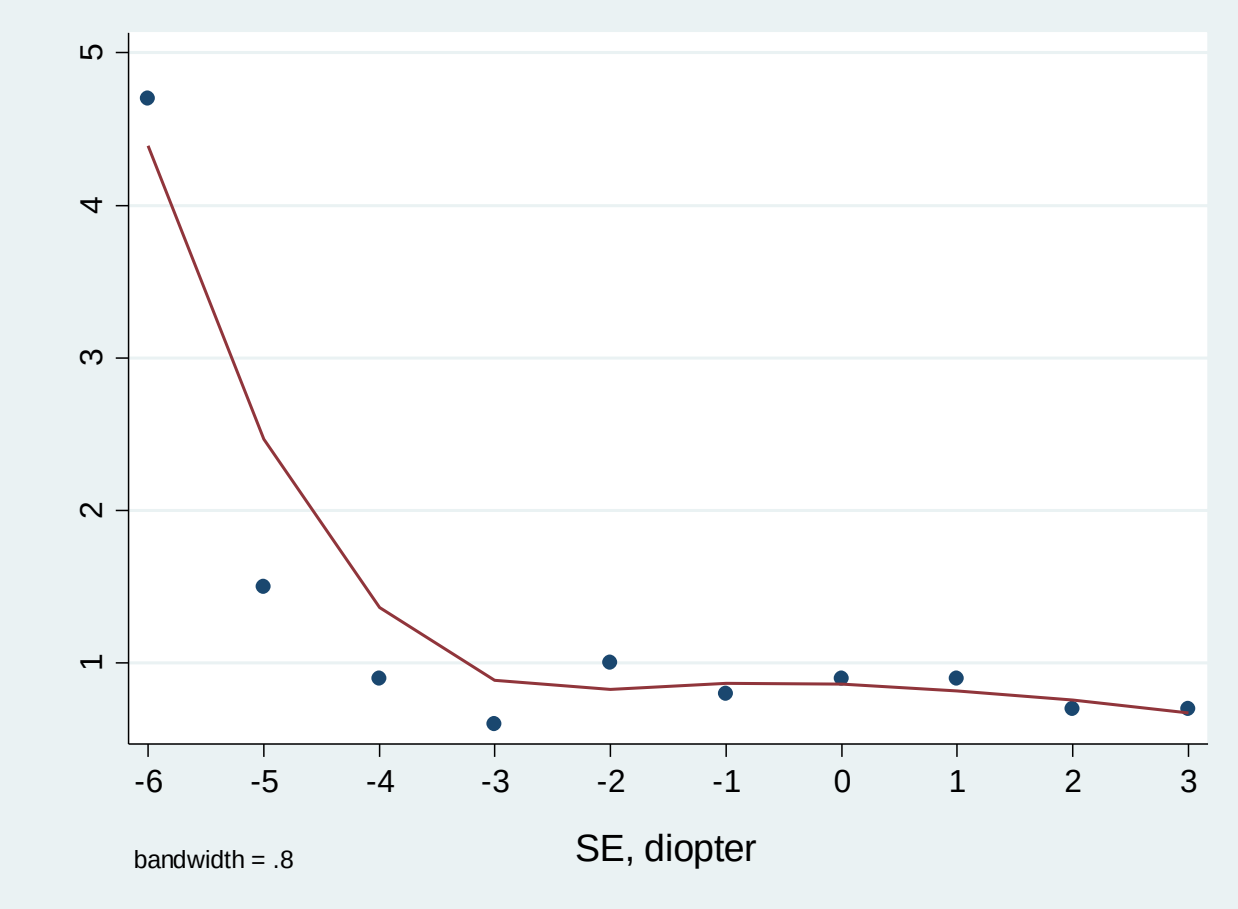


Figure 54. LOWESS Plot of the Relationship between Axial Length and Prevalence of Primary Open Angle Glaucoma

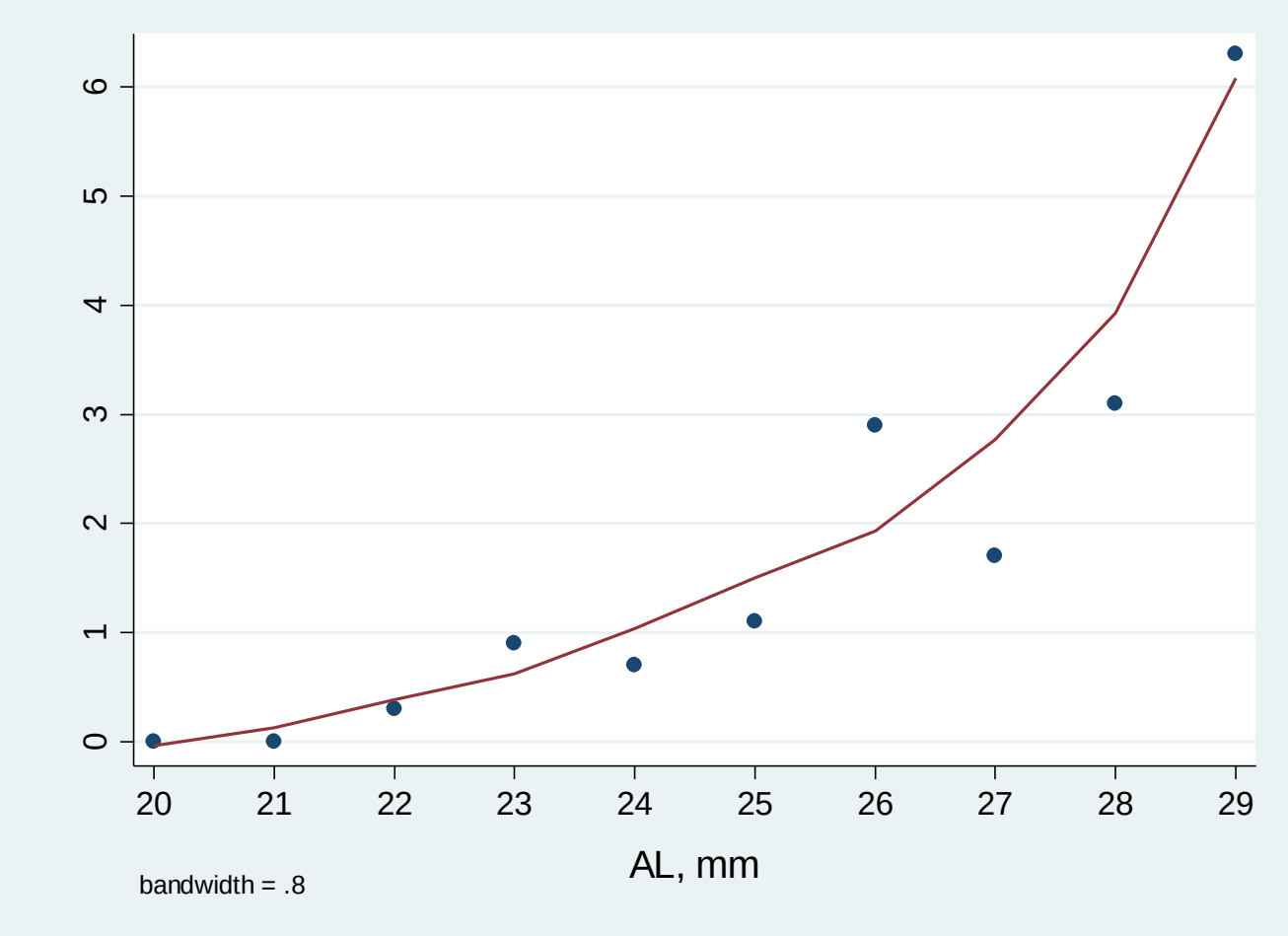


Figure 55. Forest Plot of Risk Estimates of the Association between Hyperopia and Prevalent Age-Related Macular Degeneration

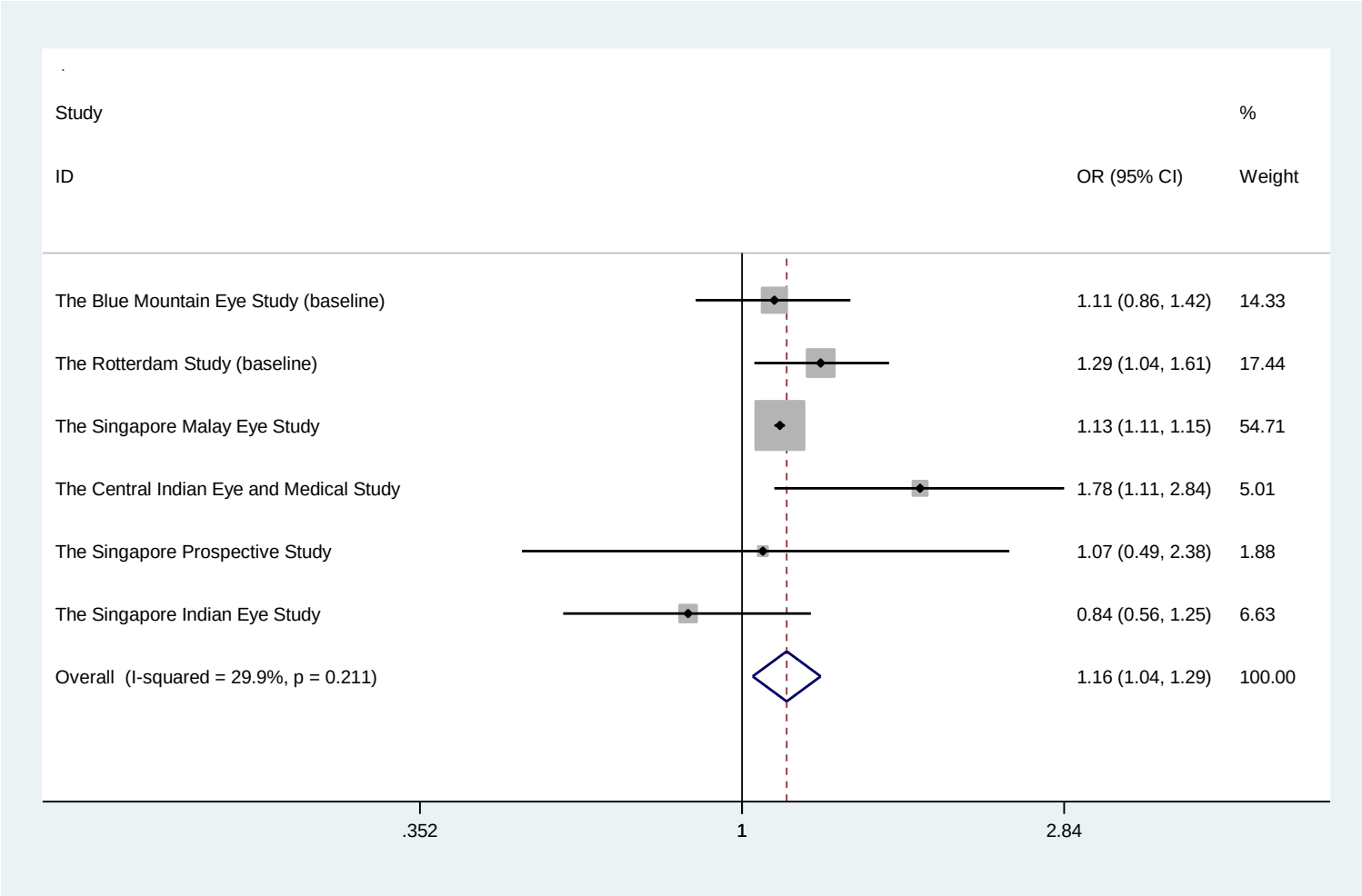


Figure 56. Forest Plot of Risk Estimates of the Association between Myopia and Prevalent Age-Related Macular Degeneration

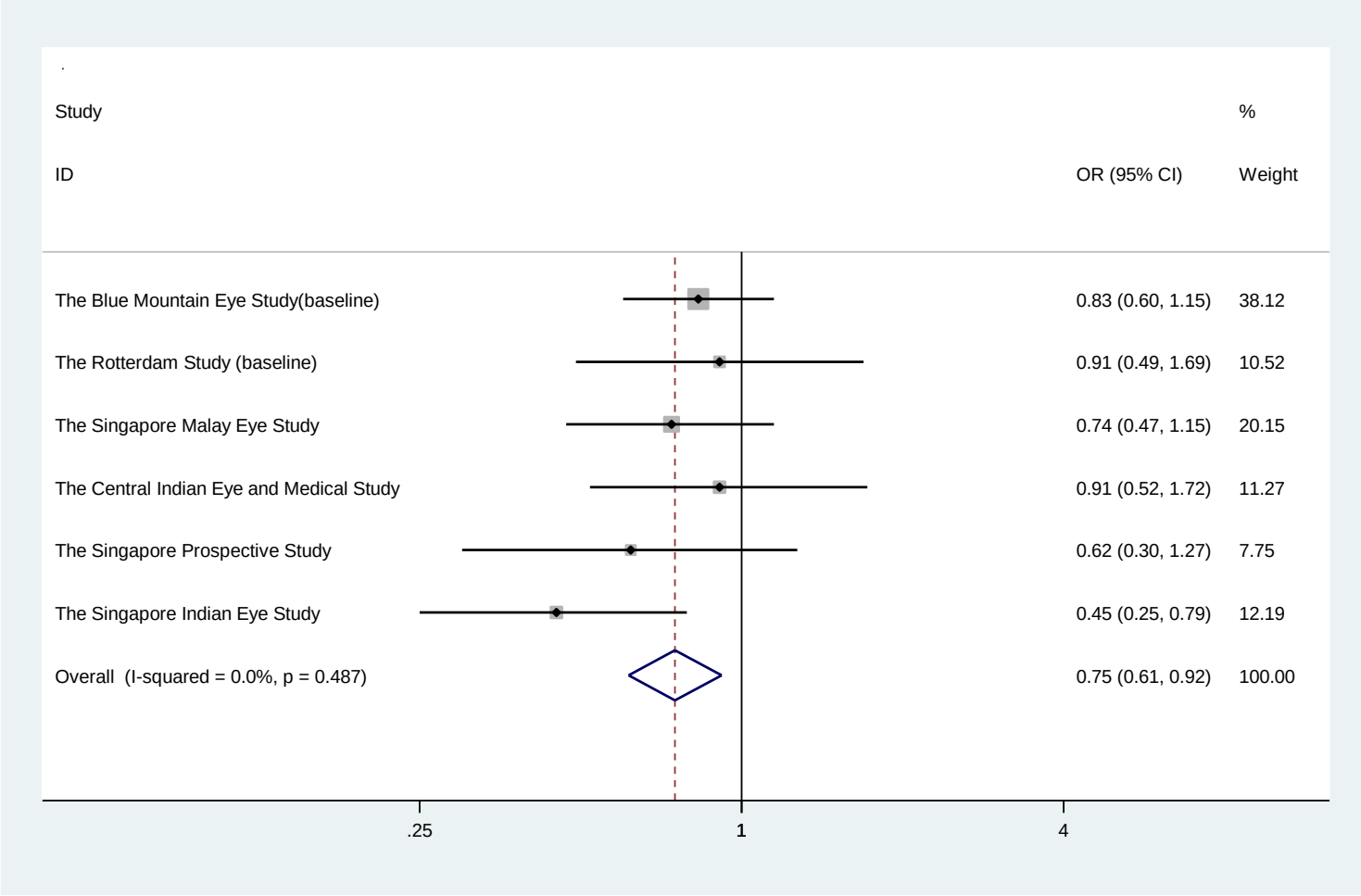


Figure 57. Forest Plot of Risk Estimates of the Association between Hyperopia and Incident Age-Related Macular Degeneration

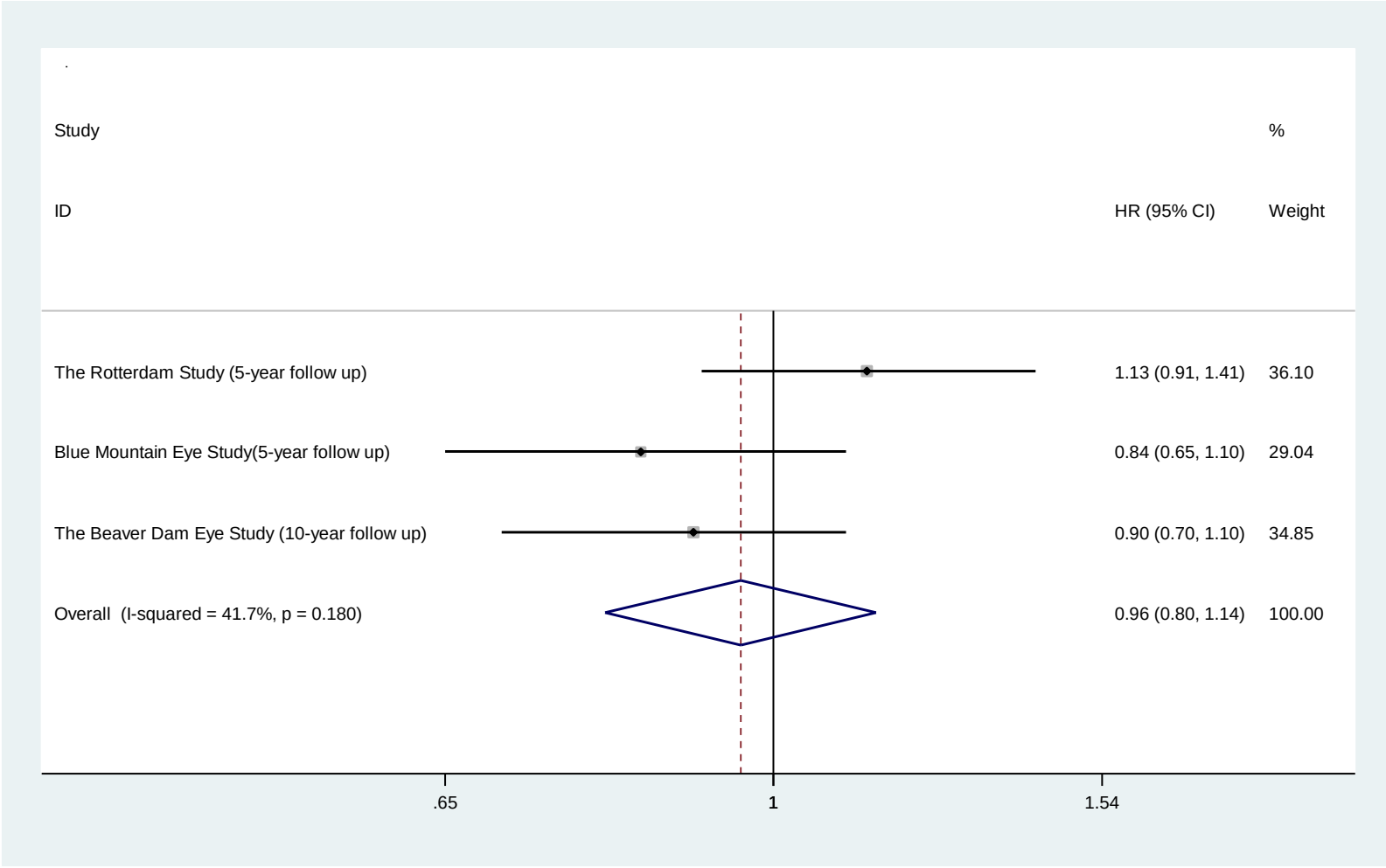
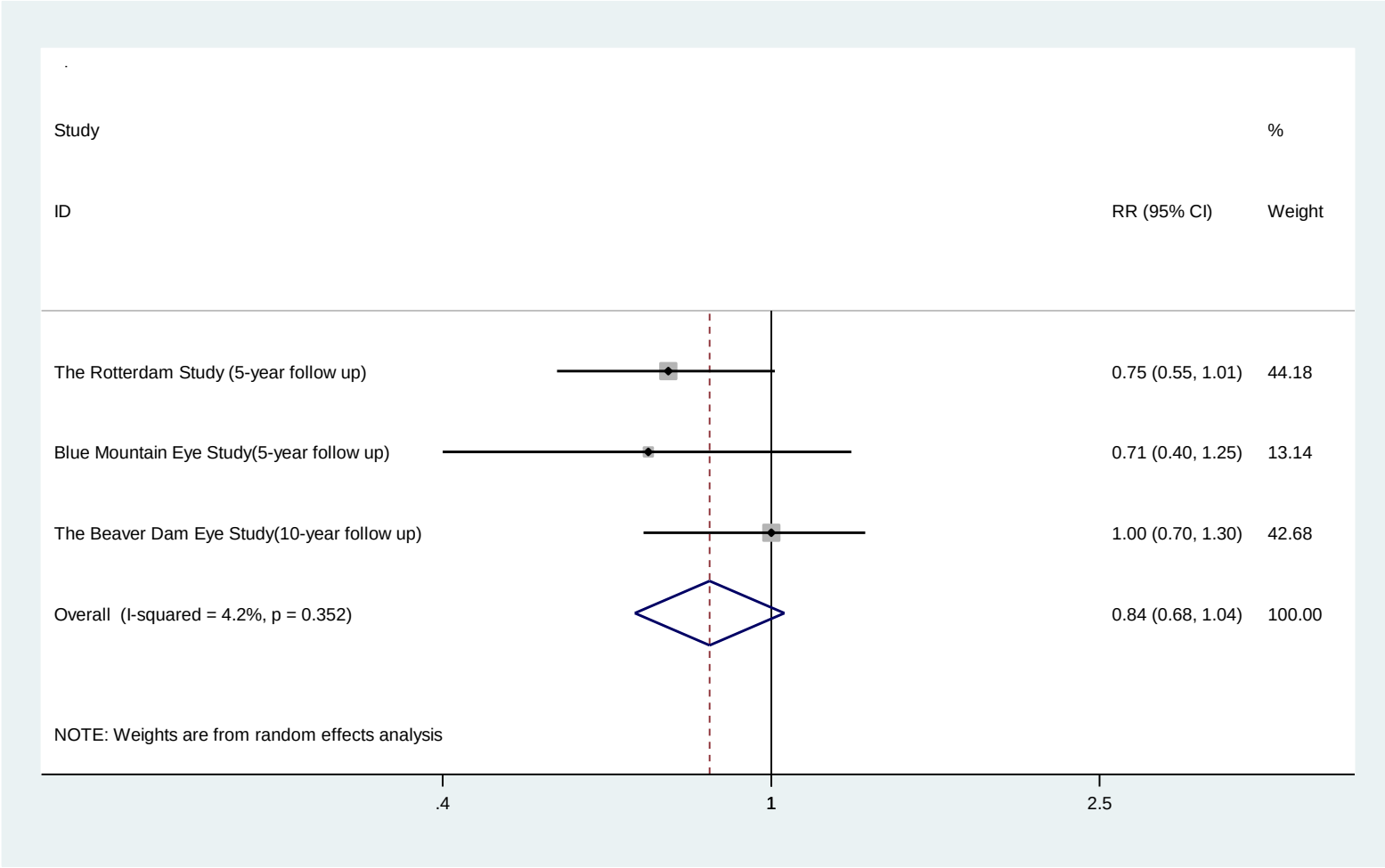


Figure 58. Forest Plot of Risk Estimates of the Association between Myopia and Incident Age-Related Macular Degeneration



APPENDICES

Appendix 1

Published manuscript entitled

‘Worldwide prevalence and risk factors for myopia’

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INVITED REVIEW

Worldwide prevalence and risk factors for myopia

Chen-Wei Pan, Dharani Ramamurthy and Seang-Mei Saw

Department of Epidemiology and Public Health, Yong Loo Lin School of Medicine, National University of Singapore, Singapore

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Correspondence: Seang-Mei Saw
E-mail address: ephssm@nus.edu.sg

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Abstract

Background: Myopia, the most common type of refractive error, is a complex trait including both genetic and environmental factors. Numerous studies have tried to elucidate the aetiology of myopia. However, the exact aetiology of myopia is still unclear.

Purpose: To summarize the worldwide patterns and trends for the prevalence of myopia and to evaluate the risk factors for myopia in population-based studies.

Recent findings: The prevalences of myopia vary across populations of different regions and ethnicities. In population-based studies on children, the prevalence of myopia has been reported to be higher in urban areas and Chinese ethnicity. The regional and racial difference is not so obvious in adult populations aged over 40 years. More time spent on near work, less time outdoors, higher educational level and parental history of myopia have been reported to increase the risk of myopia.

Conclusions: Environmental factors play a crucial role in myopia development. The effect of gene-environment interaction on the aetiology of myopia is still controversial with inconsistent findings in different studies. A relatively hyperopic periphery can stimulate compensating eye growth in the centre. Longitudinal cohort studies or randomized clinical trials of community-based health behaviour interventions should be conducted to further clarify the aetiology of myopia.

Myopia is a global public health problem leading to visual impairment and blinding complications.[1] The economic costs of myopia are also high. In Singapore, the mean annual direct cost of myopia for each Singaporean school children aged 7–9 years was estimated to be US$148.[2] In the United States, the National Health and Nutrition Examination Survey (NHANES) reported the annual direct cost of correcting distance vision impairment due to refractive errors to be between US$3.9 and US$7.2 billion.[3] The medical burden of high myopia includes pathologic complications such as myopic macular degeneration, choroidal neovascularisation, cataract and glaucoma.[1] Uncorrected refractive error could also impair vision-related quality of life and increase difficulty in performing vision-related tasks.[4]

In the past few decades, numerous epidemiology studies have provided information on the pattern of prevalence and risk factors for myopia. Population-based studies with sufficient sample sizes, high response rates and few biases provide the strongest evidence for examining the aetiology of myopia. A recent review summarized the data of prevalence and risk factors for myopia published in *Ophthalmic and Physiological Optics*.[5] However, several questions remain unanswered: Are the rates of myopia in Asia higher in East Asians than other ethnic groups in Asia? Is there any gene-environment interaction? Does outdoor activity play a crucial role in myopia development? In this perspective, we reviewed the major population-based studies on the epidemiology of myopia, summarized key findings and highlighted future challenges for the research community. The rationale for

grouping studies in this review was based on geographic location and ethnicity.

Prevalence of myopia in adults in Asian Countries

In mainland China, the prevalence of myopia for definitions of spherical equivalent (SE) of <−0.50 D, <−1.0 D, <−6.0 D, and <−8.0 D were reported to be 22.9% (95% CI 21.7, 24.2), 16.9% (95% CI 15.8, 18.0), 2.6% (95% CI 2.2, 3.1), and 1.5% (95% CI 1.1, 1.9) respectively, in the Beijing Eye Study (n = 4439, aged 40–90 years).[6] The limitation of this study is that refraction was not performed on subjects with an uncorrected visual acuity of 0.0 logMAR (Snellen 6/6) or better. The Shihpai Eye study in Taiwanese adults aged over 65 years reported the prevalence to be 19.4% and 14.5% for myopia of SE < −0.5 D and SE < −1.0 D, respectively. The prevalence of myopia in Taiwan seems to be lower than that of Beijing Eye Study. The difference in prevalence of <3.5% between Taiwan and Beijing is marginal. This difference in prevalence is attributed to the older sample in Taiwan leading to a hyperopic shift in refraction, but this difference in age would also work in the opposite direction with a potential myopic shift due to the onset of nuclear cataract in the older population.[7] In Japanese adults, the prevalence was reported to be 41.8% for myopia of SE < −0.5 D.[8] The Japanese study may have overestimated the prevalence of myopia due to younger participants and non-cycloplegic refraction.

In India, the prevalence of myopia for SE < −0.5 D in 40 year and older Indian adults in both urban and rural areas was reported to be 34.6% (n = 3723) in the Indian state of Andhra Pradesh, with a prevalence of 38.0% in rural areas and 31.9% in urban areas. The higher prevalence of myopia in the rural Indian population could be explained by higher rates of nuclear cataract in rural India leading to a myopic shift in refraction.[9] In another study of rural Indian adults aged over 39 year in Chennai (n = 2508), the prevalence was reported to be 31% for myopia of SE < −0.5 D.[10] The extent of non-participation bias cannot be elucidated as neither of the studies in India revealed details about the respondents and non-respondents.

The Tanjong Pagar Survey (TPS), the Singapore Malay Eyes Study (SiMES) and the Singapore Indian Eye Study (SINDI) analyzed the prevalence of myopia of SE < −0.50 D in Singaporean Chinese, Malay and Indian adults aged over 40 years and reported it to be 38.7%,[11] 26.2%[12] and 28.0%,[13] respectively. The difference in the prevalences may reflect secular trends over time as well as inter-ethnic variation since the TPS was conducted a few years prior to SiMES and SINDI.

In Bangladesh and Pakistani adults aged over 30 years, the prevalence of myopia (SE < −0.5 D) has been reported to be 23.8% (n = 11 624) and 36.5% (n = 14 490) respectively whereas it is about 48.1% in Indonesian young adults aged over 21 years (n = 1043).[14–16] The prevalence of myopia in Mongolian adults over 40 years was reported to be 17.2% (n = 1617).[17] In the WHO National Blindness and Low Vision Surveys in Bangladesh, non-cycloplegic refraction and subjective refraction were only performed on those with visual acuity worse than 0.30 logMAR (Snellen 6/12). Thus, the prevalence of myopia may have been overestimated (*Table 1*).

Prevalence of myopia in adults in Western Countries

In the United States, the 1999–2004 NHANES used an autorefractor to measure refractive data on a US non-institutionalized, civilian population aged 20 years or older. The age-standardized prevalence of myopia (SE < −1.0 D or less) was 33.1% (95% CI 31.5, 34.7) in 12 010 participants.[18] In this study, non-cycloplegic refraction may have caused an overestimation of myopic persons among younger participants. In the Baltimore Eye Survey (n = 5028), the prevalence of myopia (SE < −0.5 D) was 28.1% among the white and 19.4% among the black.[19] The Los Angeles Latino Eye Study reported a myopia prevalence of 16.8% in 40 years or older adults (n = 5927) in the worse eye.[20] In the Beaver Dam Eye Study, the age-gender adjusted prevalence of myopia (SE < −0.5 D) was 26.2% based on the data of the right eye.[21] The Barbados Eye Study examined the prevalence of myopia in African-Americans aged 40–84 years (n = 4709). The age-gender adjusted prevalence of myopia (SE < −0.5 D) was 21.9% (95% CI 20.6, 23.2) based on objective refraction data.[22] The Beaver Dam Eye study of adults aged over 43 years may have overestimated the prevalence of myopia in terms of the younger respondents. On the contrary, the NHANES on people aged over 20 years may have underestimated the prevalence of myopia since the younger working adults were more difficult to recruit than the older ones.

In the UK, among a total of 2487 randomly selected 44-year-old members of the 1958 British birth cohort, 1214 individuals (49%; 95% CI 48.8, 50.8) were myopic. Refraction was measured by autorefraction using the Nikon Retinomax 2 (Nikon Corp., http://www.nikon.com/), under non-cycloplegic conditions. Thus, myopia prevalence may have been overestimated.[23] In Norway, non-cycloplegic refraction was measured in a population-based sample of young (20–25 years) and middle-aged (40–45 years) adults. A total of 3137 persons (1248 young and 1889 middle-aged adults) with corrected visual acuity worse than 0.3 logMAR (Snellen 6/12) in either eye were included in the study. The prevalence of myopia (SE <

Table 1. Prevalence of myopia in adults in population-based studies

Author (year)	Country	*N*	Age	Definition	Refraction method	Prevalence (%)	95% CI
Cheng (2003)	Taiwan	1361	65+	SE < −0.5 D	Subjective	19.4	16.7, 22.1
Sawada (2007)	Japan	3021	40+	SE < −0.5 D	Subjective	41.8	40.0, 43.6
Saw (2002)	Indonesia	1043	21+	SE < −0.5 D	Objective	48.1	45.0, 51.1
Gupta (2008)	Myanmar	1863	40+	SE < −1.0 D	Objective	42.7	40.4, 44.9
Xu (2005)	China	5324	40+	SE < −0.5 D	Subjective	22.9	21.7, 24.2
Krishnaiah (2009)	India	3642	40+	SE < −0.5 D	Subjective	34.6	33.1, 36.1
Raju (2004)	India	2508	40+	SE < −0.5 D	Subjective	31.0	Not available
Shah (2008)	Pakistan	14 490	30+	SE < −0.5 D	Objective	36.5	35.7, 37.3
Bourne (2004)	Bangladesh	11 189	30+	SE ≤ −0.5 D	Objective	23.8	23.8, 23.8
Wong (2000)	Singapore	1232	40+	SE < −0.5 D	Subjective	38.7	35.5, 42.1
Saw (2008)	Singapore	2974	40+	SE < −0.5 D	Subjective	26.2	26.0, 26.4
Pan (2011)	Singapore	2805	40+	SE < −0.5 D	Subjective	28.0	25.8, 30.2
Tarczy-Hornoch (2006)	USA	5396	40+	SE ≤ −1.0 D	Subjective	16.8	Not available
Katz (1997)	USA	5028	40+	SE < −0.5 D	Subjective	28.1 (white); 19.4 (black)	Not available
Vitale (2008)	USA	12 010	20+	SE < −0.5 D	Objective	33.1	31.5, 34.7
Wu (1999)	USA	4709	40–84	SE < −0.5 D	Objective	21.9	20.6, 23.2
Wang (1994)	USA	4926	43–84	SE < −0.5 D	Objective	26.2	Not available
Wensor (1999)	Australia	4744	40–98	SE < −0.5 D	Subjective	17.0	15.8, 18.0
Attebo (1999)	Australia	3654	49–97	SE < −0.5 D	Subjective	15.0	Not available
Rahi (2011)	UK	2487	44–45	SE ≤ −0.75 D	Objective	49.0	48.8, 50.8
Midelfart (2002)	Norway	3137	20–25	SE < −0.5 D	Subjective	35.0	Not available
			40–45			30.3	

−0.5 D) was 35.0% in the young adult group and 30.3% in the middle-aged group. Prevalence of myopia was overestimated especially for the young adult group due to the non-cycloplegic refraction.[24]

In Australia, the Blue Mountains Study reported a prevalence of myopia in adults aged 40–97 years of 15.0% (n = 3654).[25] The Visual Impairment Project reported a myopia (SE < −0.5 D) prevalence of 17.0% (95% CI 15.8, 18.0).[26] A meta-analysis by the Eye Diseases Prevalence Research Group estimated the crude prevalence rates for myopia of −1.0 D or less as 25.4%, 26.6%, and 16.4% in the United States, Western Europe and Australia, respectively.[27] (*Table 1*)

Based on the published data of myopia prevalence on adults, it is still unclear whether the myopia prevalence is higher in East Asian Countries than in Western Countries. The prevalence of myopia is 38.7% in Singaporean Chinese (SE < −0.5 D).[11] However, the meta-analysis by Kempen *et al.*[27] showed that the prevalence of myopia is 25.4% and 26.6% for White subjects in the United States and Western Europe using a more conservative definition of myopia (SE < −1.0 D), respectively. The cut off used to define myopia is arbitrary but the prevalence might change significantly by a small shift in this cut-off value.[26] In Singapore, the Chinese have a higher prevalence of myopia compared with Malays and Indians living in the same country and the myopia prevalence in South Asia in the Indian population is only marginally lower than the Singaporean Chinese. The myopia prevalence reported in the Singaporean Malays[12] and Indians[28] are also lower than those from North America.[19,21]

Worldwide prevalence of myopia in children

Tables 2 and 3 summarize the overall and age-specific prevalence of myopia in children. The Refractive Error Study in Children (RESC) was conducted in different countries using the same sampling strategies, procedures to measure refraction and definitions of myopia, in order to compare the prevalence of myopia across different study populations. In Nepal, the prevalence of myopia ranged from 10.9% in 10-year-old children, 16.5% in 12-year-olds, to 27.3% in 15-year-old children living in the urban region, whereas it was <3% in 5–15 year old children in rural Nepal.[29,30] In urban India, the prevalence of myopia was 4.7%, 7.0% and 10.8% in 5, 10 and 15 year-olds, respectively. On the other hand, the prevalence of myopia was 2.8%, 4.1% and 6.7% in 7, 10 and 15-year-olds, respectively in the rural region.[31,32] Among urban Chinese children the prevalence of myopia ranged from 5.7% in 5-year-olds, 30.1% in 10-year-olds and increased to 78.4% in the 15-year-olds.[33] In rural parts of northern China, the prevalence of myopia was almost nil in 5-year-olds and steadily increased to 36.7% and 55.0%

Table 2. Prevalence of myopia in children in population-based studies

Author (Year)	Location	*N*	Age range	Myopia definition	Prevalence (%)	95% CI
Pokharel (2000)	Mechi Zone, Nepal	5067	5–15 years	≤−0.5 D	1.2	Not available
Sapkota (2008)	Kathmandu, Nepal	4282	10–15 years	≤−0.5 D	19.0	17.8, 20.2
Murthy (2002)	New Delhi, India	6447	5–15 years	≤−0.5 D	7.4	5.0, 9.7
Dandona (2002)	Andhra Pradesh, India	4074	7–15 years	≤−0.5 D	4.1	3.3, 4.9
Goh (2005)	Gombak district, Malaysia	4634	7–15 years	≤−0.5 D	20.7	17.3, 24.1
Zhao (2000)	Shunyi District, Beijing, China	5884	5–15 years	≤−0.5 D	21.6	Not available
He (2004)	Guangzhou, China	4364	5–15 years	≤−0.5 D	38.1	36.3, 39.8
He (2007)	Yangxi,Guangdong province,China	2454	13–17 years	≤−0.5 D	42.4	35.8, 49.0
Naidoo (2003)	South Africa	4890	5–15 years	≤−0.5 D	4.0	3.3, 4.8
Maul (2000)	La Florida, Chile	5303	5–15 years	≤−0.5 D	7.3	Not available
Saw (2005)	Singapore	1453	7–9 years	≤−0.5 D	36.7	34.2, 39.2
Dirani (2009)	Singapore	2369	6–72 months	≤−0.5 D	11.0	10.9, 11.2
Zadnik (1997)	USA	716	6–14.9 years	≤−0.75 D	6 years: 2, 12 years: 20	Not available
Ip (2008)	Australia	2353	12 years	≤−0.5 D	11.9	6.6, 17.2
Rudnicka (2010)	UK	1053	10–11 years	≤−0.5 D	3.4	Not available
O'Donoghue (2010)	Northern Ireland	1053	6–7 years	≤−0.5 D	2.8	1.3, 4.3
			12–13 years		17.7	13.2, 22.2
Logan (2011)	England	327	6–7 years	≤−0.5 D	9.4	Not available
			12–13 years		29.4	

in 15-year-old males and females respectively.[34] In the rural region of Southern China, 36.8% of 13-year-olds, 43.0% of 15-year-olds and 53.9% of 17-year-olds were found to be myopic.[35] In brief, the prevalence of myopia was highest (78.4%) in 15-year-old urban Chinese children[33] and lowest (1.2%) in 5–15 year old rural Nepalese children.[30]

In Singapore, the prevalence of myopia was 29.0% in 7-year-olds, 34.7% in 8-year-olds and 53.1% in 9-year-olds in the school-based population of the Singapore Cohort Study of Risk factors for Myopia (SCORM)[36] while the Strabismus, Amblyopia and Refractive error Study in Singapore Preschool Children (STARS) reported that the prevalence of myopia was 11.0% in Chinese children aged 6–72 months.[37] In Hong Kong, a large cross-sectional survey reported that the prevalence was 17.0% in children aged <7 years and which increased to 37.5% among those aged 8 years and 53.1% in children aged more than 11 years.[38] The prevalence of myopia among Taiwanese Chinese primary school children aged 7 years was 5.8% in 1983, 3.0% in 1986, 6.6% in 1990, 12.0% in 1995 and 20.0% in 2000. Among Taiwanese children aged 12 years, the myopic rates were 36.7%, 27.5%, 35.2%, 55.5% and 61.0% correspondingly. At the junior high school level, the prevalence was 64.2%, 61.6%, 74.0%, 76.0% and 81.0% respectively. Among children aged 16–18 years, the myopia prevalence was almost constant at around 74–75% in studies conducted in 1983, 1986 and 1990. However, the prevalence rate increased to 84% in studies in 1995 and 2000.[39]

The prevalence of myopia has also been reported in non-Asian populations. Among South African children, the prevalence of myopia was about 3% or 4% increasing to 6.3% in 14-year-olds and 9.6% in 15-year-olds.[40] In Chile, 3.4% of the 5-year-olds were myopic and the prevalence rate increased to 19.4% and 14.7% in the 15-year-old males and females respectively.[41] In Australia, the Sydney Myopia Study (SMS) reported the myopia prevalence to be 1.4% among 6-year-olds ($n = 1765$) with 0.8% in the White children and 2.7% among other ethnic groups.[42] Among 12-year-old children ($n = 2353$), the overall myopia prevalence was 11.9%, which was lower among European Caucasian children (4.6%) and Middle Eastern children (6.1%) and higher among East Asian (39.5%) and South Asian (31.5%) children,[43] although the sample size of non-White groups in SMS was very small. In the Orinda Longitudinal Study of Myopia (OLSM), the prevalence of myopia increased from 4.5% in 6–7-year-old children to 28% in 12-year-old children in a predominantly white population in the United States.[44] In the USA Collaborative Longitudinal Evaluation of Ethnicity and Refractive Error (CLEERE), Asians had the highest prevalence (18.5%), followed by Hispanics (13.2%). Whites had the lowest prevalence of myopia (4.4%), which was not significantly different from African Americans (6.6%). In the CLEERE study, however, children with different ethnicities were from different geographical areas so that the comparison of prevalence was affected by both genetic and environmental factors.[45]

Table 3. Age-specific prevalence of myopia in children

Author (Year)	Study design/ Population (*N*)	Response rate (%)	Cycloplegic refraction	Myopia definition	Prevalence (95% CI)
Dirani (2009)	Population-based cross-sectional study, *N* = 2369 Chinese children	72.3	Cycloplegic autorefraction	≤−0.5 D	6–11.9 months: 15.8% (10.6, 22.2) 12–23.9 months: 14.9% (11.7, 18.5) 24–35.9 months: 20.2% (16.5, 24.2) 36–47.9 months: 8.6% (6.3, 11.3) 48–59.9 months: 7.6% (5.5, 10.1) 60–72 months: 6.4% (4.5, 8.8)
Saw (2005)	School-based cross-sectional study, *N* = 1453 Chinese children	66.3	Cycloplegic autorefraction	≤−0.5 D	7 years: 29.0% (25.5, 32.6) 8 years: 34.7% (30.4, 39.0) 9 years: 53.1% (47.9, 58.4)
Sapkota (2008)	Population-based *N* = 4282 children from Kathmandu, Nepal	95.1	Cycloplegic autorefraction	≤−0.5 D	10 years: 10.9% (7.00, 14.7) 11 years: 13.8% (10.5, 17.2) 12 years: 16.5% (13.2, 19.8) 13 years: 19.4% (16.7, 22.1) 14 years: 23.3% (20.0, 26.7) 15 years: 27.3% (22.6, 32.0)
Murthy (2002)	Population-based *N* = 6447 children from New Delhi, India	92.0	Cycloplegic retinoscopy	≤−0.5 D	5 years: 4.68% (2.54, 6.83) 6 years: 5.87% (2.59, 9.15) 7 years: 3.13% (1.17, 5.08) 8 years: 5.67% (2.50, 8.84) 9 years: 5.33% (2.61, 8.05) 10 years: 6.95% (3.44, 10.5) 11 years: 9.85% (5.91, 13.8) 12 years: 9.66% (5.64, 13.7) 13 years: 10.6% (6.02, 15.2) 14 years: 10.2% (6.85, 13.5) 15 years: 10.8% (6.71, 14.8)
Dandona R (2002)	Population-based *N* = 4074 children from Andhra Pradesh, India	92.3	Cycloplegic retinoscopy	≤−0.5 D	7 years: 2.80% (1.28, 4.33) 8 years: 2.83% (1.50, 4.16) 9 years: 3.90% (2.05, 5.74) 10 years: 4.06% (2.09, 6.03) 11 years: 2.73% (1.38, 4.09) 12 years: 4.79% (2.91, 6.97) 13 years: 5.43% (3.25, 7.60) 14 years: 6.74% (3.31, 10.2) 15 years: 6.72% (4.31, 9.12)
Goh (2005)	Population-based *N* = 4634 children from Gombak district, Malaysia	32.8	Cycloplegic autorefraction	≤−0.5 D	7 years: 10.0% (6.8, 13.1) 8 years: 14.0% (10.3, 17.6) 9 years: 16.3% (11.7, 20.9) 10 years: 16.2% (11.6, 20.7) 11 years: 22.6% (17.0, 28.2) 12 years: 24.8% (19.1, 30.6) 13 years: 25.3% (19.5, 31.1) 14 years: 32.5% (25.5, 39.6) 15 years: 32.5% (25.5, 39.6)
Zhao (2000)	Population-based *N* = 5884 children from Shunyi District, Beijing, China	95.9	Cycloplegic autorefraction	≤−0.5 D	Males: 5 years: 0 15 years: 36.7% (29.9, 43.4) Females: 5 years: 0 15 years: 55.0% (49.4, 60.6)
He (2004)	Population-based cluster sampling, *N* = 4364 children from Guangzhou, China	86.4	Cycloplegic autorefraction	≤−0.5 D	5 years: 5.7% (2.3, 9.0) 6 years: 5.9% (2.6, 9.2) 7 years: 7.7% (4.7, 10.8) 8 years: 14.0% (10.4, 17.6)

Table 3. (Continued)

Author (Year)	Study design/ Population (*N*)	Response rate (%)	Cycloplegic refraction	Myopia definition	Prevalence (95% CI)
					9 years: 25.9% (22.0, 29.8) 10 years: 30.1% (24.4, 35.8) 11 years: 41.7% (37.3, 46.1) 12 years: 49.7% (44.7, 54.6) 13 years: 57.4% (52.1, 62.6) 14 years: 65.5% (62.4, 68.5) 15 years: 78.4% (74.5, 82.2)
He (2007)	Population-based *N* = 2454 children from Yangxi, Guangdong province, China	97.6	Cycloplegic autorefraction	≤–0.5 D	13 years: 36.8% (29.2, 44.3) 14 years: 38.8% (30.8, 46.7) 15 years: 43.0% (34.5, 51.4) 16 years: 46.8% (37.7, 55.9) 17 years: 53.9% (39.6, 68.1)
Giordano (2009)	Population-based cross-sectional study, *N* = 1268 African-American and *N* = 1030 White children	Not stated	Cycloplegic autorefraction	≤–1.0 D	African-American: 6–11 months: 7.5% 12–23 months: 10.5% 24–35 months: 5.9% 36–47 months: 6.2% 48–59 months: 6.6% 60–72 months: 7.4% Whites: 6–11 months: 0% 12–23 months: 2.3% 24–35 months: 1.1% 36–47 months: 0% 48–59 months: 1.5% 60–72 months: 1.1%
Naidoo (2003)	Population-based *N* = 4890 children from South Africa	87.3	Cycloplegic autorefraction	≤–0.5 D	5 years: 3.2% (0.6, 5.7) 6 years: 4.6% (2.4, 6.7) 7 years: 2.5% (0.8, 4.2) 8 years: 2.9% (1.2, 4.6) 9 years: 3.1% (1.4, 4.8) 10 years: 1.9% (0.6, 3.2) 11 years: 4.4% (2.8, 6.1) 12 years: 4.4% (2.2, 6.6) 13 years: 3.4% (1.7, 5.2) 14 years: 6.3% (3.6, 8.9) 15 years: 9.6% (6.4, 12.7)
Maul (2000)	Population-based *N* = 5303 children from La Florida, Chile	75.8	Cycloplegic autorefraction	≤–0.5 D	Males: 5 years: 3.4% (1.87, 5.00) 15 years: 19.4% (13.6, 25.2) Females: 5 years: 3.4% (1.72, 5.05) 15 years: 14.7% (10.1, 19.2)
Solang (2008)	Population-based *N* = 2441 children from Brazil	86.4	Cycloplegic autorefraction	≤–0.5 D	11 years: 5.4% (3.72, 7.08) 12 years: 4.52% (2.53, 6.65) 13 years: 5.83% (4.57, 7.08) 14 years: 6.05% (4.2, 7.89)

In a Swedish school-based sample of 1045 children aged from 12 to 13 years, refraction was performed using 1 drop of 0.5% tropicamide and measured by retinoscopy. The prevalence of myopia (SE ≤ −0.5 D) was reported to be 49.7% and the prevalence of bilateral myopia was reported to be 39.0%.[46] In another study in the UK, non-cycloplegic autorefraction data were available for 7554 children at the age of 7 from a birth cohort study. Using a definition of 'likely to be myopic' as SE ≤ −1.50 D, this study reported a prevalence of myopia of 1.5% in 7-year-old white children.[47] The Northern Ireland Childhood Errors of Refraction study,

a population-based cross-sectional study, examined 661 white 12–13-year-olds and 392 white 6–7-year-old children between 2006 and 2008. The prevalence of myopia was reported to be 2.8% (95% CI 1.3, 4.3) in the 6–7-year-old age group and 17.7% (95% CI 13.2, 22.2) in the 12–13-year-old age group.[48] The Aston Eye Study, an ongoing multi-racial sample of school children from the metropolitan area of Birmingham, England, reported preliminary cross-sectional data on 213 South Asian, 44 black African Caribbean and 70 white European children aged 6–7 years and 114 South Asian, 40 black African Caribbean and 115 white European children aged 12–13 years and found that myopia prevalence was 9.4% and 29.4% for the two age groups, respectively. Ethnic differences in myopia prevalence were found with South Asian children having higher levels than white European children (36.8% vs 18.6%) for the children aged 12–13 years.[49] The Child Heart and Health Study in England used population-based sampling stratified by socioeconomic status and reported the prevalence of myopia to be 3.4% in White children aged 10–11 years. However, non-cycloplegic refraction in this study might have led to an overestimation of the myopia prevalence.[50] In Greece and Bulgaria, four schools from the centre of a Greek city were chosen and two schools from the centre of a Bulgarian city. Non-cycloplegic autorefraction was performed on children aged 10–15 years. The prevalence of myopia (SE ≤ -0.75 D) was 37.2% in Greek children and 13.5% in Bulgarian children.[51]

In summary, the prevalence of myopia in Chinese children is higher than other ethnic groups. Moreover, the prevalence of myopia in European children seems to be lower than that in Asian children generally. Data from most studies have also documented a clear urban–rural difference in the prevalence of myopia. Studies on populations with very similar genetic backgrounds growing up in different environments in India, Nepal and China have shown that those growing up in rural environments have a lower prevalence of myopia. For the Chinese ethnicity, the prevalence of myopia in cities such as Guangzhou and Hong Kong is comparable to those reported for Singapore and urban areas of Taiwan. However, recent evidence showed that the prevalence in rural southern China is also very high. Whether this high prevalence of myopia in rural China is due to rapid economic development and high educational achievement is unclear.

Environmental risk factors of myopia and axial length

Outdoor activities

In Australia, students who performed high levels of near work but low levels of outdoor activity had the least hyperopic mean refraction. On the other hand, those who carried out low levels of near work but high levels of outdoor activity had the most hyperopic mean refraction. Furthermore, in an analysis combining the amount of outdoor activity and near work activity spent, children with low outdoor time and high near work were two to three times more likely to be myopic compared to those performing low near work and high outdoor activities.[52]

In Singapore, a cross-sectional study was conducted to analyze the effect of outdoor activities on 1249 teenagers aged 11–20 years (71.1%, Chinese, 20.7% Malays and 0.8% other ethnicities). After adjusting for confounders, there was a significant negative association between myopia and outdoor activity. Adjusting for the same confounders, for each hour increase in outdoor activity per day, SE increased by 0.17 D (i.e. a hyperopic shift) and the AL decreased by 0.06 mm.[53]

The OLSM found that children who became myopic (SE < -0.75 D) by the 8th grade spent less time in sports and outdoor activity (hours per week) at the 3rd grade compared to those who did not become myopic (7.98 ± 6.54 h vs 11.65 ± 6.97 h). In predictive models for future myopia, the combined amount of sports and outdoor hours per week was predictive of future myopia.[54]

Additional recent studies have found that outdoor activity is an independent factor negatively associated with myopia. The Sydney Myopia Study measured both near work and outdoor activities simultaneously and found that near work activities had little impact on refraction.[52] This study also found no effect of indoor sport on myopia, which implicates that more time spent outdoors, rather than sport itself, as the essential protective factor. A recent animal study on chicks found that light intensity modulates the process of emmetropization and that a low intensity of ambient light is a risk factor for developing myopia.[55] To answer questions related to cause and effect, randomized clinical trials (RCT) of community-based health behaviour interventions may be conducted. In Singapore, a RCT on children aged 7–10 years using a novel incentive-based family intervention to increase time spent outdoors is ongoing. This study aims to examine the hypothesis that children in the intervention group will show smaller shifts of refraction toward myopia as a result of increased outdoor time.

The biological mechanism behind this association is not yet clearly understood. It is postulated that higher light intensity outdoors could make the depth of field greater and reduce image blur. In addition, the release of dopamine from the retina is stimulated by light, and dopamine can inhibit eye growth.[52] However, the hypothesis that it is the high light intensity outdoors that is crucial has been contradicted by a study suggesting that it

is the spectral composition of the light, rather than the intensity, which is the primary cause of the tendency for myopia to be associated with more time indoors.[56] In a recent animal study, chicks exposed to high illuminances (15 000 lux) for 5 h per day significantly slowed compensation for negative lenses compared with those under 500 lux. Compensation for positive lenses was accelerated by exposure to high illuminances but the end point refraction was unchanged, compared with that of the 500-lux group. High illuminance also reduced deprivation myopia by roughly 60%, compared with that seen under 500 lux. This protective effect was abolished by the daily injection of spiperone, a dopamine receptor antagonist. This study showed that the retardation of myopia development by light is partially mediated by dopamine.[57] A very recent animal study (Smith *et al.*, 2011 ARVO e-abstract 3922) showed that high-light-reared monkeys exhibited significantly lower average degrees of myopic anisometropia (+0.14 ± 4.12 vs −3.56 ± 3.33 D, $p = 0.04$) and average treated-eye refractive errors that were significantly more hyperopic than those observed in monocularly form-deprived monkeys reared under normal light levels (+4.44 ± 5.24 vs −0.65 ± 3.84 D, $p = 0.03$). Thus, high ambient light levels can dramatically retard the development of form-deprivation myopia. This study indicated that absolute light levels are a fundamental variable impacting the vision-dependent regulation of ocular growth in primates and suggested that the seemingly protective effects of outdoor activities against myopia in children are due to exposure to the higher light levels normally encountered in outdoor environments. In a recent publication, Charman hypothesized that a consistent relationship between the astigmatic image fields and the retina are likely to be favourable to peripherally-based emmetropization. This condition is satisfied by outdoor environments, since dioptric stimuli may not vary widely across the visual field.[58]

Near work

In the SMS, near work was quantified by the continuous time and close reading distance in 12-year-old children.[59] Children who read continuously for more than 30 min were more likely to develop myopia compared to those who read for <30 min continuously. Meanwhile, children who performed near-work at a distance of <30 cm were 2.5 times more likely to have myopia than those who worked at a longer distance. Similarly, children who spent a longer time reading for pleasure and those who read at a distance closer than 30 cm were more likely have higher myopic refractions.

The SCORM found that children who read more than two books per week were about three times more likely to have higher myopia (SE < −3.0 D) compared with those who read <2 books per week. Children who read for more than 2 h a day were 1.5 times more likely to have higher myopia compared to those who read <2 h, but this was not significant. Every book read per week, was associated with an AL elongation of 0.04 mm. Children who read more than two books per week had 0.17 mm longer axial lengths compared to children who read two or fewer books per week.[36]

The OLSM examined 366 eighth-grade predominantly Caucasian children and found that the OR of myopia (SE < −0.75 D) was 1.02 (95% CI 1.008, 1.032) for every dioptre-hours of near work spent per week, after controlling for parental myopia and achievement scores.[60]

Near work was also shown not to be associated with myopia in several other studies.[61,62] In a 5-year follow-up longitudinal study on 1318 children aged 6–14 years, hours per week spent reading or using a computer did not differ between the groups before myopia onset. Studying and TV watching were also not significantly different before myopia onset. This study failed to show evidence of a relationship between near visual activities and the development of myopia.[63] Most studies on myopia and near work are cross-sectional which cannot examine the temporal relationship between outcomes and predictors. It is also likely that myopes engage in more near work as as it is more difficult to take part in some sporting tasks due to spectacle wear. A prospective study reported that myopic children may be more at risk of having lower levels of physical activity than their non-myopic peers.[64] This argument should be resolved by more prospective studies with longitudinal evidence. In addition, most information on near work and time outdoors in previous studies were reported by parents. Thus, recall bias or reporting bias may have occurred. In the future more accurate and more tightly standardised methodology for quantifying near work needs to be used, which should facilitate precise comparison between different studies. Some modifiable kinds of near work, such as reading posture, breaks during reading, and proper lighting should also be studied so that children could benefit through health promotion efforts of modifiable behaviour.[65]

Education

Numerous studies that have examined the effect of education on myopia have found a consistent correlation between higher educational level and higher prevalence of myopia.[19,21,26,66] There appears to be an association between myopia and higher academic achievements as well.[60,67,68] In a study on the Chinese children in Singapore and Sydney, early schooling in Singapore has also been found to be associated with the high levels of

myopia compared with schooling in Sydney.[69] This study indicated that exposure to a more intensive schooling system at an early age may be an independent risk factor for myopia. Higher educational level was also positively associated with longer AL. In Singapore Malay adults, increasing AL was associated with higher educational levels (standardized regression coefficient = 0.118, $p < 0.001$).[70] In Singapore Chinese adults, an AL increase of 0.60 mm is associated with every 10 years of education.[71]

In epidemiological studies, educational level is usually measured either as years of formal education or level of academic achievement. Both the duration and level of education are highly correlated with time spent on reading and writing. Hence, educational level may be a surrogate for near work.[72] Meanwhile, the association between education and myopia may also reflect common genetics of intelligence and refraction.

Parental myopia

In the SMS, children with one and two myopic parents had two times and eight times higher risks, respectively, of developing myopia (SE ≤ −0.5 D) compared to those with no myopic parents. In addition, an increasing severity of parental myopia led to a greater risk of myopia. The odds ratio for mild myopia (SE −0.5 to −3 D), moderate myopia (SE −3 to −6 D) and high myopia (SE at least −6 D) were 6.4 (95% CI 1.5, 27.8), 10.2 (95% CI 2.6, 40.1) and 21.8 (95% CI 5.3, 89.4) respectively.[73]

It was also reported that children with myopic parents have longer AL than those without myopic parents. Zadnik *et al.* investigated 716 Caucasian children aged 6–14 years and demonstrated that the pre-myopic eyes in children with myopic parents had a longer AL than those without myopic parents. This suggests that the size of the pre-myopic eyes might be already influenced by parental myopia. Moreover, it was found that children with two myopic parents developed myopia more often (11%) than children with one myopic parent (5%) or children without myopic parents (2%). (SE ≤ −0.75 D).[74]

The SCORM cohort showed that having one and two myopic parents was associated with an increase in AL of 0.14 and 0.32 mm, respectively, compared with no myopic parents. The study also showed that having one myopic parent and two myopic parents increased the degree of myopia by 0.39 and 0.74 D, respectively.[36]

Most studies have shown a consistently higher prevalence of myopia among those with myopic parents as compared with those without. Parental myopia is considered as a marker for both genes and a shared family environmental exposure. Myopic parents are more likely to create myopigenic environments such as more intensive education or less time spent outdoors.[60,73,75]

The gene-environment interaction for myopia is still inconclusive. The SCORM study found an interaction between parental myopia and near-work. However, both the OLSM and the SMS found all children are protected by outdoor activities but the risk declined in parallel for children with and without myopic parents, indicating there might be no interaction between outdoor activities and parental myopia. Since myopic parents may create myopigenic environments for their children, interaction observed between parental myopia and near-work may not represent gene-environment interaction.

Peripheral refraction

Central refractive error is determined by foveal vision on the visual axis. However, the foveal area is only a small part of the overall visual field and more peripheral retinal areas might also be important in refractive status. Animal studies have shown that the peripheral retina plays an important role in determining eye growth. A study in monkeys in which the central region of the retina was ablated demonstrated that treated eyes recovered as quickly from visual deprivation or lens-induced myopia as did untreated eyes.[76] This suggests that the peripheral retina has an effect on AL growth, and may participate in the process of emmetropization.

Human studies on peripheral refraction have been largely conducted on Caucasians. The OLSM assessed peripheral refractive error in 822 children aged 5–14 years. This study indicated that myopic children had greater relative hyperopia in the periphery, compared to emmetropes and hyperopes.[77] Another study included 116 subjects in the age range 18–35 years and reported that myopia had more effect on peripheral refraction along the horizontal rather than vertical visual field.[78]

A longitudinal study on 605 children aged 6–14 years explored ethnic differences and found that Asian-Americans ($n = 579$) had the largest degree of relative peripheral hyperopia, whereas African-Americans who were myopic ($n = 724$) had no significant peripheral hyperopia.[79]

One study determined relative peripheral refractive error in eyes of a group of Chinese. Central and peripheral refractive errors were obtained from cyclopleged eyes of 40 children and 42 adults. In this study, subjects with moderate myopia had relatively greater hyperopic shifts in the periphery than those with low hyperopia who showed a myopic shift ($p < 0.05$).[80]

In a recent study in Singapore, 250 Chinese children with a mean age of 83 months were included in analysis. This study found that children with high and moderate myopia had relative hyperopia at all peripheral eccentricities ($p < 0.001$), whereas children with low myopia had

relative hyperopia only at the temporal and nasal 30° ($p < 0.001$), but not at the nasal and temporal 15°. Children with emmetropia and hyperopia had peripheral relative myopia at all eccentricities ($p < 0.001$).[81]

Animal and human evidence indicates that relative peripheral hyperopia occurs in tandem with a prolate shape of the eyeball in myopic individuals. Longitudinal studies are needed to provide evidence for peripheral refraction determining the onset of myopia. However, longitudinal data with this research aim are few. In a longitudinal study on 187 children (mean age: 7.2 years) in Singapore, cycloplegic refraction was performed at five eccentricities: central axis and 15° and 30° eccentricities in the nasal and temporal visual fields. At follow-up, children who remained non-myopic ($n = 24$) retained relative peripheral myopia at all eccentricities, whereas those who became myopic ($n = 67$) developed relative peripheral hyperopia at the nasal (+0.44 ± 0.72 D) and temporal 30° (+0.13 ± 0.74 D). This study showed that baseline peripheral refraction did not predict the subsequent onset of myopia or influence myopia progression.[82]

Animal models of myopia

In animal models, macaque monkeys with surgically fused eyelids, i.e. form deprivation, experienced excessive AL elongation and eventually developed myopia.[83] Another early study on chicks found that monocular deprivation of form vision also produced myopia and eye enlargement.[84] These landmark studies ushered a new era in experimental myopia study and in the years since, models of form deprivation of myopia have been developed in a wide variety of animal species, including chicks,[85,86] tree shrews,[87,88] guinea pigs[89,90] and adult monkeys.[91] Other experimental methods using positive or negative lens as modulators of refractive error in chicks showed that the eye grows more slowly (developed hyperopia) or more rapidly (developed myopia), respectively.[85] Recent experiments also indicated that the low levels of lighting in laboratories played a major part in the development of myopia in these animal models of myopia, as they appear to be directly countered by high light levels.[57] (Smith *et al.*, 2011 ARVO e-abstract 3922) The experimental models of myopia suggest that both retinal image degradation (hyperopic and myopic defocus) and accommodation play important roles in AL elongation and myopia formation in animals.[92] Experimental models of myopia appear to suggest an important role of environmental factors in degradation of image quality, which could lead to myopia development.[83,84,87] The latest animal study on chicks also found that genetic factors are the major determinant of susceptibility to myopia induced by retinal image degradation. Selective breeding for susceptibility to myopia reveals a gene-environment interaction on refractive development.[93] However, questions remain on the applicability of animal models of myopia to physiological human myopia.[94]

Conclusions

Population-based data in children indicate that Asian populations, especially those of Chinese ethnicity, may be more susceptible to myopia compared with Western populations. However, as for adults, the situation is more complex. The prevalence of myopia in Singapore Chinese adults was only slightly higher than similarly aged white populations. In addition, studies in Taiwan, Singapore and China indicated that the rates of myopia in other Asian adult populations are not much higher than rates in White adult populations. This is possibly due to the expansion of mass intensive education in some areas such as China, Taiwan and Singapore. While the overall rates of myopia may vary between Asian populations, most studies demonstrate a clear trend of declining prevalence of myopia and mean AL with age, with younger participants generally having higher myopia rates and longer AL than older participants, which may be attributable to differences in birth cohorts and age.

The precise biological mechanisms through which the environment influences ocular refraction in humans are, however, still a matter of debate. It is still controversial that exogenous variables interact with heritable factors to modulate eye growth during ocular development. To date, time spent outdoors is an important modifiable environmental factor that may play an important role in our efforts to prevent myopic refractive shifts in children.

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For details of the authors of this review please see the next page.

Appendix 2

Published manuscript entitled

‘Prevalence and risk factors for refractive errors in Indians: the Singapore Indian Eye Study (SINDI)’

Prevalence and Risk Factors for Refractive Errors in Indians: The Singapore Indian Eye Study (SINDI)

Chen-Wei Pan,[1] *Tien-Yin Wong,*[1,2,3,4] *Raghavan Lavanya,*[2] *Ren-Yi Wu,*[2] *Ying-Feng Zheng,*[2] *Xiao-Yu Lin,*[1,2] *Paul Mitchell,*[5] *Tin Aung,*[2,3] *andSeang-Mei Saw*[1,2,3]

Purpose. To determine the prevalence and risk factors for refractive errors in middle-aged to elderly Singaporeans of Indian ethnicity.

Methods. A population-based, cross-sectional study of Indians aged over 40 years of age residing in Southwestern Singapore was conducted. An age-stratified (10-year age group) random sampling procedure was performed to select participants. Refraction was determined by autorefraction followed by subjective refraction. Myopia was defined as spherical equivalent (SE) < -0.50 diopters (D), high myopia as SE < -5.00 D, astigmatism as cylinder < -0.50 D, hyperopia as SE > 0.50 D, and anisometropia as SE difference > 1.00 D. Prevalence was adjusted to the 2000 Singapore census.

Results. Of the 4497 persons eligible to participate, 3400 (75.6%) were examined. Complete data were available for 2805 adults with right eye refractive error and no prior cataract surgery. The age-adjusted prevalence was 28.0% (95% confidence interval [CI], 25.8–30.2) for myopia and 4.1% (95% CI, 3.3–5.0) for high myopia. There was a U-shaped relationship between myopia and increasing age. The age-adjusted prevalence was 54.9% (95% CI, 52.0–57.9) for astigmatism, 35.9% (95% CI, 33.7–38.3) for hyperopia, and 9.8% (95% CI, 8.6–11.1) for anisometropia. In a multiple logistic regression model, adults who were female, younger, taller, spent more time reading and writing per day, or had astigmatism were more likely to be myopic. Adults who were older or had myopia or diabetes mellitus had higher risk of astigmatism.

Conclusions. In Singapore, the prevalence of myopia in Indian adults is similar to those in Malays, but lower than those in Chinese. Risk factors for myopia are similar across the three ethnic groups in Singapore. (*Invest Ophthalmol Vis Sci.* 2011; 52:3166–3173) DOI:10.1167/iovs.10-6210

From the [1]Department of Epidemiology and Public Health, Yong Loo Lin School of Medicine, National University of Singapore, Singapore; [2]Singapore Eye Research Institute and Singapore National Eye Centre, Singapore; [3]Department of Ophthalmology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore; [4]Centre for Eye Research Australia, University of Melbourne, Victoria, Australia; and [5]Centre for Vision Research, University of Sydney, Sydney, Australia.

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Corresponding author: Seang-Mei Saw, Department of Epidemiology and Public Health, Yong Loo Lin School of Medicine, National University of Singapore, 16 Medical Drive (MD 3), Singapore 117597; ephssm@nus.edu.sg.

Myopia and other refractive errors are global public health problems with high costs associated with correction[1] and treatment for complications such as retinal detachment.[2]

The prevalence of myopia has been reported in several Caucasian populations: 28.1% in the Baltimore Eye Survey[3] (aged 40–80+ years), 26.2% in the Beaver Dam Eye Study[4] (aged 43–84 years), 15% in the Blue Mountains Eye Study[5] (aged 49–97 years), and 17% in the Visual Impairment Project[6] (aged 40–98 years). In East Asia, the prevalence of myopia is higher: 38.7% in Singapore Chinese aged 40–79 years[7] and 41.5% in Japanese aged over 40 years.[8] In Indian population-based studies, the Andhra Pradesh Eye Disease Study[9] and the Chennai Glaucoma Study[10] reported age-adjusted prevalence rates for myopia of 34.6% and 31.0%, among adults aged 40 years or older, respectively.[9,10] The prevalence of myopia of adults aged over 30 years was 17% in Central India[11] and 19.4% in Indians with diabetes aged over 40 years.[12] An interesting finding in the Andhra Pradesh Eye Disease Study is that the prevalence of myopia was significantly higher among rural than urban residents (38.0% vs. 31.9%; $P = 0.001$),[9] in contrast to the perception that myopia is less common in rural communities.[13,14] However, the higher prevalence of myopia in rural India could be explained by the more severe nuclear cataract.[9] Nuclear cataract has been found to cause myopic shift in many studies, which reflects the increased power of the lens rather than increased axial length.[6,15–17]

Although the exact etiology of myopia is still unclear,[18–21] risk factors have been well documented, including family history,[22–24] near-work activities,[25–27] educational level,[28,29] and astigmatism.[30,31] Outdoor activity was reported as an independent protective factor of myopia.[32,33] However, only limited data are available on risk factors for other refractive errors.

Singapore has a multiethnic Asian population with Chinese (75%), Malays (15%), and Indians (7%). In younger generations, the prevalence of myopia (SE ≤ -0.5 D) in Singapore Indian male conscripts aged 17–19 years was 68.7%. However, SE was assessed using noncycloplegic autorefraction, which might have caused an overestimation of myopia.[34] The Tanjong Pagar Suvey[7] and the Singapore Malay Eye Study[35] documented the prevalence of myopia and other refractive errors among Singapore Chinese and Malays aged over 40 years, respectively. The Singapore Indian Eye Study (SINDI) was designed to estimate the prevalence and risk factors for major eye diseases, including myopia and other refractive errors, in Singapore Indian adults aged 40 years and older. Data from SINDI would allow more precise comparison of refractive errors across the three major Asian ethnic groups. As the majority (58%) of Singapore's Indian residents are from the southern regions of India (Singapore Census of Population 2000), SINDI data will also allow a comparison of urban Singapore Indian adults with persons of similar genetic background from southern India.

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METHODS

The SINDI is a population-based survey of major eye diseases, with detailed methodology reported elsewhere.[36] In brief, the study was conducted in the Southwestern part of Singapore, following the same protocol as that of the Singapore Malay Eye Study (SiMES).[37] From a list of 12,000 names of ethnic Indian Singaporeans provided by the Ministry of Home Affairs, an age-stratified random sampling strategy was adopted to select 6350 aged 40 years or older. A person was considered "ineligible" if he or she had moved from the residing address, had not been living there for >6 months, was deceased, or was terminally ill. Of the 6350 names selected, there were 4497 subjects who were eligible to participate. From August 2007 to December 2009, a total of 3400 subjects participated, representing a 75.6% participation rate.

SINDI was conducted following the tenets of the Helsinki Declaration and was approved by the Singhealth Institutional Review Board. All participants gave written informed consent at recruitment into the study.

Clinical Examination

Presenting visual acuity was measured monocularly using the logarithm of the minimum angle of resolution (log MAR) number chart (Lighthouse International, New York, NY) at a distance of 4 m, with the participant wearing their "walk-in" optical correction (spectacles or contact lenses), if any. If no numbers were read at 4 m, the participant was moved to 3, 2, or 1 m consecutively.[38] If no numbers were identified on the chart, visual acuity was assessed as counting fingers, hand movements, perception of light, or no perception of light. Best-corrected visual acuity (BCVA) was also assessed monocularly and recorded in log MAR scores using the same test protocol as presenting visual acuity. The BCVA was determined, and both the derived refraction data and visual acuity were recorded.

Objective refraction was measured using an autorefractor (Canon RK-5 Auto Ref- Keratometer; Canon Inc., Tokyo, Japan). Manual subjective refraction was then used to refine vision, using the results of the objective refraction as the starting point. In this study, refraction data were obtained from subjective refraction techniques. If subjective refraction was not available, autorefraction data were used instead.

Slit-lamp examination (model BQ-900; Haag-Streit, Koeniz, Switzerland) was performed after pupil dilation and included a clinical grading of cataract using the Lens Opacities Classification System (LOCS) III.[39]

Each participant's height was measured in centimeters using a wall-mounted measuring tape, after removing shoes. Weight was measured in kilograms using a digital scale, after removing heavy clothing (SECA, model 782 232 1009; Vogel & Halke, Hamburg, Germany). Systolic blood pressure, diastolic blood pressure, and pulse rate for all participants were recorded using the automated blood pressure monitor (Dinamap model Pro Series DP110X-RW, 100V2; GE Medical Systems Information Technologies, Milwaukee, WI).

Questionnaire and Interview

Questionnaires were administered by trained interviewers. Before the interview, the purpose of the study was explained and the participants were assured that the information provided would be strictly confidential. The questionnaire was administered in English or translated into Tamil, and back-translated into English, based on the participant's choice.

At interview, data were collected on educational level (no formal education/primary education/ high school/polytechnic/university) and near-work activities such as number of hours of computer use or reading and writing per day. Other data included smoking status (current/past/ never smoked), alcohol intake, and whether participants had previously been diagnosed with diabetes or hypertension by a doctor.

Definitions of Diseases

Spherical equivalent (SE) was defined as sphere plus half cylinder. Myopia was defined as SE of −0.50 diopter (D) or less. Other definitions of myopia such as SE less than −0.75 D or SE less than −1.00 D were also used for analyses to compare with other studies. Hyperopia was defined as SE of 0.50 D or more. Other definitions of hyperopia (SE > 2D) were also analyzed. Astigmatism was defined as cylinder less than −0.50 D, −1.00 D, or −1.50 D and anisometropia as the difference in SE greater than 1.00 D. "With the rule" astigmatism was defined when the axis was 0° to 15°, "against the rule" when 75° to 105°, and "oblique" when axes were located from 20° to 70° and 110° to 160°.

Lens nuclear opacity was graded at the slit lamp by study ophthalmologists using modified LOCS III scores.[39] Any cataract was defined as the presence of any nuclear cataract (LOCS III score for nuclear opalescence or nuclear color of 4 or more), any cortical cataract (LOCS III score of 2 or more), or any posterior subcapsular cataract (LOCS III of 2 or more) in either eye. Diabetes mellitus was defined as nonfasting glucose levels greater than 200 mg/dL (11.1 mM) or physician diagnosis of diabetes and use of antidiabetic medications according to American Diabetes Association guidelines.[40] Hypertension was defined as systolic blood pressure > 140 mm Hg or diastolic blood pressure > 90 mm Hg or self-reported history of hypertension. Body mass index (BMI) was calculated as the weight in kilograms divided by the square of the height in meters.

Statistical Methods

Participants with prior cataract surgery ($n = 502$) were excluded from these analyses. As the Spearman correlation coefficient for SE in the left and right eye was high ($r = 0.85$, $P < 0.001$), only right eye data ($n = 2805$) were used for analyses. Anisometropia was analyzed only in participants with refractive error data for both eyes and with no history of cataract surgery in either eye ($n = 2762$).

The prevalence of different refractive errors was estimated for the overall sample, and then stratified by age and sex. The age-adjusted prevalence was calculated by direct standardization of the study samples to the Singapore ethnic Indian population, using the 2000 Singapore census data (http://www.singstat.gov.sg). For risk factors, variables of interest were first analyzed in univariate models. The potential confounders considered were age, gender, education, occupation, marital status, time for reading and writing per day, time for computer use per day, alcohol use, smoking, diabetes mellitus, hypertension, height, BMI, and presence of cataract. If the P value was <0.05 in univariate models, these possible predictors were included in multiple logistic regression models, and manual backward stepwise elimination procedures were performed to choose the most parsimonious model. To control the effects of age, gender, and other potential confounders, multiple logistic regression models with sampling weights were performed. Sampling weights are the actual proportions of Indians in each age group among the entire Singapore Indian population obtained from Singapore Census 2000. The interaction terms age × cataract, age × gender, and age × education were also evaluated in multivariate models. Statistical analyses were performed using statistical software (Statistical Package for Social Science, SPSS V16.0; SPSS Inc., Chicago, IL). Two-tailed $P < 0.05$ was considered statistically significant. Odds ratios (OR) and 95% confidence intervals (95% CI) were shown.

RESULTS

Among the 3400 participants in our study, 813 (23.9%) were born in India and moved to Singapore after birth. Among these 813 participants born in India, 638 (78.5%) were from southern India, where the states of Andhra Pradesh and Tamil Nadu are located.

Participants ($n = 3400$) were significantly ($P < 0.001$) younger than nonparticipants ($n = 1093$), but there was no significant difference in gender distribution between the two groups ($P = 0.28$).

Compared with adults without cataract surgery, those with cataract surgery were older ($P < 0.001$), shorter ($P < 0.001$), less educated ($P < 0.001$), and spent less time on near-work

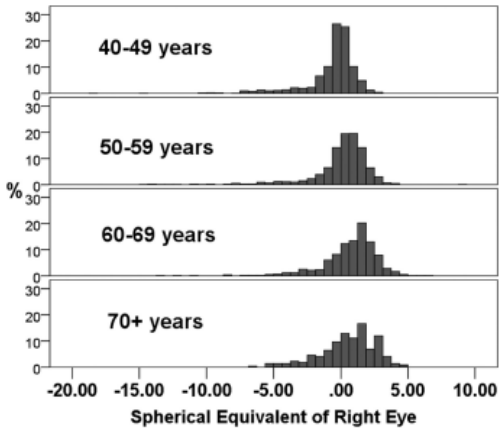

FIGURE 1. Distribution of SEs in the right eye in Indian residents in Singapore.

activities ($P < 0.001$). There was no gender difference between adults with and without cataract surgery ($P = 0.48$).

Of the 2805 subjects with right eye refraction data and no cataract surgery history, 1417 (50.5%) were male and 1388 (49.5%) female. The age ranged from 43 to 84 years with a mean of 55.5 ± 8.8 years. The mean ages of men and women were 55.9 ± 9.1 and 55.0 ± 8.3 years, respectively ($P = 0.006$).

Figure 1 shows the distribution of refraction in SE in different age groups among 2805 subjects in the analyses. The distribution of SE was skewed toward more myopic values in all age groups. The skewness values for the SE distribution were −2.74, −2.46, −1.84, and −0.80, while the kurtosis values were 11.87, 9.82, 6.68, and 0.61 for age groups 40–49, 50–59, 60–69, and 70 years or older, respectively. Both the skewness and kurtosis of the SE distribution decreased with age. The mean and median SE for this sample were −0.05 D and 0.25 D, respectively.

Table 1 shows crude and age-standardized prevalence of myopia and high myopia by different definitions. The age-standardized prevalence of myopia for three different definitions was 28.0% (for SE < −0.5 D), 23.5% (for SE < −0.75 D), and 20.4% (for SE < −1.0 D). The prevalence of myopia was slightly higher in women (28.5%) than men (26.9%), but this difference was not statistically significant ($P = 0.48$). Further, the age-standardized prevalence of high myopia (SE < −5.0 D) was 4.1% (95% CI, 3.3–5.0) with significantly higher rates in females (4.7%) than males (3.1%) ($P = 0.02$).

The prevalence of myopia was 33.3%, 23.8%, 20.3%, and 26.9% for age groups 40–49, 50–59, 60–69, and 70 years or older, respectively. A U-shaped relationship was observed between myopia prevalence and increasing age. The prevalence of myopia followed a bimodal pattern, initially decreasing with age and then increasing in older adults. The association was modified by nuclear cataract defined as LOCS III score for nuclear opalescence or nuclear color of 4 or more. Myopia prevalence increased with age among subjects with nuclear cataract ($n = 323$), while decreasing with age among subjects without nuclear cataract ($n = 2482$; Fig. 2).

Crude and age-standardized prevalence of astigmatism, hyperopia, and anisometropia are shown in Table 2. Age-standardized prevalence of astigmatism, hyperopia, and anisometropia were 54.9%, 35.9%, and 9.8%, respectively. Prevalence of other definitions of astigmatism and hyperopia are also shown in Table 2. The prevalence of both astigmatism and anisometropia increased with age. Prevalence of hyperopia initially increased with age and then decreased, with the highest rate in the 60–69 year age group (60.7%). There were no gender differences in the prevalence of astigmatism ($P = 0.14$), hyperopia ($P = 0.27$), or anisometropia ($P = 0.20$). In addition, among those with astigmatism ($n = 1585$), 62.9% had "against the rule" astigmatism, 3.2% had "with the rule" astigmatism, and 33.9% had "oblique" astigmatism. The axis of astigmatism

TABLE 1. Prevalence of Myopia and High Myopia in Singapore Indian Adults Aged More than 40 Years

		Myopia (SE < −0.5 D)	Myopia (SE < −0.75 D)	Myopia (SE < −1.0 D)	High Myopia (SE < −5.0 D)
	N	*n* (%, 95% CI)	*n* (%, 95% CI)	*n* (%, 95% CI)	*n* (%, 95% CI)
All persons					
Total	2805	733	612	533	108
Crude rate		26.1, 24.5–27.8	21.8, 20.3–23.3	19.0, 17.6–20.5	3.9, 3.1–4.6
Age-standard rate*		28.0, 25.8–30.2	23.5, 21.5–25.6	20.4, 18.6–22.4	4.1, 3.3–5.0
Men	1417	362	293	251	43
Crude rate		25.6, 23.3–27.8	20.7, 18.6–22.8	17.7, 15.7–19.7	3.0, 21.–3.9
Age-standard rate*		26.9, 24.0–30.2	21.9, 19.3–24.9	18.8, 16.3–21.5	3.1, 2.2–4.3
Women	1388	371	319	282	65
Crude rate		26.7, 24.4–29.1	23.0, 20.8–25.2	20.3, 18.2–22.4	4.7, 3.6–5.8
Age-standard rate*		28.5, 25.4–31.9	24.6, 21.7–27.8	21.7, 19.0–24.7	4.7, 3.6–6.3
P		0.476	0.139	0.079	0.023
Age group, y					
40–49	874	291	245	214	46
		33.3, 30.2–36.4	28.0, 25.1–31.0	24.5, 21.6–27.3	5.3, 3.8–6.8
50–59	1025	244	198	179	42
		23.8, 21.2–26.4	19.3, 16.9–21.7	17.5, 15.1–19.8	4.1, 2.9–5.3
60–69	690	140	119	98	16
		20.3, 17.3–23.3	17.3, 14.4–20.1	14.2, 11.6–16.8	2.3, 1.2–3.4
70–80	216	58	50	42	4
		26.9, 20.9–32.8	23.2, 17.5–28.8	19.4, 14.1–24.8	1.9, 0.004–3.7
P (trend)		<0.001	<0.001	<0.001	0.009

CI, confidence interval; D, diopter; SE, spherical eqivalent.

* Age-standardized to the Singapore 2000 census population.

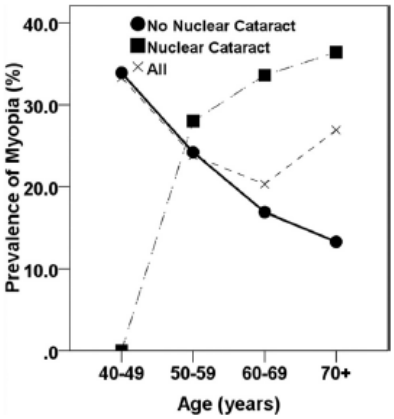

FIGURE 2. Line graphs of prevalence of myopia (right eye, SE < -0.5 D) by age for those with cataract ($n = 323$), without nuclear cataract, and all adults.

showed a peak at 90° (against-the-rule astigmatism). However, there were no statistically significant differences in the axis of astigmatism by gender ($P = 0.92$) or age group ($P = 0.15$).

Four multivariate logistic regression models were constructed to determine the risk factors for myopia (SE < -0.5 D), hyperopia (SE > 0.5 D), astigmatism (cylinder < -0.5 D), and anisometropia (SE difference > 1.0 D), as shown in Table 3. In these models, myopia was associated with time spent on reading and writing per day (OR = 1.19), height (OR = 1.04), and astigmatism (OR = 3.59), after adjusting for age and gender. The interaction between age and cataract was also significant in the multivariate model ($P = 0.03$). Age (OR = 1.07), myopia (OR = 3.59), and diabetes (OR = 1.58) were associated with astigmatism, after adjusting for other confounders, while age and astigmatism were associated with both hyperopia and anisometropia (Table 3).

DISCUSSION

In this study, we reported that 28.0% of Singaporeans of Indian ethnicity aged over 40 years had myopia. The prevalence of myopia decreased with age in adults without nuclear cataract and increased with age in adults with nuclear cataract, suggesting that the U-shape curve may be explained by differences in patterns for adults with and without nuclear cataract. Our study findings should be compared with two groups, with Indians residing in India, and with other Singaporean ethnicity (Chinese and Malays).

It was suggested that subjective refraction using a phoroptor is usually preferred in cooperative patients. Subjective refraction data were preferred for analysis since the reproducibility of subjective refraction has been found to be within 0.50 D for spherical equivalent, sphere power, and cylinder power.[41,42] Autorefraction is adequate for a preliminary refraction but is not a good substitute for subjective refraction.[41] Cycloplegic autorefraction is the gold standard technique for refractive error measurement.[43] Noncycloplegic refraction might have overestimated the myopia rates, but this effect seems to be marginal since our study subjects were middle-aged to elderly adults over 40 years who may have lower amplitude of accommodation.[44,45]

The prevalence of myopia is lower among Singaporean Indians than Indians of a similar age range residing in Southern India. In the Indian state of Andhra Pradesh, a multistage cluster, systematic, stratified random sampling method was used, and the age-gender-area adjusted prevalence of myopia of adults aged over 40 years in primarily rural areas was 34.6% ($n = 3723$).[9] In rural Chennai, the age-gender adjusted prevalence of myopia was 31.0% ($n = 2508$).[10] We noted that the Indians in urban Andhra Pradesh had lower myopia rates (31.9%) than rural Andhra Pradesh (38.0%) but higher myopia rates than Singaporean Indians. Comparing the prevalence of myopia in each age group, we found that myopia is more prevalent in our study than Indian studies for the 40–49 years age group, reflecting a potentially "myopigenic" environment in Singapore. In the 50–59 years age group, Indian Indians exceed Singaporean Indians in the prevalence of myopia due to earlier onset of nuclear cataract or nuclear sclerosis among Indian Indians.[9,10] In the age groups over 60 years, the differences in prevalence of myopia between Indian Indians and Singaporean Indians seem to be enlarged due to the more severity of nuclear opacity (Fig. 3). In the Andhra Pradesh Eye Disease Study, the population attributable risk percentage (PAR%) for lens nuclear opacity (NO) 2–3.5 and NO > 3.5 of myopia were estimated to be 76% and 23%, respectively.[9] The high PAR% for nuclear opacity indicates that the main cause of myopia in Indian adults is nuclear cataract. Thus, if we remove the nuclear cataract patients in India from analysis, the prevalence of myopia in Indians residing in India would probably be lower than that of the Singaporean Indians due to the urban versus rural differences as expected (Fig. 3).

Our study could be directly compared with Singapore Chinese adults (the Tanjong Pagar Survey) and Malay adults (the SiMES), which used identical study protocols, to explore the effect of ethnic variation within the same environment.[7,35] However, the sampling process of the Tanjong Pagar Survey was less rigorous than that of SINDI and SiMES. Comparing our results with the Tanjong Pagar Suvery[7] and the SiMES,[35] the prevalence of myopia is highest among Chinese in almost all age groups in both men and women (Fig. 4). The Tanjong Pagar Survey was conducted nearly 10 years ago. The difference in the prevalence of the Tanjong Pagar Survey, SiMES, and SINDI may reflect secular trends over time as well as interethnic variation. The higher prevalence of myopia in Chinese than other ethnicities is possibly attributed to interethnic variability in risk factors such as differences in lifestyle, including more time spent on school work, fewer outdoor activities, or ethnic-specific genes relevant to Chinese. In Singapore children, Chinese were reported to spend the most time on near-work activities[26] but the least time outdoors.[33] The mean time outdoors was reported to be 3.05, 3.94, and 3.21 hours per day for Chinese, Malays, and Indians, respectively ($P < 0.001$).[33]

People with high myopia are reported to have a substantially higher risk of cataract, glaucoma, myopic macular degeneration, and retinal detachment.[2] The age-standardized prevalence of high myopia (SE < -5.0D) in our study was 4.1%, which is significantly lower than that of Chinese population (9.1%)[7] but slightly higher than that of Malay adults (3.9%)[35] of the same age range. Compared with Indian adults in India, the rate was slightly lower than that of the Andhra Pradesh Eye Disease Study (4.5%)[9] but slightly higher than reported in the Chennai Glaucoma Study (3.7%).[10] This rate was also higher than in most other ethnic population such as whites and blacks aged over 40 years in the Baltimore Eye Study (1.4%),[3] white persons aged 49 to 97 years in Blue Mountain Study (3.0%),[5] Indians in Bangladesh (2.2%)[46] aged over 30 years, and Hispanics (2.4%) aged over 40 years in the Los Angeles Latino Eye Study.[47]

A U-shaped relationship between myopia prevalence and increasing age was observed in our study. This similar pattern was also found in Singapore Chinese and Malays of the same age range[7,35] and was modified by nuclear cataract. In subjects

TABLE 2. Prevalence of Astigmatism, Hyperopia, and Anisometropia in Singapore Indian Adults Aged More than 40 Years

		Astigmatism (<−0.5 Cylinder)	Astigmatism (<−1.0 Cylinder)	Astigmatism (<−1.5 Cylinder)	Hyperopia (SE > +0.5 D)	Hyperopia (SE > +2.0 D)		Anisometropia (>+1.0 D Difference)
	*N**	*n* (%, 95% CI)	*n* (%, 95% CI)	*n* (%, 95% CI)	*n* (%, 95% CI)	*n* (%, 95% CI)	*N*†	*n* (%, 95% CI)
All persons								
Total	2805	1585	595	282	1147	277	2762	272
Crude rate		56.5, 54.7–58.3	21.2, 19.7–22.7	10.1, 8.9–11.2	40.9, 39.1–42.7	9.9, 8.8–11.0		9.9, 8.7–11.0
Age-standard rate‡		54.9, 52.0–57.9	21.3, 19.5–23.2	10.2, 8.9–11.5	35.9, 33.7–38.3	8.6, 7.5–9.7		9.8, 8.6–11.1
Men	1417	820	310	156	565	121	1391	147
Crude rate		57.9, 55.3–60.4	21.9, 19.7–24.0	11.0, 9.4–12.6	39.9, 37.3–42.4	8.5, 7.1–10.0		10.6, 9.0–12.2
Age-standard rate‡		57.1, 52.9–61.6	23.0, 20.3–26.0	11.9, 9.9–14.1	35.9, 32.7–39.4	7.8, 6.4–9.6		10.7, 8.9–12.9
Women	1388	765	285	126	582	156	1371	125
Crude rate		55.1, 52.5–57.7	20.5, 18.4–22.7	9.1, 7.6–10.6	41.9, 39.3–44.5	11.2, 9.6–12.9		9.1, 7.6–10.6
Age-standard rate‡		55.6, 51.1–60.4	22.0, 19.1–25.3	9.8, 7.9–12.2	38.2, 34.7–42.0	11.1, 9.1–13.5		9.9, 8.0–12.3
P		0.141	0.38	0.09	0.268	0.02		0.201
Age group, y								
40–49	874	372	122	52	154	10	865	54
		42.6, 39.3–45.9	14.0, 11.7–16.3	6.0, 4.4–7.5	17.6, 15.1–20.2	1.1, 0.4–1.9		6.2, 4.6–7.9
50–59	1025	547	177	87	459	79	1010	75
		53.4, 50.3–56.4	17.3, 15.0–19.6	8.5, 6.8–10.2	44.8, 41.7–47.8	7.7, 6.1–9.3		7.4, 5.8–9.1
60–69	690	487	192	86	419	140	678	98
		70.6, 67.2–74.0	27.8, 24.5–31.2	12.5, 10.0–14.9	60.7, 57.1–64.4	20.3, 17.3–23.3		14.5, 11.8–17.1
70–83	216	179	104	57	115	48	209	45
		82.9, 77.8–87.9	48.2, 41.4–54.9	26.4, 20.5–32.3	53.2, 46.5–60.0	22.2, 16.6–27.8		21.5, 15.9–27.2
P (trend)		<0.001	<0.001	<0.001	<0.001	<0.001		<0.001

CI, confidence interval; D, diopter; SE, spherical eqivalent.

* Number of subjects included in the analyses of astigmatism and hyperopia.

† Number of subjects included in the analysis of anisometropia.

‡ Age-standardized to the Singapore 2000 census population.

TABLE 3. Multiple Logistic Regression Models of the Risk Factors Associated with Refractive Errors*

	Myopia			Astigmatism			Hypercopia			Anisometropia		
	Beta	Multivariable OR (95% CI)	*P*	Beta	Multivariable OR (95% CI)	*P*	Beta	Multivariable OR (95% CI)	*P*	Beta	Multivariable OR (95% CI)	*P*
Age, y†	−0.001	0.9994 (0.9991–0.9997)	0.001	0.07	1.07 (1.05–1.10)	<0.001	0.11	1.12 (1.09–1.14)	<0.001	0.04	1.04 (1.00–1.08)	0.04
Sex, female	0.77	2.17 (1.30–3.61)	0.003	−0.18	0.84 (0.61–1.15)	0.27	0.06	1.07 (0.77–1.48)	0.7	0.08	1.08 (0.63–1.86)	0.78
Education	-	-	-									
No formal education				0	1.00 (referent)		0	1.00 (referent)		0	1.00 (referent)	
Primary education				−0.42	0.65 (0.29–1.50)	0.32	0.31	1.36 (0.62–2.98)	0.44	−0.13	0.88 (0.27–2.87)	0.84
Secondary education				−0.46	0.63 (0.27–1.48)	0.29	0.03	1.03 (0.46–2.32)	0.94	0.03	1.03 (0.30–3.56)	0.97
Polytechnic				−0.72	0.49 (0.20–1.22)	0.13	−0.08	0.92 (0.38–2.25)	0.86	0.56	1.76 (0.47–6.59)	0.40
University education				−0.55	0.58 (0.23–1.48)	0.26	−0.23	0.80 (0.32–1.99)	0.63	0.99	2.69 (0.72–10.04)	0.14
Time for reading and writing per day, h	0.17	1.19 (1.06–1.33)	0.003	-	-	-	-	-	-	-	-	-
Height, cm	0.04	1.04 (1.01–1.07)	0.005	-	-	-	-	-	-	-	-	-
Any cataract	−1.55	0.21 (0.05–0.91)	0.05	0.15	1.16 (0.78–1.74)	0.46	-	-	-	0.42	1.53 (0.81–2.89)	0.20
Astigmatism	1.28	3.59 (2.52–5.12)	<0.001	-	-	-	−0.67	0.51 (0.37–0.72)	<0.001	0.90	2.47 (1.36–4.48)	0.003
Myopia	-	-	-	1.28	3.59 (2.50–5.15)	<0.001	-	-	-	-	-	-
Diabetes mellitus	-	-	-	0.46	1.58 (1.10–2.27)	0.01	-	-	-	-	-	-
Cataract × age-square			0.03									

CI, confidence interval; OR, odds ratio.
* Models were run with sampling weights applied for each strata.
† Age-square for the model for myopia to examine the U-shape distribution.

FIGURE 3. Line graphs of prevalence of myopia (right eye, SE < −0.5 D) by age in Andhra Pradesh Eye Disease Study, Chennai Glaucoma Study, and Singapore Indian Eye Study.

without nuclear cataract, the prevalence of myopia declined with age. This pattern may represent an increase in the prevalence of myopia in younger generations, possibly through a more competitive education system, or an intrinsic age-related decline in myopia prevalence.[48] In subjects with nuclear cataract, the prevalence of myopia increased with age due to increasing nuclear lens opacity in elderly populations.[49] However, the prevalence of myopia increased with age in India. The difference in the age-adjusted pattern of myopia prevalence between Singapore and India could be due to a higher prevalence of nuclear cataract in India[9,10] (Fig. 3).

The risk factors for myopia in our study were increased time spent on near-work activities, height, and astigmatism.[25,50,51] It has been reported that taller people are more likely to be myopic, because of longer axial length.[52,53] Although astigmatism was only recently reported to be a risk factor in children,[30,31] the association of myopia and astigmatism was very strong in our study (OR = 3.59; 95% CI, 2.52–5.12).

The prevalence of astigmatism was 54.9% in our study, which was significantly higher than that of Singapore Chinese (37.8%) and Malays (33.3%) of the same age range.[7,35] This prevalence is also higher than that of Andhra Pradesh Eye Disease Study (37.6%), but similar to that reported from the Chennai Glaucoma Study (54.8%).[9,10] Prevalence of astigmatism increased with age, which is consistent with the findings of previous studies.[3,5,17,54] "With-the-rule" astigmatism, where the vertical curve is greater than the horizontal, is common in children and adolescents. The dominant proportion of "against the rule" astigmatism (62.9%) in our study further confirmed that "with-the-rule" astigmatism tends to disappear or even reverse itself to an "against-the-rule" astigmatism with increasing age.[55] The main risk factor for astigmatism in our study was diabetes mellitus, which was positively associated with astigmatism. In a multivariate logistic model in the SiMES, the association between astigmatism and diabetes mellitus was only of borderline significance ($P = 0.06$).[35] Two cross-sectional studies on diabetic patients have reported quite high prevalence of astigmatism: 87.8% in Taiwan and 47.4% in India. However, there were no controls. It is possible that diabetes may lead to astigmatism as fluctuating blood sugar levels might

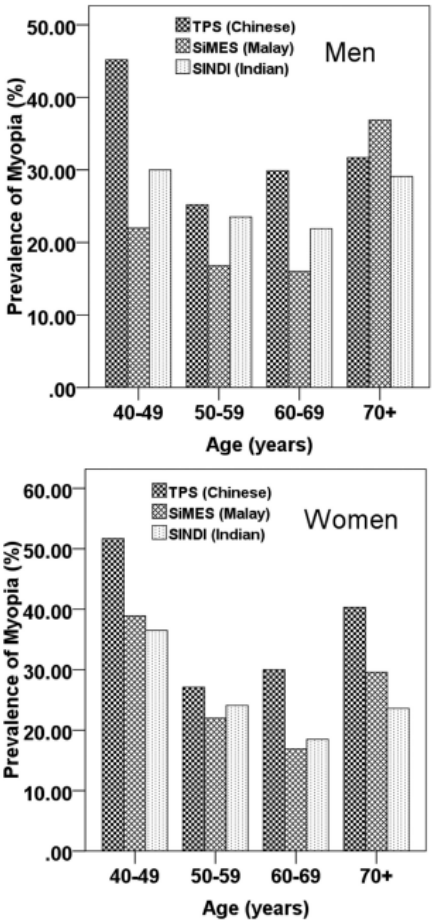

FIGURE 4. Prevalence of myopia (right eye, SE < -0.5 D) in the Tanjong Pagar Survey, Singapore Malay Eye Study, and Singapore Indian Eye Study.

alter the refractive index and curvature of the crystalline lens.[56]

The hyperopia prevalence (35.9%) in this study is also higher than that that of Singapore Chinese (28.4%)[7] and Malays (27.4%),[35] but lower than that of white populations in the Beaver Dam Eye Study (49.0%)[4] and the Blue Mountains Eye Study (57.0%).[5] The prevalence of hyperopia generally increased with age, possibly due to a decrease in the refractive power of the lens,[57] changes in lens position,[4] or decreased axial length.[58] In persons aged over 70 years, decreased prevalence of hyperopia was observed in our study, possibly due to lens-induced myopic shift.[8] The increasing trend in myopia and decreasing hyperopia could also be explained by the cohort effect, which has been observed in Singapore. In the 1960s and 1970s, only 20%–30% or 40%–50% of male conscripts were myopic,[59] and around 80% of male conscripts were found to be myopic in the 1990s.[34] In view of the limitation of cross-sectional design, we could not separate the age-related hyperopic shift from the cohort effect in our study.

The strengths of our study include its large and population-based sample. In addition, myopia was assessed by different definitions so that our study could be compared with other studies using different myopia definitions. However, it has a few limitations. First, it was a cross-sectional design so that we cannot separate cause from effect when examining risk factors. Second, nonparticipants were older than the participants, so that the prevalence of myopia and other refractive errors could be overestimated or underestimated. In addition, subjects with cataract surgery excluded from analyses were older, shorter and less educated and spent less time on near-work activities compared with subjects without cataract surgery. Thus, the prevalence of myopia in this population may be overestimated. Finally, noncyclopegic refraction might have possibly overestimated the prevalence of myopia in our study.

In summary, the myopia prevalence in Singapore adult Indians is similar to that of Singapore Malays but lower than Singapore Chinese aged over 40 years. The higher myopia prevalence rates recorded among Indians in India compared with Singaporean Indians may be due to the high nuclear cataract rates in older adults in India. We also found that prevalence of astigmatism and hyperopia was higher than those recorded in Singapore Chinese and Malays. Our study completes a gap in knowledge about adult myopia and other refractive errors in an urban population in Singapore.

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Appendix 3

Published manuscript entitled

‘Ocular biometry in an urban Indian population: the Singapore Indian Eye Study (SINDI)’

Ocular Biometry in an Urban Indian Population: The Singapore Indian Eye Study (SINDI)

Chen-Wei Pan,[1] Tien-Yin Wong,[1,2,3] Lan Chang,[1] Xiao-Yu Lin,[2] Raghavan Lavanya,[2] Ying-Feng Zheng,[2,3] Yee-Onn Kok,[1] Ren-Yi Wu,[2] Tin Aung,[2,3] and Seang-Mei Saw[1,2,3]

Purpose. To describe the distribution and determinants of ocular biometric parameters in adult Singapore Indians.

Methods. A population-based, cross-sectional study was conducted on 3400 Indians aged 40 to 83 years residing in Singapore. Ocular components including axial length (AL), anterior chamber depth (ACD), and corneal radius (CR) were measured by partial coherence interferometry. Refraction was recorded in spherical equivalent (SE).

Results. After 502 individuals with previous cataract surgery were excluded, ocular biometric data on 2785 adults were analyzed. The mean AL, ACD, and CR were 23.45 ± 1.10, 3.15 ± 0.36, and 7.61 ± 0.26 mm, respectively. The mean AL/CR ratio was 3.08 ± 0.13. The mean AL was 23.53, 23.49, 23.35, and 23.25 mm in 40- to 49-, 50- to 59-, 60- to 69-, and 700 to 83-year age groups, respectively ($P < 0.001$). Men had significantly longer ALs than women (23.68 mm versus 23.23 mm, $P < 0.001$). In multivariate linear regression models, AL was found to be longer in adults who were taller ($P < 0.001$), better educated (University, $P < 0.001$), and more apt to spend time reading ($P < 0.001$). Increasing CR was associated with increasing height ($P = 0.008$). AL was the strongest determinant for refraction in all age groups, whereas lens nuclear opacity was a predictor in adults aged 60 to 83 years.

Conclusions. The AL in Indians living in Singapore was similar to that of Malays in Singapore, but longer than that of Indians living in India. Time spent reading, height, and educational level were the strongest determinants of AL. AL was the strongest predictor of SE in all age groups. (*Invest Ophthalmol Vis Sci.* 2011;52:6636–6642) DOI:10.1167/iovs.10-7148

Myopia is a complex trait associated with various genetic and environmental factors.[1,2] The exact etiology of myopia remains unclear.[3] The refractive status is influenced by ocular biometric parameters such as axial length (AL) and corneal radius (CR) of curvature. The prevalence of myopia in adults over 40 years has been reported in several population-based studies with different results. It is still unclear whether myopia prevalence is higher in East Asian countries than in Western countries. The Tanjong Pagar study reported a prevalence of 51.7% myopia in with and 45.2% in men in the 40 to 49 years age group in Singaporean Chinese (spherical equivalent [SE] < −0.5 D).[4] However, the meta-analysis by Kempen et al.[5] reported a prevalence of 46.3% for North American white females and 36.8% for males using a more conservative definition of myopia (SE < −1.0 D). The myopia prevalence reported in the Singaporean Malays[6] and Indians[7] are also lower than those from North America.[8,9] Understanding the interrelationship between refraction and ocular biometry may help to explain the trends and patterns of refractive errors observed in different populations and ethnicities.[10,11] However, although the epidemiology of refractive errors has been reported in different countries and ethnicities worldwide, only a small fraction of population-based studies have described ocular biometry distribution.[10,12]

Most studies on ocular biometric parameters have focused on children[13,14] and adolescents[15] or on selected groups, such as university students[16,17] and microscopists.[18] In addition, there is evidence that the AL/CR ratio of an emmetropic eye is usually very close to 3.0, and a higher AL/CR ratio was reported to be a risk factor in myopia.[19,20] However, few population-based studies have reported the AL/CR ratio and its association with refractive error.

There are approximately 1 billion Indians worldwide, including approximately 25 million migrants who live outside India. The Central India Eye and Medical Study measured the ALs of Indians over 30 years of age living in India.[21] To further understand the patterns of ocular biometric parameters in Indians living outside India, we examined the distribution and determinants of ocular biometric parameters and their relationship with refractive status in adult Singaporean Indians.

Methods

Study Cohort

The Singapore Indian Eye Study (SINDI) is a population-based, cross-sectional study, designed to assess various ocular disorders of adult Indians over 40 years of age. Approximately 7% of the Singaporean population is Indian and most of our study subjects (65%) were born in Singapore. The detailed study protocol has been published elsewhere[22] and follows the protocol of the Singapore Malay Eye Study (SiMES).[23] In brief, Indian adults over 40 years of age residing in South-west Singapore were selected from the Ministry of Home Affairs database by using an age-stratified random sampling process. Of the 4497 subjects eligible from the sampling frame ($n = 6350$), 3400 (75.6% response rate) were examined between 2007 and 2009. Subjects were ineligible ($n = 1853$) if they had no longer lived at the registered address or were terminally ill.

This study was approved by the ethics committee of Singapore National Eye Center and was conducted in accordance with the tenets

From the Departments of [1]Epidemiology and Public Health and [3]Ophthalmology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore; and the [2]Singapore Eye Research Institute and Singapore National Eye Centre, Singapore.

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Corresponding author: Seang-Mei Saw, Department of Epidemiology and Public Health, Yong Loo Lin School of Medicine, National University of Singapore, 16 Medical Drive (MD 3), Singapore 117597; ephssm@nus.edu.sg.

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of the World Medical Association's Declaration of Helsinki. Written informed consent was obtained from all participants.

Clinic Examination

Ocular biometric parameters of AL and anterior chamber depth (ACD) were measured using noncontact partial coherence interferometry (IOL Master, ver, 3.01; Carl Zeiss Meditec AG, Jena, Germany).

Noncycloplegic refraction was used in our study. Refraction (sphere, cylinder, and axis) and corneal radius in the horizontal and vertical meridians were initially estimated with an autorefractor (RK-5 Autorefractor-Keratometer; Canon, Inc. Ltd., Tokyo, Japan). A mean value along each meridian was recorded, and the mean CR was calculated as the average of the steep and flat curvatures. Refraction was subjectively refined by study optometrists until the best visual acuity was obtained. These subjective refraction results were used in analysis. If the subjective refraction was not available, results of autorefraction were used instead.

All participants underwent a standardized slit-lamp (model BQ-900; Haag-Streit, Köniz, Switzerland) examination. Other examinations included weight, height, blood pressure, blood glucose, and cholesterol measurements. Weight was assessed in kilograms by a digital scale, with subjects removing the outer layers. Height was measured by a wall-mounted metric measuring tape with shoes removed. Blood pressure was measured with a digital automatic blood pressure monitor (Dinamap model Pro Series DP110X-RW, 100V2; GE Medical Systems Information Technologies, Inc., Hermosa Beach, CA) with the subject in a seated position, after 5 minutes of rest. Venous blood was collected to determine nonfasting blood glucose, total cholesterol, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol.

Questionnaires and Interview

A detailed interview was administered using a standardized questionnaire to collect information on medical history, cigarette smoking (never smoked/current smoker/past smoker), alcohol consumption (yes/never), educational level (no formal education/primary education/secondary education/polytechnic/university), and near-work activities (number of hours spent reading and using the computer per day).

Definitions of Diseases

Lens opacity was graded under the slit-lamp using modified Lens Opacities Classification System III (LOCS III) scores.[24] Any cataract was defined as the presence of any nuclear cataract (LOCS III score for nuclear opalescence or nuclear color of 4 or more), any cortical cataract (LOCS III score of 2 or more), or any posterior subcapsular cataract (LOCS III of 2 or more) in either eye. Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or a physician diagnosis. Diabetes mellitus was identified from nonfasting blood glucose ≥200 mg/dL (11.1 mmol/L), or self-reported use of diabetic medication, or physician-diagnosed diabetes. Body mass index (BMI) was calculated as the weight divided by the square of the height (kilograms per meter squared).

Statistical Analyses

Among the 3400 subjects, those with cataract surgery history (n = 502) were excluded from analyses. We also excluded phakic participants without ocular biometry data (n = 113). As a result, 2785 (84.6%) participants were included in the analyses. Since ocular biometric parameters for the right and left eyes correlated highly (Pearson correlation coefficient for AL = 0.94, $P < 0.001$; ACD = 0.89, $P < 0.001$; and CR = 0.99, $P < 0.001$), analyses were performed on right eyes only.

Mean biometry data were compared across each age group stratified by sex, and linear test for trend was used to investigate significance for each age group. Possible predictors for each biometric parameter were assessed in univariate analyses. Variables with a $P < 0.05$ in univariate analyses and of scientific importance were included in multiple linear regression models, and manual backward stepwise elimination procedures were performed based on a criterion of $P < 0.05$ to achieve the final, most parsimonious model. Linear regression models were then constructed to evaluate independent effects of lens opacity and ocular biometric components (independent variables) on refraction (dependent variable) in all age groups. Standardized regression coefficients in these models were used to determine the relative importance of nuclear opacity (NO) and each biometric component on refraction (SPSS 16.0; SPSS Inc., Chicago, IL).

Table 1. AL, ACD, CR, and AL/CR Ratio by Age and Sex

	n	AL (mm)	ACD (mm)	CR (mm)	AL/CR
All persons	2785	23.45 ± 1.10	3.15 ± 0.36	7.61 ± 0.26	3.08 ± 0.13
Men	1406	23.68 ± 1.06	3.19 ± 0.36	7.68 ± 0.26	3.09 ± 0.12
Women	1379	23.23 ± 1.10	3.10 ± 0.35	7.55 ± 0.25	3.08 ± 0.14
P		<0.001	<0.001	<0.001	0.37
All persons					
40–49 years	871	23.53 ± 1.08	3.24 ± 0.35	7.62 ± 0.26	3.09 ± 0.14
50–59 years	1019	23.49 ± 1.15	3.18 ± 0.35	7.61 ± 0.26	3.09 ± 0.14
60–69 years	682	23.35 ± 1.14	3.05 ± 0.35	7.60 ± 0.26	3.07 ± 0.13
70–83 years	213	23.25 ± 0.78	2.92 ± 0.36	7.61 ± 0.26	3.06 ± 0.10
P_{trend}		<0.001	<0.001	0.22	0.11
Men					
40–49 years	427	23.71 ± 1.01	3.27 ± 0.36	7.68 ± 0.26	3.09 ± 0.13
50–59 years	498	23.72 ± 1.07	3.23 ± 0.34	7.68 ± 0.25	3.09 ± 0.12
60–69 years	357	23.68 ± 1.19	3.11 ± 0.36	7.68 ± 0.26	3.08 ± 0.13
70–83 years	124	23.36 ± 0.70	2.97 ± 0.34	7.64 ± 0.27	3.06 ± 0.09
P_{trend}		0.02	<0.001	0.44	0.09
Women					
40–49 years	444	23.36 ± 1.12	3.20 ± 0.33	7.57 ± 0.26	3.09 ± 0.15
50–59 years	521	23.28 ± 1.18	3.13 ± 0.34	7.55 ± 0.25	3.09 ± 0.15
60–69 years	325	22.99 ± 0.96	2.98 ± 0.33	7.51 ± 0.24	3.06 ± 0.13
70–83 years	89	23.09 ± 1.25	2.85 ± 0.32	7.58 ± 0.25	3.05 ± 0.11
P_{trend}		<0.001	<0.001	0.06	0.12

Data are the mean ± SD.

RESULTS

Participants in the study (n = 3400, mean age: 57.8 ± 10.1 years) were younger than nonparticipants (n = 1097, mean age: 61.1 ± 10.5 years; $P < 0.001$), but there was no difference in sex ($P = 0.28$).

Table 1 shows the means of ocular biometric parameters by age and sex. The mean AL, ACD, and CR for the overall population were 23.45 ± 1.10, 3.15 ± 0.36, and 7.61 ± 0.26 mm, respectively. The mean AL/CR ratio was 3.08 ± 0.13. The men had significantly longer AL ($P < 0.001$), deeper ACD ($P < 0.001$), and flatter CR ($P < 0.001$) than the women had. There was a significant trend of decreasing AL and ACD with increasing age for the population as a whole and for the men and women separately. On average, persons aged 40 to 49 years, when compared with those aged 70 to 83 years, had longer ALs (mean difference, 0.18 mm) and deeper ACDs (mean difference, 0.32 mm). CR did not vary significantly with age ($P = 0.22$). There were no age ($P = 0.11$) or sex ($P = 0.37$) differences seen in AL/CR ratio comparisons.

The distribution of ALs is shown in Figures 1 and 2. ALs for the overall population did not demonstrate normal distribution (kurtosis = 6.1; skewness = 1.4; P for Kolmogorov-Smirnov [K-S] test < 0.001). When stratified by age groups, only AL followed a normal distribution in the oldest age group (70–83 years; kurtosis = 1.3; skewness = 0.05; P for K-S test = 0.68). In younger age groups, the distributions of ALs were all positively skewed. The distributions ALs were also positively skewed in the men (kurtosis = 8.7, skewness = 1.2, P for K-S test <0.001) and the women (kurtosis = 4.7, skewness = 1.4; P for K-S test <0.001). Both ACDs and CRs were normally distributed in this population.

The correlation between SE and AL/CR ($r = -0.78$; $P < 0.01$) was stronger than that between SE and AL ($r = -0.65$; $P < 0.01$). Persons with a more negative SE had longer AL or higher AL/CR ratio. The relationship between AL and SE was different in adults with and without nuclear cataract (Fig. 3). CR showed a weak positive relationship with AL ($r = 0.48$, $P < 0.05$), but there was no relationship with CR and SE ($r = 0.08$, $P = 0.65$). ACD correlated positively with AL ($r = 0.47$, $P < 0.01$), but was negatively associated with SE ($r = -0.31$, $P < 0.01$). The relationship between AL and CR was stronger in nonmyopic eyes than in myopic eyes (Fig. 4).

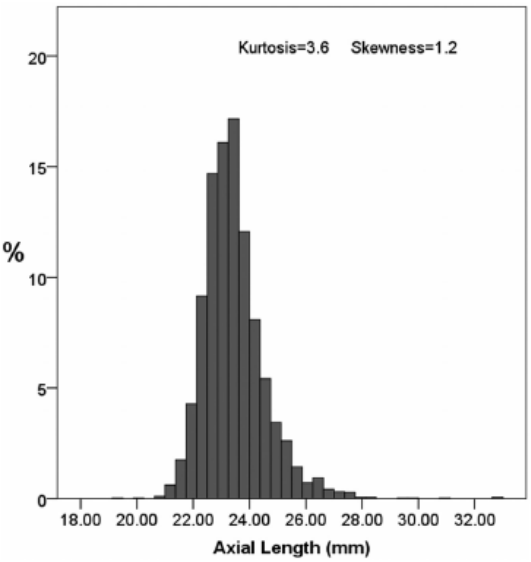

FIGURE 1. Distribution of AL in the overall sample.

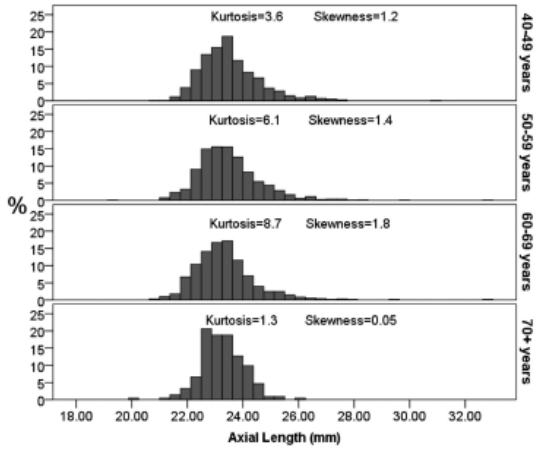

FIGURE 2. Distribution of AL by age groups.

Three multivariate linear regression models were constructed to explore the determinants for AL, ACD, and CR. After adjustment for age, sex, diabetes, and nuclear cataract, each centimeter of height increase was associated with 0.034-mm increase in AL. For every additional hour spent on reading and writing per day, there was a 0.064-mm increase in AL. Adults with a university education had 0.408-mm longer mean AL than those with no formal education. Deeper ACDs were found in adults who were younger (regression coefficient = −0.01 mm, $P < 0.001$), taller (regression coefficient = 0.004 mm, $P < 0.001$), and read more per day (regression coefficient = 0.01 mm, $P = 0.02$). Increasing CRs were positively associated with height (regression coefficient = 0.009 mm, $P = 0.008$; Table 2).

Linear regression models were constructed to evaluate the independent effect of biometric components on SE in all age groups. In model 1, AL, CR, and NO (LOCS III) were analyzed as independent variables, with SE as the dependent variable. In model 2, the AL/CR ratio and NO (LOCS III) were analyzed as

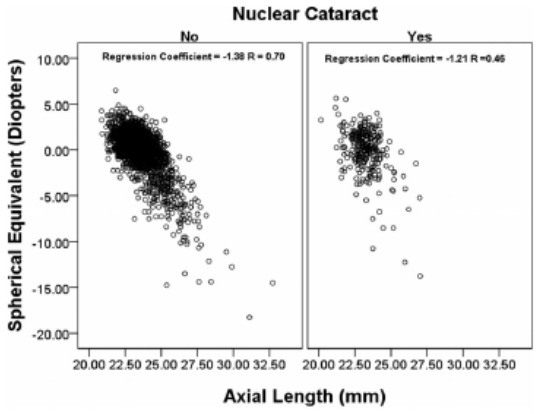

FIGURE 3. Association between AL and SE in adults with and without nuclear cataract.

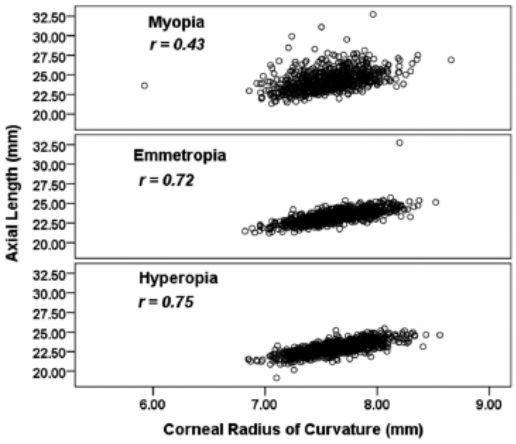

FIGURE 4. Correlations between AL and CR by refractive status.

independent variables, with SE as the dependent variable. A standardized regression coefficient was used to estimate the relative effect of each biometric component on SE. In all age groups, AL or the AL/CR ratio was the highest relative predictor of SE, with the standardized regression coefficient being the largest. NO was not a significantly predictor of SE in the 40- to 59-year age group. However, NO played a more important role in older age groups. The standardized regression coefficients were −0.27 in model 1 and −0.31 in model 2 for NO in the 70- to 83-year age group (Table 3).

DISCUSSION

This study documented population-based data on ocular biometry of Indians in urban Singapore. The mean AL, ACD, and CR of this population were 23.45, 3.15, and 7.61 mm, respectively. A more myopic refraction was predominately explained by longer AL or greater AL/CR ratio throughout the whole age range, although lens NO was also a predictor of refraction in older age groups. Height, time spent reading, and educational level were the most important predictors of AL.

In previous studies,[10,25–27] AL was measured by A-scan ultrasound biometry which requires corneal surface contact, and the measurement is more time consuming. The noncontact optical biometry measurement which uses partial coherence interferometry technology (IOL Master; Carl Zeiss Meditec) eliminates the deficiency of A-scan ultrasound measurement. It was suggested that the IOL Master is a better predictor of normative ocular biometric data than is ultrasound biometry.[21] Biometry data from ultrasound and laser interferometry may be slightly different.[28] ACD using ultrasound was found to be significantly shorter than that with noncontact measuring systems.[29] Compared with A-scan ultrasound, IOL Master could either overestimate[30] or underestimate[31] AL. IOL Master also does not provide lens thickness measurements.

It is worthwhile comparing our findings with those of the Central India Eye and Medical Study on Indians living in India. The mean AL in that study (22.6 mm) was significantly shorter than in our SINDI study (23.45 mm). The magnitude of the difference is considerable, and it is unlikely to be explained by differences in AL measurement method or age range of the participants. The difference in AL may be explained by a greater degree of urbanization in Singapore and subsequently a higher rate of axial myopia.

Comparing the mean AL among different population-based studies would help to clarify the interethnic variation in AL and its association with refractive errors. Compared with the other two major ethnic groups in Singapore, the mean AL in this Singaporean Indian cohort is similar to that of the Singaporean Malays in the SiMES, but slightly longer than that of Singaporean Chinese in the Tanjong Pagar Survey. However, different age and sex distributions may account for the differences observed among these population-based studies. To compare the association between AL and SE more accurately, we compared the mean AL and SE in different population-based studies in the 40 to 49 years age group since SE is mostly explained by AL and influence by lens opacity is minimal in this age group (Table 4). We found longer AL to be associated with more negative SE. Singaporean Chinese with the longest mean AL have the most negative mean SE. As can be seen in Table 4, there was a trend toward longer AL among the populations with more negative SE, although there was no significant difference ($P = 0.08$ for men and $P = 0.13$ for women) due the small sample size.

In our study, older adults tended to have shorter ALs. This has also been observed in Singaporean Chinese[10] and Singaporean Malays,[12] but not in Latinos,[25] Burmese,[26] and Mongolians.[27] In addition, age was only associated with AL in univariate analyses, and the association disappeared when height and education were adjusted in the multivariate model in our study. This suggests that younger subjects may be generally taller and

TABLE 2. Multiple Linear Regression Models of Ocular Biometric Parameters

	AL (mm)			ACD (mm)			CR (mm)		
	β	95% CI	*P*	*β*	95% CI	*P*	*β*	95% CI	*P*
Age, y	−0.001	−0.007 to 0.004	0.61	−0.011	−0.018,−0.004	<0.001	0.001	−0.004,0.006	0.67
Female	0.098	−0.018 to 0.215	0.10	−0.028	−0.061 to 0.005	0.16	−0.009	−0.125 to 0.107	0.88
Reading hours per day	0.064	0.034 to 0.094	<0.001	0.013	0.004 to 0.022	0.02	—		—
Education level				—		—	—		—
No formal education	0		—						
Primary education	0.065	−0.104 to 0.235	0.45						
Secondary education	0.166	−0.020 to 0.351	0.08						
Polytechnic	0.350	0.142 to 0.558	0.001						
University	0.408	0.192 to 0.624	<0.001						
Height, cm	0.034	0.0034 to 0.028	<0.001	0.004	0.0008 to 0.007	<0.001	0.009	0.002 to 0.015	0.008
Diabetes	−0.078	−0.164 to 0.007	0.07	—		—	—		—
Nuclear cataract	0.001	−0.142 to 0.143	0.99	—		—	—		—

Beta, regression coefficient.

TABLE 3. Multivariable Linear Regression Models for Spherical Equivalent Refraction, by AL, CR, AL/CR ratio and NO (LOCS III) Stratified by Age

	Unstandardized Regression Coefficient	Standardized Regression Coefficient	P
All persons			
Model 1			
AL	−1.88	−0.91	<0.001
CR	4.39	0.53	<0.001
NO (LOCS III)	−0.009	−0.005	0.73
Model 2			
AL/CR	−13.5	−0.8	<0.001
NO (LOCS III)	0.02	0.01	0.47
40–49 years			
Model 1			
AL	−1.81	−0.95	<0.001
CR	4.2	0.54	<0.001
NO (LOCS III)	0.18	0.005	0.76
Model 2			
AL/CR	−12.8	−0.84	<0.001
NO (LOCS III)	−0.03	−0.01	0.57
50–59 years			
Model 1			
AL	−1.94	−0.97	<0.001
CR	4.62	0.52	<0.001
NO (LOCS III)	−0.44	−0.04	0.02
Model 2			
AL/CR	−14.1	−0.84	<0.001
NO (LOCS III)	0.004	0.002	0.93
60–69 years			
Model 1			
AL	−1.81	−0.87	<0.001
CR	4.36	0.52	<0.001
NO (LOCS III)	−0.8	−0.14	<0.001
Model 2			
AL/CR	−13.1	−0.74	<0.001
NO (LOCS III)	−0.28	−0.15	<0.001
70–83 years			
Model 1			
AL	−1.5	−0.57	<0.001
CR	4.42	0.57	<0.001
NO (LOCS III)	−1.12	−0.27	<0.001
Model 2			
AL/CR	−11.5	−0.55	<0.001
NO (LOCS III)	−0.54	−0.31	<0.001

In each regression model, noncycloplegic refraction is the dependent variable. In model 1, AL, CR, and NO (LOCS III) are the independent variables. In model 2, AL/CR ratio, and NO (LOCS III) are the independent variables.

more educated, which correspondingly make AL longer than those of older counterparts. In SiMES, age was also associated with AL in univariate analysis ($P < 0.001$), but was not a significant determinant of AL in the multiple logistic model ($P = 0.55$). Although AL may decrease with increasing age,[32] the age pattern for AeL is more likely due to cohort effect than age effect, at least in Singapore.

In our study, longer ALs were found in adults who were taller, more educated, and spent more time on reading. Height was the strongest predictor of AL in prior studies.[10,25,26,33–35] The association between more time on near work and longer ALs was reported in studies on children, and our study confirmed this association. It was found in Singapore that children who read more than two books per week had ALs that were 0.17 mm longer compared with children who read two or fewer books per week.[14] The mechanism of how near work elongates AL may be the growth induced by excessive accommodation,[36] but this theory remains debatable and has not been supported by findings in animal studies.[37,38] Previous population-based studies on adults have found an association between educational level and AL.[39] In SiMES, increasing AL was associated with higher education level (standardized $\beta = 0.118$, $P < 0.001$).[12] In the Tanjong Pagar Survey on Singaporean Chinese adults, AL increase by 0.60 mm for every 10 years of education (95% CI, 0.34–0.85).[10] Our study found that this association exists only at college or university educational level. The implications of AL as an endophenotype compared with refractive error should be considered. AL is used as an endophenotype for refraction, since refraction is affected both by genetic and environmental factors, whereas AL may provide a simpler phenotype.[40] However, our study showed that AL is also associated with environmental factors such as near work and educational level, in addition to height. Moreover, AL may be related to genetic variants too. Thus, AL as an endophenotype for refraction is still controversial and should be studied further. Both refraction and AL should be examined in detail in further epidemiologic studies of myopia.

AL is the most important predictor of refraction, with standardized regression coefficients of AL being the largest in all age groups (Table 3). In younger age groups such as 40 to 49 years and 50 to 59 years, AL accounts for most of the variation in refraction. Although lens opacity became an additional significant predictor of refraction in older age groups, explaining why there was a myopic shift from 60 to 69 to 70 to 83 years. Lens opacity affect refraction through increased power of the more sclerotic lens rather than increased AL.[41–44] This pattern is supported by the Tanjong Pagar Survey[10] and the Los Angeles Latino Eye Study.[25]

In our study, taller adults were also found to have deeper ACDs and flatter corneas, indicating an overall increase in eye globe size. However, SE correlated weakly with CR or ACD, confirming other reports that AL is the main determinant of SE, whereas CR and ACD are of relatively minor importance. AL/CR ratio correlated even more highly with SE than AL alone in our study. This correlation indicates that longer eyes, includ-

TABLE 4. Mean Axial Length and Spherical Equivalent in Adults 40–49 Years of Age in Different Population-Based Studies

Study	Ethnicity	Measurement of AL	Mean SE (Diopters)		Mean AL (mm)	
			Men	Women	Men	Women
The Los Angeles Latino Eye Study[25]	Latinos	Ultrasound	−0.3	−0.3	23.7	23.2
The Mongolian Study[27]	Mongolians	Ultrasound	0.1	−0.3	23.4	23.0
The Tanjong Pagar Survey[10]	Chinese	Ultrasound	−1.4	−2.1	23.8	23.4
The Meiktila Eye Study[26]	Burmese	Ultrasound	−0.4	−0.6	23.2	22.6
The Singapore Malay Eye Study[12]	Malay	IOL Master	−0.6	−1.1	23.8	23.6
The Singapore Indian Eye Study	Indians	IOL Master	−0.5	−0.8	23.7	23.2

ing those that are long because of overall body stature, are not necessarily myopic. Eyes that are long because of excessive axial elongation are in fact myopic. In our study, ALs correlated less with CRs in myopic eyes than in nonmyopic eyes, indicating that emmetropization is substantially based on matching AL to CR, and thus this ratio normalizes for overall eye size and its relationship to height.

Our study has several strengths. First, it provides the first population-based data on ocular biometry measured by IOL Master in urban Indians. Furthermore, the sample size is sufficient and the response rate (75.6%) is reasonable. Finally, our study used standardized protocols to obtain biometric measurements and refractive error, which allows comparison of our data to other population-based data. However, there are several limitations of our studies. First, there may be selection bias, as participants were generally younger than nonparticipants. Second, cross-sectional study design could not separate cause from effect when assessing determinants of ocular biometric parameters. Finally, the IOL Master does not measure other important biometric parameters, such as lens thickness and vitreous chamber depth.

In conclusion, in this urban Indian population in Singapore, the mean ocular AL was longer than that of those living in rural India. Longer AL was associated with more time spent reading, higher educational level, and taller stature. Refraction was mostly explained by AL and was partially explained by lens NO in older age groups.

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Appendix 4

Published manuscript entitled

‘Variation in prevalence of myopia between generations of migrant Indians living in Singapore’

Variation in Prevalence of Myopia Between Generations of Migrant Indians Living in Singapore

CHEN-WEI PAN, YING-FENG ZHENG, TIEN-YIN WONG, RAGHAVAN LAVANYA, REN-YI WU, GUS GAZZARD, AND SEANG-MEI SAW

• PURPOSE: To assess the influence of factors related to migration and acculturation on myopia in migrant Indians in Singapore.

• DESIGN: Population-based cross-sectional study.

• METHODS: A total of 3400 Singaporean Indians (75.6% response rate) aged over 40 years participated in this study. Information regarding country of birth, migration age, and language of interview were collected from interviews. Indians born outside of Singapore were defined as "first-generation" immigrants, while Indians born in Singapore were defined as "second-generation (or higher)" immigrants. Refraction was determined by autorefraction and refined by subjective refraction. Ocular biometry including axial length (AL), anterior chamber depth (ACD), and corneal radius (CR) were measured by partial coherence interferometry. Myopia and high myopia were defined as spherical equivalents (SE) of less than −0.5 diopter (D) for myopia, and < −5 D for high myopia, respectively.

• RESULTS: The prevalence of myopia (30.2% vs 23.4 %) and high myopia (4.8% vs 2.5%) were higher in second-generation immigrants compared with first-generation immigrants. Second-generation immigrants had longer AL (23.50 mm vs 23.37 mm, $P = .004$) than first-generation immigrants after multivariate adjustment. The excess prevalence of myopia was reduced by 37.5% but remained statistically significant ($P = .02$) after further controlling for educational level. Among first-generation immigrants, those migrating to Singapore before the age of 21 had significantly higher prevalence of myopia (odds ratio [OR]: 1.85; 95% confidence interval [CI]: 1.32, 2.59) and longer AL (regression coefficient: 0.27; 95% CI: 0.11, 0.43) than those migrating after 21 years of age. Also, first-generation immigrants interviewed in English had higher prevalence of myopia (OR: 1.46; 95% CI: 1.00, 2.17) than their non-English-interviewed counterparts.

• CONCLUSIONS: The prevalence of myopia among second-generation (or higher) Indian immigrants in Singapore is higher than first-generation immigrants. Country-specific environmental factors may be important for the increasing prevalence of myopia in Asia. (Am J Ophthalmol 2012;xx:xxx. © 2012 by Elsevier Inc. All rights reserved.)

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From the School of Public Health (C.W.P., T.Y.W., S.M.S.) and Department of Ophthalmology (T.Y.W., S.M.S.), National University of Singapore, Singapore; Singapore Eye Research Institute and Singapore National Eye Centre (Y.F.Z., T.Y.W., R.L., R.Y.W., S.M.S.), Singapore; and Moorfield Eye Hospital (G.G.), London, United Kingdom.

Inquiries to Seang-Mei Saw, School of Public Health, National University of Singapore, 16 Medical Drive (MD 3), Singapore 117597; e-mail: ephssm@nus.edu.sg

IT IS WELL KNOWN THAT BOTH GENETIC AND ENVIRONmental factors contribute to the etiology of myopia.[1–3] Because the prevalence of myopia has increased significantly in many urban Asian cities,[4] it has been suggested that this reflects major shifts in environmental factors such as increasing education pressure and urbanization.[2,5] Migrant studies may provide further clues to the role of environmental effects on myopia. In migrant studies, people moving from one country to another are compared with people born in the new country of the same genetic heritage and thus help to tease the effects of environmental exposures from genetics. Such information is also important from a public health perspective, considering that there are more than 200 million people traveling internationally and another 750 million people migrating within their own country around the world.[6]

Few myopia migrant studies have been reported previously. Studies on the Inuit populations showed that the prevalence of myopia increased among generations as people moved into new settlements.[7–10] The Los Angeles Latino Eye Study (LALES) reported that US-born Latino immigrants had higher prevalence of myopia than those born outside the United States (22.66% vs 13.99%).[11] In addition to the effect of migration, the degree to which people acculturate to the main culture may also influence the prevalence of myopia. The LALES found that higher acculturation level as measured by a 9-item questionnaire increased the risk of myopia.[11]

To the best of our knowledge, there have been few migration studies on myopia in urbanized Asian countries. Singapore is a highly urbanized city-state located in southeast Asia, consisting of immigrants of Chinese, Malaysian, and Indian ancestries. Indians account for about 9.2% of the whole Singapore population. Singaporean Indians who originated from the Indian subcontinent including India, Pakistan, Bangladesh, and Sri Lanka migrated to Singapore, mostly in the early part of the 20th century. This population structure provides us a unique opportunity to explore the variation of myopia prevalence between different generations of immigrants.

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In this report, we compared the prevalence of myopia and ocular biometric parameters between "second-generation (or higher)" and "first-generation" Indian immigrants living in Singapore. We also assessed the influence of factors related to migration and acculturation on myopia.

METHODS

• STUDY COHORTS: The Singapore Indian Eye Study is a population-based, cross-sectional study of 3400 Indian adults aged over 40 years living in Singapore. The detailed study protocol has been described elsewhere.[12–15] Briefly, an age-stratified random sampling strategy was conducted to select 6350 names of Indian ethnicity in southwest Singapore. Of these, 4497 individuals were deemed eligible to participate, and 3400 participants took part in the study, giving a 75.6% response rate. In general, participants on average were younger than nonparticipants ($P < .001$), but there was no sex difference ($P = .28$).

• DEFINITION OF IMMIGRANT STATUS: Participants were categorized as 2 cohorts based on the country of birth: Singaporean Indian residents born outside of Singapore were defined as "first-generation" immigrants, while Singaporean Indian residents born in Singapore were defined as "second-generation (or higher)" immigrants. Among the 3400 Indian participants, 2024 (59.5%) were born in Singapore, 813 (23.9%) were born in India, 495 (14.6%) were born in Malaysia, and the other 68 (2.0%) were born in other southeast Asian countries such as Pakistan, Bangladesh, Brunei, and Sri Lanka; thus, 1376 (40.5%) were classified as first-generation immigrants and 2024 (59.5%) were classified as second-generation (or higher) immigrants.

• REFRACTION AND OCULAR BIOMETRY ASSESSMENT: Noncycloplegic autorefraction was performed using an autorefractor (Canon RK-5 Autorefractor Keratometer; Canon Inc, Tokyo, Japan). Refraction was then subjectively refined by study optometrists until the best visual acuity was obtained. These subjective refraction results were used in analysis. If the subjective refraction was not available, results of autorefraction were used instead. Myopia and high myopia were defined as spherical equivalent (SE) of less than −0.5 diopter (D) for myopia, and < −5 D for high myopia, respectively.[14]

Ocular biometric parameters including axial length (AL), anterior chamber depth (ACD), and corneal radius of curvature (CR) were measured by noncontact partial coherence interferometry (IOL Master V3.01, Carl Zeiss Meditec AG, Jena, Germany).[13]

TABLE 1. Characteristics of the First- and Second-Generation (or Higher) Indian Immigrants Living in Singapore[a]

	First Generation (N = 1109)	Second (or Higher) Generation (N = 1877)	*P* Value[b]
Age	59.1 (10.1)	54.2 (7.8)	<.001
Female sex	525 (47.3)	959 (51.1)	.05
Height (cm)	161.9 (9.4)	162.7 (9.1)	.03
BMI (kg/m²)	25.8 (4.2)	26.5 (4.9)	<.001
Education (no formal education)	109 (9.8)	107 (5.7)	<.001
Monthly income (<SGD$1000)	394 (36.5)	439 (24.0)	<.001
Housing type (1- to 2-room flat)	60 (5.4)	63 (3.4)	.002
Time spent reading and writing per day (h)	1.8 (1.4)	1.9 (1.5)	.05
Lens nuclear opacity (LOCS III)	2.4 (1.4)	2.0 (1.1)	<.001

BMI = body mass index; LOCS = Lens Opacities Classification System; SGD = Singapore dollar.

[a]Data presented are means (standard deviations) or number (%), as appropriate for variable.

[b]Comparing the differences between the 2 generations of immigrants, based on χ^2 test or *t* test, as appropriate.

• MEASUREMENT AND DEFINITIONS OF RISK FACTORS: All participants underwent a detailed interview using standardized questionnaires. Information on country of birth, migration age to Singapore, socioeconomic status (eg, education, income, house type), and lifestyle risk factors (smoking and time spent reading per day) were collected. The questionnaires were administered in 3 languages, including English, Tamil, and Malay, based on the participant's preference. English questionnaires were translated into the other 2 languages using a "forward-backward" translation procedure.

Lens nuclear opacity was graded under the slit lamp using Lens Opacities Classification System III (LOCS III) scores.[16]

• STATISTICAL ANALYSES: Statistical analyses were performed using statistical software (Statistical Package for Social Science, SPSS V16.0; SPSS Inc, Chicago, Illinois, USA). Odds ratios (OR) and 95% confidence intervals (95% CI) were shown. *P* values less than .05 were taken to indicate statistical significance.

Since both SE and ocular biometric parameters were highly correlated in the left and right eye, only right eye data were used for analyses.[13,14] The age- and sex-standardized prevalence was calculated by direct standardization of the study samples to the Singapore ethnic Indian population, using the 2000 Singapore census data.[17] We also calculated the mean refraction, AL, ACD, and CR

TABLE 2. Prevalence of Myopia, High Myopia, Mean Spherical Equivalent, Axial Length, Anterior Chamber Depth, and Corneal Radius of Curvature Between Different-Generation Immigrants

	First-Generation Immigrants[a] (N = 1109)	Second-Generation (or Higher) Immigrants[a] (N = 1877)	*P* Value
Prevalence of myopia (SE <−0.5 D) (%)			
Age and sex standardized	23.4; 20.6, 26.1	30.2; 28.1, 33.0	
Prevalence of high myopia (SE <−5.0 D) (%)			
Age and sex standardized	2.5; 1.3, 3.7	4.8; 4.0, 5.7	
Spherical equivalent (D)			
Age and sex adjusted	−0.05; −0.19, 0.10	−0.37; −0.49, −0.24	<.001
Multivariate adjusted[b]	0.01; −0.12, 0.15	−0.13; −0.23, −0.02	.11
Axial length (mm)			
Age and sex adjusted	23.40; 23.33, 23.46	23.59; 23.53, 23.65	<.001
Multivariate adjusted[b]	23.37; 23.31, 23.44	23.50; 23.45, 23.55	.004
Anterior chamber depth (mm)			
Age and sex adjusted	3.15; 3.12, 3.17	3.15; 3.14, 3.17	.64
Multivariate adjusted[b]	3.15; 3.12, 3.17	3.15; 3.13, 3.17	.53
Corneal radius of curvature (mm)			
Age and sex adjusted	7.61; 7.59, 7.63	7.61; 7.60, 7.62	.75
Multivariate adjusted[b]	7.61; 7.60, 7.63	7.61; 7.60, 7.63	.94

D = diopter.

[a]Data are presented as value and 95% confidence interval.

[b]Adjusted for age, sex, educational level, height, and lens nuclear opacity score.

TABLE 3. Effect of Potential Explanatory Factors on the Excess Prevalence of Myopia and High Myopia in Second-Generation (or Higher) Immigrants Compared With First-Generation Immigrants

	Myopia (SE <−0.5 D)				High Myopia (SE <−5.0 D)			
Model	OR[a]	95% CI	*P* Value	% Reduction Excess Prevalence[b]	OR[a]	95% CI	*P* Value	% Reduction Excess Prevalence[b]
1	1.40	1.14, 1.71	.001	Reference	2.54	1.56, 4.15	<.001	Reference
2	1.37	1.13, 1.67	.002	7.5	2.57	1.58, 4.19	<.001	−1.0
3	1.25	1.05, 1.49	.02	37.5	1.70	1.08, 2.66	.02	33.1
4	1.42	1.16, 1.73	.001	−5.0	2.46	1.51, 4.01	<.001	3.1
5	1.25	1.04, 1.50	.01	37.5	1.70	1.09, 2.66	.02	33.1

CI = confidence interval; D = diopters; OR = odds ratio.

[a]Odds ratio (95% confidence interval) of myopia (SE <−0.5 D) and high myopia (SE <−5.0 D), comparing the first-generation immigrants and the new immigrants, adjusted for the following variables: model 1: age and sex; model 2: age, sex, and height; model 3: age, sex, and educational level; model 4: age, sex, and lens nuclear opacity score; model 5: age, sex, height, educational level, and lens nuclear opacity score.

[b]% reduction in excess prevalence defined by the formula: (Ra−Rb)/(Ra−1), where Ra is the OR of myopia in second-generation (or higher) immigrants vs the first-generation immigrants adjusted for age and sex only (model 1, Reference) and Rb is the OR after additional adjustment for the variables in models 2 to 5.

in both first- and second-generation immigrants, using analysis of covariance to adjust first for age and sex and then further for educational level, height, and lens nuclear opacity. Multivariate regression models were fitted to estimate the associations of acculturation factors (age at migration and preferred language for interview) with the prevalence of myopia, SE, and AL adjusting for age, sex, educational level, lens nuclear opacity score, and height.

To evaluate the extent that education level and other risk factors may explain the excess prevalence of myopia and high myopia in second-generation immigrants compared with first-generation immigrants, we estimated the percentage reduction in odds associated with adjustment for these factors according to the following formula: $(Ra-Rb)/(Ra-1) \times 100$, where Ra is the odds ratio of myopia in second-generation immigrants compared with first-generation immigrants, adjusted for age and sex only

TABLE 4. Associations of Age at Migration With Prevalence of Myopia (Spherical Equivalent <−0.5 D), Spherical Equivalent, and Axial Length

Migration Age	Spherical Equivalent (D)			Axial Length (mm)			Myopia (SE <−0.5 D)		
	Beta[a]	95% CI	*P* Value	Beta[a]	95% CI	*P* Value	Odds Ratio	95% CI	*P* Value
Model 1[b]									
Per year earlier	−0.02	−0.03, −0.01	<.001	0.01	0.007, 0.014	<.001	1.02	1.01, 1.03	<.001
Model 2[b]									
First-generation (born outside Singapore): migration age ≥21 years (educated outside Singapore)	Reference			Reference			Reference		
First-generation (born outside Singapore): migration age: <21 years (educated in Singapore)	−0.40	−0.69, −0.11	.006	0.19	0.06, 0.33	.005	1.85	1.32, 2.59	<.001
Second-generation (or higher) (born in Singapore)	−0.55	−0.80, −0.31	<.001	0.30	0.19, 0.42	<.001	1.99	1.49, 2.65	<.001

CI = confidence interval; D = diopter.
[a]Regression coefficient.
[b]Multivariate models adjusted for age, sex, educational level, lens nuclear opacity score, and height.

(reference model), and Rb is the odds ratio in models after additional adjustment.

RESULTS

AFTER EXCLUDING PARTICIPANTS WITH PREVIOUS CATARACT surgery, 1109 first-generation and 1877 second-generation Asian Indian immigrants contributed to this analysis. A total of 685 first-generation immigrants (61.8%) and 1418 second-generation immigrants (75.5%) completed the interview in English, respectively. Among first-generation immigrants, the average migration age to Singapore was 20.0 years (standard deviation [SD] = 12.7). Compared with second-generation Indian immigrants, first-generation immigrants were older ($P < .001$), shorter ($P = .03$), and less educated ($P < .001$). They had lower body mass index ($P < .001$), lower monthly income ($P < .001$), smaller houses ($P = .002$), and higher lens nuclear opacity score ($P < .001$) (Table 1).

Table 2 compares the prevalence of myopia (SE <−0.5 D), high myopia (SE <−5.0 D), and mean ocular biometric parameters between first- and second-generation immigrants. Second-generation immigrants had higher prevalence of myopia (30.2% vs 23.4%) and high myopia (4.8% vs 2.5%) than first-generation immigrants. They also had longer AL (23.50 mm vs 23.37 mm; $P = .004$) after adjusting for age, sex, educational level, height, and lens nuclear opacity score. ACD and CR were not significantly different between the 2 groups.

We estimated the reduction in odds of myopia and high myopia associated with second-generation immigrants with adjustment of myopia-related factors. Adjustment for height or educational level led to reduction in the excess prevalence of myopia in second-generation immigrants by 7.5% or 37.5%, respectively. On the contrary, adjustment for lens nuclear opacity score increased the excess prevalence of myopia in second-generation immigrants by 5.0%. The prevalence of high myopia in second-generation immigrants was reduced by 33.1% when educational level was adjusted (Table 3).

Younger age at migration (as a continuous variable) was significantly associated with higher prevalence of myopia (OR, 1.02; 95% CI: 1.01, 1.03; $P = .02$), after adjusting for age, sex, educational level, lens nuclear opacity score, and height. Per-year decrease in age at migration was associated with a 0.02 D decrease in refraction (95% CI: −0.03, −0.01; $P < .001$) and 0.01 mm increase in AL (95% CI: 0.007, 0.014; $P < .001$). Those who migrated to Singapore before the age of 21 years and thus were educated in Singapore before turning 21 years old had higher odds of myopia (OR: 1.85; 95% CI: 1.32, 2.59; $P < .001$), more myopic refraction (regression coefficient: −0.40; 95% CI: −0.69, −0.11; $P = .006$), and longer AL (regression coefficient: 0.19; 95% CI: 0.11, 0.43; $P = .001$) compared with those who migrated and thus were educated in Singapore after 21 years of age (Table 4).

Among first-generation immigrants, the adults who were interviewed in English had higher prevalence of myopia (OR = 1.46; 95% CI: 1.00, 2.17; $P = .05$) compared with those not interviewed in English, after adjusting for age, sex, educational level, lens nuclear opacity score, and height. However, there was no significant difference in the prevalence of myopia between those who were and were not interviewed in English among second-generation immigrants ($P = .73$).

DISCUSSION

IN THE CURRENT STUDY OF INDIAN IMMIGRANTS AGED over 40 years living in Singapore, we found that myopia

was more prevalent and ALs were longer among second-generation immigrants compared with first-generation immigrants. Among first-generation immigrants, those who migrated to Singapore at an early age and those who preferred to be and were interviewed in English were more likely to be myopic than their counterparts.

Migrant studies offer a unique insight into how environmental factors may influence myopia at the population level, by comparing the prevalence and patterns of myopia among different generations of migrants with the same genetic heritage. The pattern of myopia in migrants may be influenced by the retention of ethnic identity and culture after resettlement and by the length of residence in the new country vs the country from which they have derived. However, migrant studies on myopia are few. Our finding is consistent with previous studies, which showed the prevalence of myopia increased spectacularly among generations as people moved into settlements.[7–11] Our study found that second-generation immigrants had both more myopic refraction and longer ALs than first-generation immigrants. These findings are important given the age range of over 40 years of the study population, as spherical refraction may also reflect the effects of age-related lenticular changes. Unlike refractive error, AL is known not to be affected by nuclear cataract or nuclear sclerosis.[18] Our study thus demonstrates that second-generation immigrants were more likely to have axial myopia than first-generation immigrants.

A number of studies have already shown the strong correlation between higher educational level and higher risk of myopia.[19–23] Our study now demonstrated that 37.5% of the excess prevalence of myopia in second- as compared to first-generation immigrants was explained by higher educational level in second-generation immigrants.

The mean migration age for first-generation immigrants in our study was about 20 years, and therefore most of them completed primary education outside Singapore. They may have been exposed to a less intensive schooling system at an early age and were less likely to receive preschool education compared with Singapore-born Indians. For example, most Singaporean children attend preschool such as kindergarten or a childcare center, and the syllabus may be more structured and vigorous, with a greater use of information technology.[24] There may be other early childhood lifestyle factors in Singapore that may contribute to the excess prevalence of myopia, including outdoor time, stress levels, and the like. In addition, 90% of the Singaporean children are reported to live in high-rise buildings,[25] which may also reduce outdoor time. Singapore is a small urban city-state with more intensive population density and higher per capita gross domestic product compared with India or neighboring countries (http://www.singstat.gov.sg). Difference in religion, culture, or even diet between Singapore and India or neighboring countries may also explain part of the difference in myopia prevalence between the 2 generations of immigrants. Further studies are needed to examine the influence of other factors related to myopia such as time spent outdoors, population density, stress, or even diet among different generations of immigrants.

After adjusting for educational level, those who migrated to Singapore before the age of 21 and thus were educated in Singapore before 21 years of age had higher prevalence of myopia and longer AL than those who migrated after 21 years of age and who were educated outside Singapore before the age of 21. However, myopia rates do not appear to vary much between Indians born outside of Singapore but educated in Singapore and Indians born in Singapore (Table 4). Thus, our findings could be interpreted that exposure to the Singapore schooling system at an early age may be an independent risk factor for myopia. Singapore's schooling is highly competitive and academically oriented, with an emphasis on very early educational achievements and passing examinations. Therefore, it is possible that those who migrated to Singapore before the age of 21 were under greater educational "pressure" than those who migrated to Singapore after the age of 21. This may reflect a combination of higher level of reading exposure with large amounts of near-work activity, corresponding lower levels of outdoor physical activity, and other factors.

The preferred language for interview was reported as a measure for acculturation in migrant Asians,[26] and we found that first-generation immigrants were more myopic if they were interviewed in English. Our finding is consistent with those reported in LALES, which used a 9-item questionnaire that recorded Spanish, English, and preferred language for speech, reading, and writing to reflect acculturation level.[11] Preferred language for interview as proxy measures of acculturation may not fully reflect the complex acculturation processes, but it places minimal cognitive demands on participants and can be easily translated as well. Further studies should be conducted to identify the specific factors related to myopia during acculturation.

Strengths of our study include its large and population-based sample, standard assessment of refraction and ocular biometry, and detailed classification of the different generations of immigrants. Limitations of this study should also be noted. First, baseline refraction was not available for first-generation immigrants before they moved to Singapore. Longitudinal studies might be helpful to examine the association between change of refraction and lifestyle-related factors. Second, there was no detailed evaluation of early childhood factors of first-generation immigrants from their home country compared with second-generation immigrants in Singapore. Third, our study is limited by the use of interview language as a proxy measure of acculturation, which may not fully reflect the complex acculturation processes.

In summary, the data from the Singapore Indian Eye Study confirm that myopia is more prevalent and ALs are

longer among second-generation immigrants of Indian residents living in Singapore compared with first-generation immigrants, suggesting that country-specific environmental factors play a major role in the increasing prevalence of myopia observed in new urbanized Asian societies. Further studies are needed to understand the specific environmental, societal, and lifestyle changes during immigration and acculturation that underline the risk of myopia, which is now a major public health concern in Asia.

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Appendix 5

Accepted manuscript entitled

‘Differential associations of myopia with major age-related eye diseases: The Singapore Indian Eye Study’

Differential Associations of Myopia with Major Age-Related Eye Diseases:

The Singapore Indian Eye Study

Running head: Myopia and Major Eye Diseases

Chen-Wei Pan, MD,[1] Carol Y. Cheung, PhD,[2,3] Tin Aung, MD, PhD,[2,3]
Chiu-Ming Cheung, MD, [2,3] Ying-Feng Zheng, MD,[2] Ren-Yi Wu, MD, PhD,[2]
Paul Mitchell, MD, PhD,[4] Raghavan Lavanya, MD,[2] Mani Baskaran, MD,[2,3]
Jie Jin Wang, PhD,[4,5] Tien Yin Wong, MD, PhD,[1,2,3,5] Seang-Mei Saw, MPH, PhD[1,2]

[1]Saw Swee Hock School of Public Health, National University of Singapore, Singapore

[2]Singapore Eye Research Institute, Singapore National Eye Centre, Singapore

[3]Department of Ophthalmology, National University of Singapore, Singapore

[4]Centre for Vision Research, University of Sydney, Sydney, Australia

[5]Centre for Eye Research Australia, University of Melbourne, Melbourne, Australia

Corresponding to:

Seang-Mei Saw, MPH, PhD.

Saw Swee Hock School of Public Health

National University of Singapore

16 Medical Drive (MD 3)

Singapore 117597

(Phone) 65-6516 4976 / (Fax) 65-6779 1489 / Email: ephssm@nus.edu.sg

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ABSTRACT

Purpose: To determine the associations of myopia and axial length (AL) with major age-related eye diseases including age-related macular degeneration (AMD), diabetic retinopathy (DR), age-related cataract and primary open angle glaucoma (POAG).

Design: Population-based, cross-sectional study.

Participants: 3,400 Indians (75.6% response rate) aged 40-84 years in Singapore

Methods: Refractive error was determined by subjective refraction and AL by non-contact partial coherence laser interferometry. AMD and DR were defined from retinal photographs according to the Wisconsin Age-Related Maculopathy Grading System and Airlie House classification system, respectively. Age-related cataract was diagnosed clinically using the Lens Opacity Classification System (LOCS) III system. Glaucoma was defined according to International Society for Geographical and Epidemiological Ophthalmology criteria.

Main Outcome Measures: AMD, DR, age-related cataract and POAG.

Results: Myopic eyes (spherical equivalent [SE] < -0.5 diopter [D]) were less likely to have AMD (either early or late AMD) (odds ratio [OR]: 0.45; 95% confidence interval [CI] 0.25, 0.79) or DR (OR: 0.68; 95% CI, 0.46, 0.98) compared with emmetropic eyes; each mm increase in AL was associated with a lower prevalence of AMD (OR: 0.76; 95% CI, 0.65, 0.89) and DR (OR: 0.73; 95% CI, 0.63, 0.86).

Myopic eyes were more likely to have nuclear (OR: 1.57; 95% CI 1.13, 2.20) and posterior subcapsular (OR: 1.73; 95% CI, 1.10, 2.72) cataract, but not cortical cataract (P = 0.64); each mm increase in AL was associated with a higher prevalence of posterior subcapsular cataract (OR: 1.29; 95% CI 1.07, 1.55), but not nuclear (*P* = 0.77) or cortical (*P* = 0.39) cataract. Eyes with high myopia (SE < -6.0D) were more likely to have POAG (OR: 5.90; 95% CI, 2.68, 12.97); each mm increase in AL was associated with a higher prevalence of POAG (OR: 1.43; 95% CI, 1.13, 1.80).

Conclusions: Myopic eyes are less likely to have AMD and DR but more likely to have nuclear cataract, posterior subcapsular cataract and POAG. The associations of myopia with AMD, DR and POAG are mostly explained by longer AL. However, the association between myopia and nuclear cataract is explained by lens refraction rather than AL.

Myopia is a common ocular condition, affecting approximately 1.6 billion people worldwide. An increasing trend of myopia has been observed throughout the world and the prevalence of myopia is expected to increase to 2.5 billion by the year 2020.[1]

Age-related macular degeneration (AMD), diabetic retinopathy (DR), age-related cataract and primary open angle glaucoma (POAG) are four of the most common age-related eye diseases, which lead to visual impairment and blindness.

An important clinical and public health question is whether myopia is associated with these age-related eye diseases. Previous studies have assessed the associations of refractive errors with some of these ocular diseases, but the findings to date have been inconsistent. The US Beaver Dam Eye Study of adults 43–84 years reported the cross-sectional association between myopia and nuclear cataract (odds ratio [OR], 1.67; 95% confidence interval [CI], 1.23, 2.27), but provided no evidence of a relationship between myopia and 5-year incident cataract.[2] This study also reported an association between myopia and prevalent POAG[3] (OR, 1.6; 95% CI, 1.1, 2.3) while no association was found between myopia and incident AMD.[4] The Australian Blue Mountain Eye Study of adults aged over 49 years reported that low (OR 2.1; 95% 95%CI 1.4, 3.5), moderate (OR 3.1; 95% CI 1.6, 5.7) and high (OR 5.5; 95% CI 2.8, 10.9) myopia was associated with posterior subcapsular cataract (PSC), but only high myopia was associated with all three types of age-related cataract.[5] Myopia was also found to be associated with higher risk of POAG[6] (OR 2.4; 95% CI 1.5, 4.0) while hyperopia was weakly related to prevalent AMD[7] (OR 1.3; 95% CI 0.9, 1.9) but not

incident AMD.[8] In Asian studies, where the prevalence of myopia is higher, a study on Malays aged 40-80 years in Singapore reported that moderate myopia is positively associated with POAG[9] but inversely associated with DR[10] and AMD.[11] Furthermore, although the associations of myopia and these major eye diseases have been assessed, few population-based studies have assessed whether these observed associations were explained by longer axial length (AL), reflecting axial myopia. Finally, no study has comprehensively examined the relationship of myopia and AL with the different age-related eye diseases in a single analysis.

In this study, we described the associations of myopia and AL with four major vision-threatening eye diseases (AMD, DR, age-related cataract and POAG) in a population-based study of ethnic Indians aged 40 to 84 years living in Singapore.

METHODS

Study Cohort

The Singapore Indian Eye Study is a population-based, cross-sectional study of ethnic Indians aged 40-84 years living in Singapore. Details of the study have been reported previously.[12] Briefly, from a list of 12,000 Singaporeans of Indian ethnicity residing in South-west Singapore provided by the Ministry of Home Affairs, an age-stratified random sampling strategy was conducted to select 6,350 adults aged over 40 years. Subjects were ineligible (n=1,853) if they had no longer lived at the registered address or were terminally ill. The eligible population consisted of 4,497

subjects. Of these, 3,400 (75.6%) participated in the study. 1,097 eligible subjects did not participate in the study, among whom 1,021 refused to participate and the other 76 were not contactable. The main reasons for refusing to participate were 'too busy to attend' or 'not interested'. Non-participants on average were older than participants ($P < 0.001$), but there was no gender difference ($P = 0.28$). The mean age was 57.8±10.1 years for the study sample and 58.6±10.3 years for the eligible subjects from sampling frame. 49.8% of the study sample and 50.3% of the eligible subjects from sampling frame were females. All examinations were conducted after obtaining informed consent. This study was approved by the Singapore Eye Research Institute Institutional Review Board and the conduct of the study adhered to the Declaration of Helsinki.

Assessment of Eye Diseases

A digital retinal camera (Canon CR-DGi with a 10-D SLR back; Canon, Tokyo, Japan) was used to obtain color photographs centered at the optic disc and macula of each eye. The photographs were graded for AMD signs based on the Wisconsin Age-Related Maculopathy Grading System.[13] Early AMD was defined as soft indistinct drusen, or soft distinct drusen plus retinal pigment epithelium (RPE) abnormalities. Neovascular AMD lesions were defined as the presence of RPE detachment; neurosensory detachment; subretinal or sub-RPE hemorrhages; or intraretinal, subretinal, or sub-RPE scar tissue. Subretinal hemorrhages or hard

exudates within the macular area also were considered signs of neovascular AMD if other retinal vascular diseases as the alternative causes were excluded. Geographic atrophy was defined by presence of visible choroidal vessels and a discrete atrophic area with a sharp border with an area of at least 175 μm in diameter. Late AMD was defined as the presence of either neovascular AMD or geographic atrophy. Any AMD was defined as the presence of early AMD or late AMD.

Retinopathy lesions were graded according to a scale modified from the Airlie House classification system.[14] Retinopathy severity was categorized into minimal non-proliferative diabetic retinopathy (NPDR; level 15 through 20), mild NPDR (level 35), moderate NPDR (level 43 through 47), severe NPDR (level 53), and proliferative diabetic retinopathy (PDR, level more than 60). Macular edema was defined by hard exudates in the presence of microaneurysms and blot hemorrhage with one disc diameter from the foveal center or presence of focal photocoagulation scars in the macular areas. Those with macular edema were further divided into cases with clinically significant macular edema (CSME) and without CSME. CSME was defined by macular edema within 550 μm of the foveal center or if focal photocoagulation scars were present in the macular area. Vision-threatening diabetic retinopathy (VTDR) was defined as the presence of severe NPDR, PDR, or CSME.

Age-related cataract was diagnosed clinically using the Lens Opacity Classification System (LOCS) III system.[15] LOCS III includes an assessment of nuclear opalescence (NO), cortical cataract (C), and PSC (P). A LOCS III score of 4.0

or more for NO was defined as significant nuclear cataract, a score of 2.0 or more for C as significant cortical cataract, and a score of 2.0 or more for P as significant PSC.

Glaucoma cases were defined according to the International Society for Geographical and Epidemiological Ophthalmology criteria based on 3 categories.[16] Category 1 cases were defined based on structural and functional evidence. It required cup-disc ratio (CDR) or CDR asymmetry ≥ 97.5th percentile for the normal population or a neuroretinal rim width reduced to ≤ 0.1 CDR (between 11- and 1-o'clock or 5- and 7-o'clock) with a definite glaucomatous visual field defect. Category 2 was based on advanced structural damage with unproved field loss. This included those subjects in whom visual field could not be determined or were unreliable, with CDR or CDR asymmetry ≥ 99.5th percentile for the normal population. Category 3 consisted of persons with an IOP ≥ 99.5th percentile for the normal population, whose optic discs could not be examined because of media opacities. POAG was defined as an eye with evidence of glaucomatous optic neuropathy with an angle appearance in which the pigmented/posterior trabecular meshwork was seen for 270° or more of the angle circumference during static gonioscopy, in the absence of secondary pathologic processes.

All glaucoma suspects have a visual field test in our study. Definite visual field defect was considered to be present if the following were found: (1) glaucoma hemifield test result outside normal limits, and (2) a cluster of three or more nonedge, contiguous points, not crossing the horizontal meridian, with a probability of <5% of

the age-matched normal on the pattern deviation plot on two separate occasions. In our study, 78 subjects out of 370 glaucoma suspects had definite visual field defects.

Assessment of Refractive Error and Axial Length

Each subject's refractive status was obtained by an autorefractor (Canon RK-5 Auto Ref-Keratometer; Canon, Inc., Ltd., Tokyo, Japan), after which subjective refraction was performed to achieve best-corrected visual acuity. The final subjective refraction results were used in the analyses. Spherical equivalent (SE) was defined as sphere plus half negative cylinder. Refractive errors were defined as any myopia (SE < –0.5 D) and hyperopia (SE > +0.5D). Mild myopia was defined as -3.0D≤SE<-0.5D; moderate myopia was defined as -6.0D≤SE<-3.0D; high myopia was defined as SE < -6.0D. AL was measured by noncontact partial coherence laser interferometry (IOLMaster version 3.01; Carl Zeiss Meditec AG, Jena, Germany).

Assessment of Other Covariates

A questionnaire asking about smoking history, monthly income and educational level was administered by trained research staff. Diabetes mellitus was defined as non-fasting glucose levels >200 mg/dL (11.1 mmol/L) or physician diagnosis of diabetes and use of diabetic medications.[17] Hypertension was defined as systolic blood pressure of 140mmHg or more or diastolic blood pressure of 90mmHg or more, or use of antihypertensive medication. Non-fasting venous blood samples were drawn and sent for biochemistry tests, including analysis of total cholesterol, high density

lipoprotein cholesterol (HDL), low density lipoprotein cholesterol (LDL), triglycerides, glucose, and hemoglobin A1c (HbA1c). HbA1c was measured by high-performance liquid chromatography (HPLC). Central corneal thickness (CCT) was measured in each eye with an ultrasound pachymeter (Advent; Mentor O & O Inc, Norwell, Massachusetts). Goldmann applanation tonometry (AT900, Haag-Streit AG International, Switzerland) was used to measure intraocular pressure (IOP) of each eye.

Statistical Analyses

Eyes with previous cataract surgery were excluded from the analyses related to refractive error. For the analyses related to DR, the diabetes cohort as a whole was analyzed. AMD or early AMD lesions including drusen or retinal pigmentary abnormality, DR or VTDR, POAG, and age-related cataract were analyzed as binary outcome variables. Generalized estimating equation (GEE) models with the right and left eye data combined were fitted to estimate the associations (ORs and 95% CIs) between refractive errors or AL and the four ocular outcomes. For multivariate analysis, only age, gender and factors that were significantly different in univariate comparison ($P < 0.10$) or of scientific importance were retained in the model. Finally, AL was entered into analysis of covariance models to determine whether it explains the difference in mean refraction between eyes with and without a specific eye disease. The relative proportion of the association explained by AL (%) was defined as

[(Difference in mean refraction in the reference model – Difference in mean refraction in models with AL added)/Difference in mean refraction in the reference model]. The reference model adjusted for age, gender, and factors that were significantly different in univariate comparison ($P < 0.10$) or of scientific importance for a specific ocular disease. Statistical analyses were performed using SPSS 16.0 (SPSS Inc., Chicago, IL). $P < 0.05$ indicated statistical significance.

RESULTS

3,337 (98.1%) participants had sufficient quality photographs for AMD grading in at least one eye. Among the 3,337 participants, there were 188 (5.6%) cases of early AMD, 14 (0.4%) cases of late AMD, totaling 202 (6.1%) cases with any AMD. AMD was present in 1.6% of myopic eyes, 3.3% of emmetropic eyes and 4.0% of hyperopic eyes, respectively. **Table 1** shows the multivariate-adjusted associations of refractive error and AL with AMD (either early or late AMD) or specific AMD lesions after adjusting for age, gender, smoking, education, body mass index, hypertension and total cholesterol level. Myopic eyes had lower odds of AMD (OR: 0.45; 95% CI, 0.25, 0.79) than emmetropic eyes. When myopia was categorized into mild, moderate and high myopia, only mild myopia was significantly correlated with a lower odd of AMD (OR: 0.44; 95% CI 0.23, 0.83). Moderate and high myopia were associated with a lower odd of AMD though the associations were not statistically significant (P = 0.24 for moderate myopia; P = 0.17 for high myopia). Increasing

severity of myopia was associated with a decreasing odd of AMD (P for trend = 0.01). Each mm increase in AL was associated with lower odds of AMD (OR: 0.76; 95% CI 0.65, 0.89). Myopic eyes also had lower odds of drusen (OR: 0.61; 95% CI, 0.43, 0.86) and RPE abnormality (OR: 0.50; 95% CI, 0.35, 0.70) compared with emmetropic eyes. Each mm increase in AL was also associated with decreased odds of drusen (OR: 0.77; 95% CI 0.69, 0.86) and RPE abnormality (OR: 0.79; 95% CI 0.70, 0.89).

Among the 1,119 diabetic subjects, 1,110 (98.3%) had sufficient quality photographs for DR grading in at least one eye. 403 (36.6%) diabetic subjects had DR. DR was present in 21.7% of myopic eyes, 30.3% of emmetropic eyes and 29.4% of hyperopic eyes, respectively. **Table 2** shows the multivariate-adjusted associations of refractive error and AL with DR or VTDR after adjusting for age, gender, education, body mass index, HbA1c, hypertension and total cholesterol level. Myopic eyes had lower odds of DR than emmetropic eyes (OR: 0.68; 95% CI, 0.46, 0.98). Increasing severity of myopia was associated with a decreasing odd of DR (P for trend < 0.001). Each mm increase in AL was associated with a lower odds of DR (OR: 0.73; 95% CI 0.63, 0.86). However, both refractive error and AL were not significantly associated with VTDR.

Nuclear cataract was present in 13.4% of myopic eyes, 8.0% of emmetropic eyes and 11.8% of hyperopic eyes, respectively. Cortical cataract was present in 22.9% of myopic eyes, 20.4% of emmetropic eyes and 33.5% of hyperopic eyes, respectively. PSC was present in 4.9% of myopic eyes, 2.4% of emmetropic eyes and 2.4% of

hyperopic eyes, respectively. **Table 3** shows the multivariate-adjusted associations of refractive error and AL with age-related cataract after adjusting for age, gender, education, diabetes and smoking. Nuclear cataract was more prevalent in myopic eyes (OR: 1.57; 95% CI 1.13, 2.20) and less prevalent in hyperopic eyes (OR: 0.63; 95% CI 0.46, 0.87) than emmetropic eyes. Nuclear cataract was not associated with AL. Cortical cataract was not related to either refractive errors or AL. PSC was found to be more frequent in myopic eyes (OR: 1.73; 95% CI 1.10, 2.27) and positively associated with longer AL (OR: 1.29; 95% CI 1.07, 1.55). When any myopia was categorized into mild, moderate and high myopia, only high myopia was significantly correlated with a higher odd of nuclear cataract (OR: 3.42; 95% CI 1.67, 7.00) and PSC (OR: 5.90; 95% CI 2.68, 12.97) but not with cortical cataract. Increasing severity of myopia was associated with an increasing odd of nuclear cataract (P for trend = 0.02) but not with cortical cataract or PSC (both P for trend > 0.1).

POAG was present in 2.3% of moderate myopic eyes, 0.7% of low myopic eyes, 1.0% of emmetropic eyes and 0.8% of hyperopic eyes, respectively. **Table 4** shows the multivariate-adjusted associations of refractive error and AL with POAG after adjusting for age, gender, education, HbA1c, total cholesterol level, IOP and CCT. Any myopia was not associated with POAG (P=0.68). Only high myopia but not mild or moderate myopia was associated with a higher odd of POAG (OR: 6.97; 95% CI 2.20, 22.16). POAG was associated with each mm increase in AL (OR: 1.43; 95%CI 1.13, 1.80).

Additional analyses were performed by excluding eyes with the other eye diseases of interest in the comparison groups. For example, for the analysis of AMD, eyes with cataract, DR, POAG were excluded from analysis. Excluding eyes with the other eye diseases of interest in the comparison groups did not change the associations between myopia and major eye diseases. Compared with emmetropic eyes, myopic eyes still had lower odds of AMD (OR: 0.45; 95% CI 0.25, 0.81) and DR (OR: 0.71; 95% CI 0.48, 1.04) but higher odds of nuclear cataract (OR: 1.65; 95% CI 1.13, 2.41) and PSC (OR: 1.90; 95% CI 1.17, 3.11). Any myopia were not associated with cortical cataract (P = 0.30) or POAG (P=0.41).

In **Table 5**, the difference in mean refraction between eyes, with and without a specific ocular disease, was compared between models with AL entered versus the reference model without AL. The relative proportion of the refractive association with the ocular condition that is explained by AL was estimated by the amount of attenuation in the association after adding AL in the reference model. In general, adding AL attenuated the difference in mean refraction between eyes with and without AMD, DR or POAG by 76.2%, 76.6% or 64.7%, respectively. AL accounted for only 2.0% or 27.6% of the difference in mean refraction between eyes with and without nuclear cataract or PSC.

DISCUSSION

Our study provides new population-based data on the associations of myopia and

AL with major eye diseases in ethnic Indian persons. We found that myopic eyes were less likely to have AMD and DR, but more likely to have nuclear cataract, PSC and POAG. In addition, we showed that variation in AL explained most of the associations of refractive error with AMD, DR or POAG, but not the associations with age-related nuclear cataract, which results from changes in the refractive power of the lens associated with nuclear cataract.

In the present study, we found that myopia was inversely associated with AMD while hyperopia did not confer any increased odds. When any myopia was categorized into mild, moderate and high myopia, only mild myopia was significantly correlated with AMD. The insignificant correlation between moderate and high myopia with AMD may be explained by the small numbers of AMD in moderate and high myopia, leading to a reduction in statistical power. Results from several other population-based studies have shown an inconsistent association between refractive errors and AMD. The Singapore Prospective Study on multiethnic Asian cohorts reported that myopia was protective for AMD in men (OR: 0.45 95% CI 0.28, 0.70) but not in women (OR: 0.45 95% CI 0.28, 0.70).[18] The baseline report of the Blue Mountain Eye Study[7], Rotterdam Study[19] and the Singapore Malay Eye Study [11] showed that early AMD was more prevalent in hyperopic eyes. The Beaver Dam Eye Study and the Blue Mountain Eye Study found non-significant associations between baseline refractive errors and incident AMD.[4, 8] The biological plausibility of refractive error and AMD is not elucidated. One possible explanation is the use of

spectacles in myopic persons may reduce UV exposure in sunlight, which is known to be a risk factor of AMD.[20] However, this assumption was not supported by our study. In our study sample, only 26.3% of myopic participants and 12.0% of hyperopic participants did not wear glasses. Additional adjustment for glass wear did not alter the significant inverse association between myopia and age-related macular degeneration (data not shown). In addition, lower level of vascular endothelial growth factors has been found in myopic eyes, which may protect eyes against AMD.[21] Myopic eyes with longer AL were observed to have less rigid and compact sclera compared with hyperopic ones.[22] Previous studies have found that increased ocular scleral rigidity, which impairs the transfer of oxygen and nutrients, may be a significant risk factor for the development of AMD.[23]

The association between refractive error and DR is less well studied. In population-based studies, the Visual Impairment Project did not find any significant association between prevalent DR and myopia.[24] The Singapore Malay Eye Study showed that myopic refraction was associated with lower prevalence of DR, particularly VTDR.[10] In a longitudinal study, myopia was associated with a lower risk of progression to PDR in younger-onset diabetes.[25] Our study demonstrates that myopia was associated with lower prevalence of DR, consistent with the findings from the Singapore Malay Eye Study. However, we did not observe a significant association between myopia and VTDR, which differs from findings of the Singapore Malay Eye Study. The mechanisms underlying the protective effect of myopia on DR

currently are unclear. The retinal and choroidal thickness in myopic eyes was observed to be thinner than in hyperopic eyes.[26-27] Thus, the myopic retina may be linked with a lower oxygen and nutrients demand compared with hyperopic retina, which may underline the protective effect of myopia on DR. Another explanation may be relatively narrower retinal arterioles in myopic eyes. Myopic eyes with longer AL were observed to have narrower retinal arterioles than non-myopic eyes.[28] Recent studies also support that widening of retinal vascular caliber is associated with increasing risk of DR.[29-31] The mechanisms behind the relationship may involve the impairment of vascular autoregulation and hyperperfusion, tissue hypoxia and ischemia, and aggravating DR risk factors such as hypertension.[32-34] Finally, Quigley *et al* attributed the pressure attenuation in retinal arterioles in myopic eyes to the observed association between myopia and DR.[35] He believed that myopia results in blood flowing through a longer arteriolar tree in the retina on its course to the capillary bed, the site of disease in clinical diabetic retinopathy.[36]

The cross-sectional association between nuclear cataract and myopia has been demonstrated in several population-based studies.[37-41] This association is believed to reflect increasing nuclear sclerosis of the lens with age, leading to a myopic shift in refraction. In longitudinal cohort studies, the Barbados Eye Study also revealed an associated risk between myopia at baseline and incident nuclear cataract.[42] However, the Beaver Dam Eye Study showed no relationship between baseline refraction and 5-year incident nuclear cataract while eyes with severe nuclear sclerosis at baseline

were more likely to have a myopic change in refraction after 10 years, compared with a hyperopic change in eyes with only mild nuclear sclerosis.[2] Our findings that nuclear cataract was associated with myopia but not with AL provide evidence to support that nuclear sclerosis increases the refractive index and refractive power of the lens. Our study also supports findings from most previous studies that cortical cataract is not related to refractive errors[5, 43-44] but contradicts the Visual Impairment Project[45], where myopia was found to be associated with cortical cataract. The relationship between myopia and PSC is significant in our study. The Blue Mountains Eye Study found that early onset of myopia, defined as a history of wearing spectacles for distance before the age of 20 years may be a risk factor for development of PSC.[5] It is argued that the observed association between myopia and PSC have been confounded by difficulty in grading PSC in the presence of advanced nuclear cataract.[5] Our study now suggests that PSC is related not only to myopia but also longer AL, indicating that the refractive component of myopia is independently associated with PSC since AL is not associated with nuclear cataract. However, AL only accounted for 27.6% of the associations between refractive error and PSC in our study. Other ocular biometric components rather than AL (eg. lens thickness) may be the main biometric constituent that explains the observed association. Our study further demonstrated that only high myopia was significantly associated with nuclear cataract and PSC, indicating that there may be a threshold effect in the refractive association with age-related cataract.

The association of myopia, especially high myopia, with POAG has been confirmed by a systematic review and meta-analysis of 13 population-based studies.[46] Our study now provided additional insights into this association by showing that AL explained 64.7% of the association between refractive error and POAG. Many hypotheses have attempted to explain the association between myopia or increased AL and glaucoma. One explanation is that increased cup-to-disc ratio found in myopic persons may increase risk for damage to ganglion cell axons.[47] In addition, alterations in connective tissue and sclera rigidity, as well as exaggerated shearing forces across the lamina cribrosa found in myopic eyes, may lead to the greater susceptibility of the optic nerve.[48]

Our findings have important clinical and public health implications. There is an emerging epidemic of myopia observed worldwide, especially in Asian societies. AMD, DR, age-related cataract and POAG are also common eye disorders observed in both clinics and general populations. Many researches target modifiable risk factors of these eye disorders to relieve the future public health burden. Although myopia seems to have some protective effect on AMD and DR in our study, the association is still inconsistent among different studies and the magnitude of associations is low. In contrast, myopia, especially high myopia, as risk factor for age-related cataract and POAG is more consistently documented with relatively high magnitude of associations. Findings of our study re-emphasize the importance of the prevention of myopia, especially high myopia, in the general population.

The strengths of our study are its large and population-based sample, reasonable response rate (75.6%) and analyses on both refractive error and AL. We used the GEE models with the right and left eye data combined to increase the statistical power. The GEE method also affords greater precision of estimation and is less sensitive to missing data for some eyes.[49] Our study has a number of limitations which should be considered. First, participants were significantly younger than non-participants, thus selection bias may have occurred. Excluding an older cohort which contains relatively more AMD, cataract and POAG cases due to its older age distribution might also have caused an imprecision in the estimation of associations due to reduced number of cases. Second, the cross-sectional design has limitations as we cannot determine causal relationships. Finally, there may be inaccuracies in the diagnosis of eye diseases. For example, diagnosis of glaucoma in high myopic eyes may be difficult. It may also be difficult to grade the myopic fundus for macular RPE changes.[19] DR was graded based on two digital images per eye, which may have underestimated the prevalence of DR, but the underestimation may not be substantial.[50]

In conclusion, our population-based study of Singapore Indians shows that myopic eyes appear less susceptible to AMD and DR but more susceptible to PSC and POAG. The refractive associations with AMD, DR and POAG are mostly explained by longer AL. In contrast, the association between myopia and nuclear cataract is explained by lens refraction but not AL. Further well-designed cohort studies are warranted to confirm these associations of both myopia and AL with these major

vision-threatening eye diseases.

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Table 1. Associations of Refractive Error and Axial Length with AMD or Specific AMD Signs

	N	Age-Related Macular Degeneration†					Drusen					Retinal Pigmentary Abnormality				
		n	%	OR*	95%CI	P	n	%	OR*	95%CI	P	n	%	OR*	95%CI	P
Refractive error																
Any Myopia	1428	23	1.6	0.45	0.25,0.79	0.005	68	4.8	0.61	0.43,0.86	0.004	61	4.3	0.50	0.35,0.70	<0.001
Emmetropia	1870	61	3.3		Reference		135	7.2		Reference		139	7.4		Reference	
Hyperopia	2315	92	4.0	0.84	0.56,1.25	0.38	254	11.0	1.06	0.81,1.37	0.68	182	7.9	0.88	0.67,1.16	0.37
Refractive error																
High Myopia	143	1	0.7	0.24	0.03,1.81	0.17	4	3.0	0.46	0.17,1.27	0.13	3	2.2	0.29	0.09,0.91	0.03
Moderate Myopia	307	6	2.0	0.55	0.20,1.51	0.24	6	2.0	0.26	0.10,0.69	0.007	10	3.3	0.32	0.14,0.72	0.006
Mild Myopia	987	16	1.6	0.44	0.23,0.83	0.01	58	5.9	0.75	0.53,1.06	0.10	48	4.9	0.58	0.40,0.84	0.004
Emmetropia	1870	61	3.3		Reference		135	7.2		Reference		139	7.4		Reference	
Hyperopia	2315	92	4.0	0.84	0.56,1.25	0.38	254	11.0	1.06	0.81,1.37	0.68	182	7.9	0.88	0.67,1.16	0.37
SE (per diopter increase)	5613	176	3.1	1.14	1.02,1.28	0.02	457	8.1	1.13	1.06,1.21	<0.001	382	6.8	1.14	1.07,1.23	<0.001
AL (per mm increase)	6460	264	4.1	0.76	0.65,0.89	0.001	616	9.5	0.77	0.69, 0.86	<0.001	496	7.7	0.79	0.70.0.89	<0.001

* Adjusted for age, gender, smoking, education, body mass index, hypertension and total cholesterol level in generalized estimating equation models. †Age-related macular degeneration refers to either early or late AMD.

Any myopia: SE < -0.5D; Emmetropia: -0.5D≤SE≤0.5D; Hyperopia: SE > 0.5D; High Myopia: SE<-6.0D; Moderate Myopia: -6.0D≤SE<-3.0D; Mild Myopia: -3.0D≤SE<-0.5D

OR = Odds Ratio; CI = Confidence Interval; SE = Spherical Equivalent; AL = Axial Length; D = Diopter; AMD = Age-Related Macular

Table 2. Associations of Refractive Error and Axial Length with Diabetic Retinopathy or Vision-threatening Diabetic Retinopathy

	N	Diabetic Retinopathy					Vision-threatening Diabetic Retinopathy				
		n	%	OR*	95%CI	P	n	%	OR*	95%CI	P
Refractive error											
Any Myopia	411	89	21.7	0.68	0.46,0.98	0.04	19	4.6	0.96	0.46,2.01	0.79
Emmetropia	512	155	30.3		Reference		31	6.1		Reference	
Hyperopia	756	222	29.4	1.13	0.82,1.56	0.44	58	7.7	1.58	0.87,2.87	0.13
Refractive error											
High Myopia	43	6	14.0	0.39	0.12,1.24	0.11	3	7.0	1.36	0.25,7.43	0.72
Moderate Myopia	80	18	22.5	0.57	0.27,1.20	0.14	3	3.8	0.82	0.20,3.32	0.78
Mild Myopia	288	65	22.6	0.75	0.50,1.13	0.17	13	4.5	0.93	0.40,2.14	0.86
Emmetropia	512	155	30.3		Reference		31	6.1		Reference	
Hyperopia	756	222	29.4	1.13	0.82,1.56	0.44	58	7.7	1.58	0.87,2.87	0.13
SE (per diopter increase)	1679	466	27.8	1.14	1.05,1.23	0.001	108	6.4	1.15	0.94,1.39	0.18
AL (per mm increase)	1701	474	27.9	0.73	0.63,0.86	<0.001	109	6.4	0.73	0.49,1.09	0.13

*Adjusted for age, gender, education, body mass index, hemoglobin A1c, hypertension and total cholesterol level in generalized estimating equation models.

Any myopia: SE < -0.5D; Emmetropia: -0.5D≤SE≤0.5D; Hyperopia: SE > 0.5D; High Myopia: SE<-6.0D; Moderate Myopia: -6.0D≤SE<-3.0D; Mild Myopia: -3.0D≤SE<-0.5D

Table 3. Associations of Refractive Error and Axial Length with Age-Related Cataract

	N	Nuclear Cataract					Cortical Cataract					Posterior Subcapsular Cataract				
		n	%	OR*	95% CI	P	n	%	OR*	95% CI	P	n	%	OR*	95% CI	P
Refractive error																
Any Myopia	1498	199	13.4	1.57	1.13, 2.20	0.007	339	22.9	1.06	0.84,1.33	0.64	72	4.9	1.73	1.10,2.72	0.02
Emmetropia	1909	150	8.0		Reference		380	20.4		Reference		45	2.4		Reference	
Hyperopia	2361	271	11.8	0.63	0.46,0.87	0.005	767	33.5	1.08	0.88,1.32	0.45	56	2.4	0.63	0.40,1.02	0.06
Refractive error																
High Myopia	145	18	12.4	3.42	1.67,7.00	<0.001	34	23.4	0.65	0.37,1.14	0.13	14	9.7	5.90	2.68,12.97	<0.001
Moderate Myopia	324	37	11.4	1.38	0.78,2.45	0.27	71	21.9	0.87	0.58,1.30	0.49	15	4.6	1.72	0.83,3.57	0.14
Mild Myopia	1029	144	14.0	1.46	1.02,2.07	0.04	234	22.7	1.01	0.79,1.29	0.94	43	4.2	1.39	0.87,2.22	0.17
Emmetropia	1909	150	8.0		Reference		380	20.4		Reference		45	2.4		Reference	
Hyperopia	2361	271	11.8	0.63	0.46,0.87	0.005	767	33.5	1.08	0.88,1.32	0.45	56	2.4	0.63	0.40,1.02	0.06
SE (per diopter increase)	5768	620	11.0	0.85	0.80,0.89	<0.001	1486	26.4	0.99	0.95,1.03	0.56	173	3.1	0.83	0.77,0.88	<0.001
AL (per mm increase)	6656	707	11.0	1.02	0.88,1.19	0.77	1610	24.2	0.96	0.87,1.05	0.39	240	4.0	1.29	1.07,1.55	0.007

*Adjusted for age, gender, education, diabetes and smoking in generalized estimating equation models.

Any myopia: SE < -0.5D; Emmetropia: -0.5D≤SE≤0.5D; Hyperopia: SE > 0.5D; High Myopia: SE<-6.0D; Moderate Myopia: -6.0D≤SE<-3.0D; Mild Myopia: -3.0D≤SE<-0.5D

OR = Odds Ratio; CI = Confidence Interval; SE = Spherical Equivalent; AL = Axial Length; D = Diopter

Table 4. Associations of Refractive Error and Axial Length with Primary Open Angle Glaucoma

	N	Primary Open Angle Glaucoma				
		n	%	OR*	95%CI	P
Refractive error						
Any Myopia	1403	17	1.2	1.20	0.50,2.89	0.68
Emmetropia	1826	19	1.0		Reference	
Hyperopia	2249	18	0.8	0.64	0.30,1.36	0.24
Refractive error						
High Myopia	132	7	5.3	6.97	2.20,22.16	<0.001
Moderate Myopia	287	3	1.0	1.10	0.23,5.36	0.90
Mild Myopia	984	7	0.7	0.62	0.27,1.45	0.27
Emmetropia	1826	19	1.0		Reference	
Hyperopia	2249	18	0.8	0.64	0.30,1.36	0.24
SE (per diopter increase)	5478	54	1.0	0.84	0.75,0.93	0.001
AL (per mm increase)	6167	61	1.0	1.43	1.13,1.80	0.003

*Adjusted for age, gender, education, hemoglobin A1c, total cholesterol level, intraocular pressure and central corneal thickness in generalized estimating equation models.

Any myopia: SE < -0.5D; Emmetropia: -0.5D≤SE≤0.5D; Hyperopia: SE > 0.5D; High Myopia: SE<-6.0D; Moderate Myopia: -6.0D≤SE<-3.0D; Mild Myopia: -3.0D≤SE<-0.5D

Table 5. Difference in Mean Refraction between Eyes with and without Ocular Disease, Adjusted for Axial Length

Models	Mean Refraction (D)				
	Present	Absent	Difference in Means	P†	Relative Proportion (%)
Age-Related Macular Degeneration					
(reference)*	0.28	-0.14	0.42	0.02	Reference
(reference+AL)	-0.02	-0.12	0.10	0.55	76.2
Diabetic Retinopathy					
(reference)*	0.27	-0.20	0.47	<0.001	Reference
(reference+AL)	0.11	0	0.11	0.32	76.6
Nuclear Cataract					
(reference)*	-1.08	-0.06	-1.02	<0.001	Reference
(reference+AL)	-1.08	-0.08	-1.00	<0.001	2.0
Posterior Subcapsular Cataract					
(reference)*	-1.47	-0.13	-1.34	<0.001	Reference
(reference+AL)	-1.13	-0.16	-0.97	<0.001	27.6
Primary Open Angle Glaucoma					
(reference)*	-1.31	-0.15	-1.16	0.04	Reference
(reference+AL)	-0.50	-0.09	-0.41	0.17	64.7

AL = axial length; D = diopter

*For age-related macular degeneration, reference model was adjusted for age, gender, smoking, education, body mass index, hypertension and total cholesterol level. For diabetic retinopathy, reference model was adjusted for age, gender, education, body mass index, hemoglobin A1c,

hypertension and cholesterol level. For nuclear cataract or posterior subcapsular cataract, reference model was adjusted for age, gender, education, diabetes and smoking. For primary open angle glaucoma, reference model was adjusted for age, gender, education, hemoglobin A1c, total cholesterol level, intraocular pressure and central corneal thickness.

†Probability represents the difference in mean refraction between eyes with and without a specific eye disease, adjusted for other covariates.

Relative proportion defined as (difference in mean refraction in reference model - difference in mean refraction in models with AL added /difference in mean refraction in reference model).

Appendix 6

Submitted manuscript entitled

‘Refractive errors and age-related macular degeneration: a systematic review and meta-analysis’

Refractive Errors and Age-Related Macular Degeneration:

A Systematic Review and Meta-Analysis

Running Head: Refractive Error and Age-Related Macular Degeneration

Chen-Wei Pan, MD,[1] M. Kamran Ikram, PhD,[2,3] Carol Y.L.Cheung, PhD,[2,3]
Hyung-Won Choi, PhD,[1] Chiu-Ming Cheung, MD,[2,3] Jost B. Jonas, MD,[4]
Seang-Mei Saw, MPH, PhD,[1,2,3] Tien-Yin Wong, MD, PhD,[1,2,3]

[1]Saw Swee Hock School of Public Health, National University of Singapore, Singapore

[2]Singapore Eye Research Institute and Singapore National Eye Centre, Singapore

[3]Department of Ophthalmology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore

[4]Department of Ophthalmology, Medical Faculty Mannheim of the Ruprecht-Karls-University Heidelberg, Mannheim, Germany

Corresponding Author:

Tien Yin Wong, MD, PhD

Singapore Eye Research Institute

11 Third Hospital Ave, #05-00

Singapore 168751

Tel: 65 6322 4584 / Fax : 65 6323 1903 / Email: ophwty@nus.edu.sg

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INTRODUCTION

Age-related macular degeneration (AMD) is a major cause of irreversible vision loss that affects significant number of elderly people.[1-4] Despite numerous epidemiological studies, besides smoking, few risk factors have been consistently associated with AMD.[5]

Recent studies have suggested that refractive error may be associated with AMD, although the data have been conflicting and inconclusive. Among white populations, the Rotterdam Study (n=6,209, aged over 55 years) reported that hyperopia was related to both prevalent and incident AMD. Among Asian populations, the Singapore Malay Eye Study (n=3,070, aged over 40 years) reported that subjects with hyperopia were 1.5 times more likely to have early AMD compared to those with myopia, even after adjustment for risk factors such as age, sex, smoking, education, height, and systolic blood pressure. Another study on multiethnic Asian cohorts (n=3,172, aged over 40 years) suggested that eyes with myopia were less likely to have AMD while eyes with hyperopia did not confer any increased risk in males but not females.[6] Two other longitudinal cohort studies found that neither myopia nor hyperopia were associated with the development of AMD.[7-8]

A clearer understanding of the relationship between refractive error and AMD may provide insights into the pathophysiology of AMD. To address this gap, we conducted a systematic review and meta-analysis to examine the association of refractive errors (including both myopia and hyperopia) and AMD from available

cross-sectional and longitudinal studies. Where the data were available, we also examined the relationship between axial length (AL) and AMD

METHODS

Search Strategy

We conducted a systematic review and meta-analysis to examine the association of refractive errors with AMD based on the Meta-analysis of Observational Studies in Epidemiology guidelines.[9] We searched the electronic database of PubMed for relevant papers on the association between refractive error and AMD published up to March 27, 2012, with the following search terms: ((("myopia"[MeSH Terms] OR "myopia"[All Fields]) OR ("hyperopia"[MeSH Terms] OR "hyperopia"[All Fields]) OR ("refractive errors"[MeSH Terms] OR ("refractive"[All Fields] AND "errors"[All Fields]) OR "refractive errors"[All Fields] OR ("refractive"[All Fields] AND "error"[All Fields]) OR "refractive error"[All Fields]) AND ("age-related maculopathy"[All Fields] OR "age related maculopathy"[All Fields] OR "age-related macular degeneration"[All Fields] OR "age related macular degeneration"[All Fields] OR "macular degeneration"[All Fields]) AND (("risk factors"[MeSH Terms] OR ("risk"[All Fields] AND "factors"[All Fields]) OR "risk factors"[All Fields] OR ("risk"[All Fields] AND "factor"[All Fields]) OR "risk factor"[All Fields]) OR ("risk factors"[MeSH Terms] OR ("risk"[All Fields] AND "factors"[All Fields]) OR "risk factors"[All Fields]) OR ("association"[MeSH Terms] OR "association"[All Fields]) OR associated[All Fields])). In addition, the reference lists of all identified studies

were examined.

Inclusion and Exclusion Criteria:

Studies were included if they were population-based, reported refractive error as an independent covariate and AMD or early AMD as the outcome measure. We only included studies in which AMD was assessed from fundus photographs based on standardized protocols, such as the Wisconsin grading system[10] or the International AMD Classification[11]. Furthermore, we included studies only if the association estimates such as the odds ratio (OR) or hazards ratios (HR) with 95% confidence interval (CI) were reported in the paper, or allowed for the calculation of it based on the data presented in the paper. Studies were excluded if they were clinic-based studies, did not have photographs, did not have standardized AMD grading, or were published in a non-English language.

Data Extraction and Quality Assessment

For each study, the following information were extracted: (i) first author, (ii) publication year, (iii) study name, (iv) sample size, (v) age range of the study participants, (vi) definitions of refractive errors and AMD, (vii) effect estimate including OR or HR and corresponding 95% CI, (viii) confounding factors adjusted for.

The study quality was assessed with the tool described by Sanderson et al.[12] The variables examined included the methods for selecting study participants, methods for

measuring exposure (refractive error) and outcome variable (AMD), design-specific sources of bias (excluding confounding), methods for controlling confounding, statistical methods (excluding control of confounding), and conflict of interest.

Statistical Analyses

Meta-analysis was performed using Stata version 12.0 (StataCorp, College Station, TX). The fully-adjusted, study-specific ORs or HRs were combined to estimate the pooled OR or HRs with 95% CI using the random effects model, which accounts for both within-study and inter-study variability. Any AMD including both early and late AMD was analyzed as the outcome measure. For studies that only reported the result of early AMD, we assumed that early AMD is equal to any AMD since the prevalence and incidence of late AMD is extremely low in general populations. Myopia, hyperopia, per diopter increase towards hyperopia in spherical equivalent (SE) and per mm increase in AL were analyzed as independent covariates. We also included the unpublished data from the Singapore Indian Eye Study, which was conducted by our team using the same study protocols as the Singapore Malay Eye Study[13], in this meta-analysis. The methodology of this study has been described elsewhere.[14-17] For the Singapore Prospect Study which reported results for men and women separately, we combined the two ORs and subsequently included the pooled OR in the meta-analysis.[6] For studies that only reported stratified ORs or HRs, we pooled the ORs or HRs to obtain an overall estimate for any myopia or hyperopia. Most studies defined myopia and hyperopia using cutoff values, with a group of

emmetropic eyes as reference category. The definitions of myopia or hyperopia varied among different studies. Myopia was treated as the reference category in the Singapore Malay Eye Study. We therefore converted the OR by using emmetropia as the reference category in conformity with other studies.[13] No refractive error cutoff values were reported in the Central India Eye and Medical Study[18] , we therefore contacted the principle investigator to obtain the full dataset and calculated the OR of myopia and hyperopia with AMD for the Central India Eye and Medical Study. Statistical heterogeneity among studies was evaluated using I^2 Statistic.[19] Values of 0 to 24%, 25% to 49%, 50% to 74%, and more than 75% denote no, low, moderate, and high heterogeneity, respectively.[20] Heterogeneity due to study design was avoided by separating the meta-analysis into cross-sectional studies and cohort studies. Publication bias was evaluated with the use of Egger regression asymmetry test[21] and the Begg's test[22]. Forest plots of association estimates between myopia and prevalent AMD, myopia and incident AMD, hyperopia and prevalent AMD and hyperopia and incident AMD were presented, respectively.

RESULTS

The literature search yielded 163 titles from PubMed. After screening these titles, we found 32 abstracts related to the topic. After screening the abstracts, 15 articles were selected for full paper review. After a thorough review of the 15 full-text to determine whether they met our inclusion critieria, 6 population-based cross-sectional studies[6, 18, 23-24] (including the Singapore Indian Eye Study) and 3 population-based

longitudinal studies[7-8, 24] were selected to be included in the meta-analysis. Among the 6 cross-sectional studies, 4 were conducted in Asia, 1 was conducted in Australia and the other was conducted in Europe. Among the 3 cohort studies, 1 was conducted in US, 1 was conducted in Australia and the other was conducted in Europe. Characteristics of the studies are presented in **Table 1**.

Table 2 summarizes the pooled effect estimates on associations of refractive error and AMD. In the meta-analysis of 6 cross-sectional studies, hyperopia was associated with higher prevalence of AMD (pooled OR: 1.16, 95% CI, 1.04, 1.29; *P*=0.01) with low heterogeneity among the studies (I^2=29.9%; *P*= 0.21). (**Figure 1**) Persons with myopia were less likely to have prevalent AMD (pooled OR: 0.75, 95% CI, 0.61, 0.92; *P*=0.005) with no evidence of heterogeneity among the studies (I^2=0%; *P*= 0.49). (**Figure 2**)

In the meta-analysis of 3 longitudinal cohort studies, no significant associations were observed between hyperopia and incident AMD (pooled HR: 0.96, 95% CI, 0.80, 1.14; P=0.63) with low heterogeneity among the studies (I^2=41.7%; *P*= 0.18). However, myopia tended to be related, albeit non-significantly, to a decreased risk of AMD compared with emmetropia. (pooled HR: 0.84, 95% CI, 0.68, 1.04; P=0.10) with no evidence of heterogeneity among the studies (I^2= 4.2%; *P* = 0.35) (**Figures 3 & 4**).

The association of per diopter increase in SE and AMD was reported in 5 cross-sectional studies and 2 cohort studies. (**Table 1**) When combining the effect estimate of these studies, per diopter increase in SE towards hyperopia was associated

with both prevalent (pooled OR: 1.09; 95% CI: 1.06, 1.12) and incident (pooled HR: 1.06; 95% CI: 1.02, 1.10) AMD. The data on the association of per mm increase in AL and AMD were available in the Singapore Malay Eye Study, Singapore Indian Eye Study and the Central Indian Eye and Medical Study. When combining the effect estimate of these studies, per mm increase in AL was associated with lower odds of prevalent AMD (pooled OR: 0.76; 95% CI: 0.69, 0.85)

There was no evidence of publication bias as indicated by a non-significant Egger test (all $P > 0.05$) and Begg's test (all $P > 0.05$) in all analyses.

DISCUSSION

This meta-analysis shows that eyes with hyperopia were more likely to have AMD while eyes with myopia were less likely to have AMD. Longitudinal data support this by showing that myopia tended to be related to a decreased risk of AMD, albeit non-significantly, but in analysis of SE as a continuous variable, each diopter increase in refraction toward hyperopia is associated with a 6-9% risk of both prevalent and incident AMD. Furthermore, longer AL was associated with a reduced risk of AMD.

The biological plausibility of the observed association has not been elucidated. We offer several theories. First, one possible explanation is the use of spectacles in myopes may reduce ultraviolet exposure in sunlight, which is known to be a risk factor of AMD.[25-29]

Second, difference in sclera rigidity between myopic and hyperopic eyes may

explain this relationship. Longer eyeballs have been observed to have less rigid and compact sclera compared with shorter ones,[30-31] and previous studies have found that increased ocular scleral rigidity may be a significant risk factor for the development of AMD.[32-33]

Third, the observed association may be explained by the variation of the intraocular concentration of vascular endothelial growth factors (VEGF) between myopic and hyperopic eyes. VEGF is now known to play a key role in AMD pathophysiology.[5] VEGF is a key regulator of angiogenesis, and withdrawal or interference with its function leads to cessation of vascular growth and neovascular regression.[34] Recent finding indicated that the intraocular concentration of VEGF decreased significantly with increasing myopia as well as increasing AL [35], which may partially explain why myopic eyes have a lower prevalence of AMD. AL may be related to ocular volume, and larger intraocular volume of the myopic eyes may lead to a more marked dilution of VEGF, which may lower the risk of AMD.[35]

Fourth, myopic eyes are more likely to have posterior vitreous detachment (PVD).[36-37] It has been suggested that PVD is associated with a reduced likelihood of progression to neovascularization, which may explain the protective effect of myopia on AMD.[38] This protective effect may be attributed to the removal of the vitreous scaffold for neovascular proliferation, as well as to improved oxygen diffusion across the liquefied vitreous. From a clinical perspective, if a lack of PVD may be one of the causative reasons for the development of AMD, future studies may address the possibilities to induce a PVD as preventive step for AMD.

There were few studies which examined the association of refractive error with late AMD. The refractive association with late AMD was reported in the Singapore Malay Eye Study, Blue Mountain Eye Study and Beaver Dam Eye Study with non-significant findings in all studies. This may be explained by the small number of late AMD cases in population-based sample, leading to an insufficient statistical power to detect a positive association. Further studies with sufficient sample size and late AMD cases are warranted to examine the association between refractive and late AMD.

A clearer understanding of the associations between refractive errors and other vision-threatening eye diseases is important for both clinicians and patients. The association between glaucoma and high myopia has been evidenced with high magnitude of association.[39] However, a potential association between low to moderate myopia and glaucoma has remained unclear with relatively low magnitude of association. The Beaver Dam Eye Study clarified no relationship between baseline refraction and 5-year incident nuclear cataract while eyes with severe nuclear sclerosis at baseline were more likely to have a myopic change in refraction after 10 years.[40] Thus, it is nuclear cataract lead to a myopic shift but not the other way round. Myopia and longer AL has been reported to be associated with lower risk of diabetic retinopathy.[41] The mechanisms of this "protective relationship" of diabetic retinopathy are likely to be similar to AMD. Thus, in view of these findings, we may conclude that eyes with low to moderate myopia may be a good refractive status to have, since the risk for AMD and diabetic retinopathy is reduced, what may more than

compensate the increased risk for rhegmatogenous retinal detachment. Low to moderate myopia may not necessarily increase the risk for cataract or glaucoma as well. Thus, the myopic shift (at least the shift toward low to moderate myopia) observed in the young generations in Asian metropolis[42-44] may be less harmful as it appears to be.

There are several strengths of this meta-analysis. First, only population-based studies were included, which is likely to minimize the possibility of selection bias. Second, cross-sectional studies and cohort studies were analyzed separately so that heterogeneity due to study design was avoided. Third, we included only data on AMD in which retinal photographs were graded based on standardized classification system. Limitations of this meta-analysis should also be acknowledged. The application of formal meta-analysis to observational studies has been known to be controversial.[45] One of potential biases in the original studies, due to the cross-sectional design in nature, makes the calculation of a single summary estimate of effect of exposure potentially misleading. Another selection bias may happen when persons with cataract surgery are excluded from analysis. Excluding an older cohort which contains relatively more AMD cases due to its older age distribution might also cause an imprecision in the estimation of associations due to reduced number of cases. In addition, the different adjustment strategies among the original studies can influence the precision and magnitude of measure of the association between refractive error and AMD. Another limitation of the current meta-analysis is that only 3 cohort studies are available for the meta-analysis so that the result of meta-analysis for refractive

error and incident AMD may be inconclusive. Finally, publication bias could be of concern because studies that report statistically significant results are more likely to get published than studies that report non-significant results, and this could have distorted the findings of our meta-analyses. However, Egger test and Begg's test indicated little evidence of publication bias in this meta-analysis.

In conclusion, this systematic review and meta-analysis found that eyes with hyperopia were more likely to have AMD while eyes with myopia were less likely to have AMD. Longitudinal data suggest that myopia tended to be related to a decreased risk of AMD, albeit non-significantly, but analysis of refractive error as a continuous variable show that for each diopter increase in SE refraction, there is a 6-9% increased risk of prevalent and incident AMD. Further studies are needed to elucidate the exact underlying mechanisms linking refractive error to AMD.

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Table 1. Characteristics of the Included Studies in the Meta-Analysis.

Author (year)	Study	Sample Size	Age	AMD Assessment	Definition Hyperopia	Definition Myopia	OR(HR)CI Hyperopia	OR(HR)CI Myopia	OR(HR)CI Per D increase in SE	Adjusted Covariates
Cross-sectional Studies										
Wang et al (1998)	BMES	3654	49+	W	>1.0D	<-1.0D	1.11, 0.86-1.42	0.83, 0.60-1.15	1.05, 1.0-1.11	age, gender, family history and smoking
Ikram et al (2003)	Rotterdam	6209	55+	I	≥0.5D	≤-0.5D	1.29, 1.04 -1.61	0.91, 0.49-1.69	1.09, 1.04-1.13	age and gender
Lavanya et al (2010)	SiMES	3070	40+	W	>0.5D	<-0.5D	1.13, 1.11-1.15	0.74, 0.47-1.15	1.08, 1.01-1.16	age, gender, smoking, education, height, and systolic blood pressure
Jonas et al (2012)	CIEMS	4542	30+	W	>0.5D	<-0.5D	1.78, 1.11-2.84	0.91, 0.52-1.72	1.15, 1.06-1.25	age, corneal refractive power
Cheung et al (2011)	SPS	3172	40+	W	>0.5D	<-0.5D	1.07, 0.49-2.38	0.62, 0.30-1.27	-	age, race, chronic kidney disease
Unpublished	SINDI	3337	40+	W	>0.5D	<-0.5D	0.84, 0.56-1.25	0.45, 0.25-0.79	1.14, 1.02-1.28	age, gender, smoking, education, BMI, hypertension and cholesterol level
Cohort Studies										

Ikram et al (2003)	Rotterdam	4822	5-year follow up	I	≥0.5D	≤-0.5D	1.13, 0.91-1.41	0.75, 0.55-1.01	1.05, 1.01-1.10	age, gender and follow-up time
Wang et al (2004)	BMES	2335	5-year follow up	W	≥1.0D	≤-1.0D	0.84, 0.65-1.10	0.71, 0.40-1.25	1.10 0.98-1.15	age, sex, smoking and the correlation between the two eyes
Wong et al (2002)	BDES	3306	10-year follow up	W	≥1.0D	≤-1.0D	0.90, 0.7-1.1	1.0, 0.7-1.3	-	age

W = Wisconsin grading system; I = international AMD classification

OR=odds ratio; HR=hazards ratio; CI=95% confidence interval

BMES = Blue Mountain Eye Study; SiMES = Singapore Malay Eye Study; CIEMS = Central Indian Eye and Medical Study; SPS = Singapore Prospective Study; SINDI = Singapore Indian Eye Study; BDES = Beaver Dam Eye Study.

Table 2. Pooled Estimates on the Associations of Refractive Error and Age-related Macular Degeneration

	Number of studies available	Pooled OR(HR)	95%CI	P value
Cross-sectional studies				
Hyperopia versus Emmetropia	6	1.16	1.04-1.29	0.01
Myopia versus Emmetropia	6	0.75	0.61-0.92	0.005
Per diopter increase in SE	5	1.09	1.06-1.12	<0.001
Per mm increase in AL	3	0.76	0.69-0.85	<0.001
Cohort studies				
Hyperopia versus Emmetropia	3	0.96	0.80-1.14	0.63
Myopia versus Emmetropia	3	0.84	0.68-1.04	0.10
Per diopter increase in SE	2	1.06	1.02-1.10	0.002
Per mm increase in AL	0	-	-	-

SE = spherical equivalent; AL = axial length; OR = odds ratio; HR = hazards ratio; CI = confidence interval

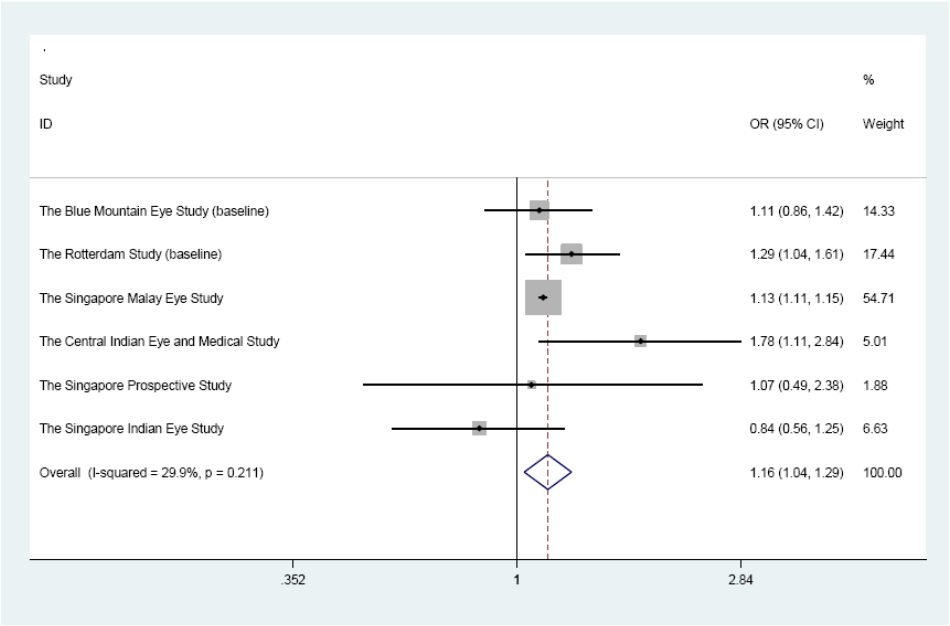

Figure 1. Forest Plot of Risk Estimates of the Association between Hyperopia and Prevalent Age-Related Macular Degeneration

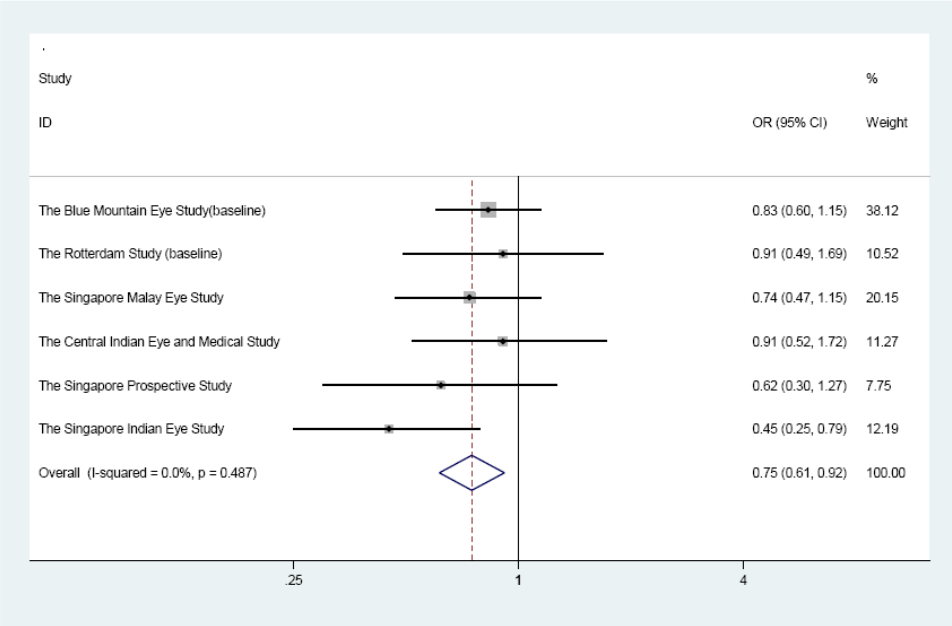

Figure 2. Forest Plot of Risk Estimates of the Association between Myopia and Prevalent Age-Related Macular Degeneration

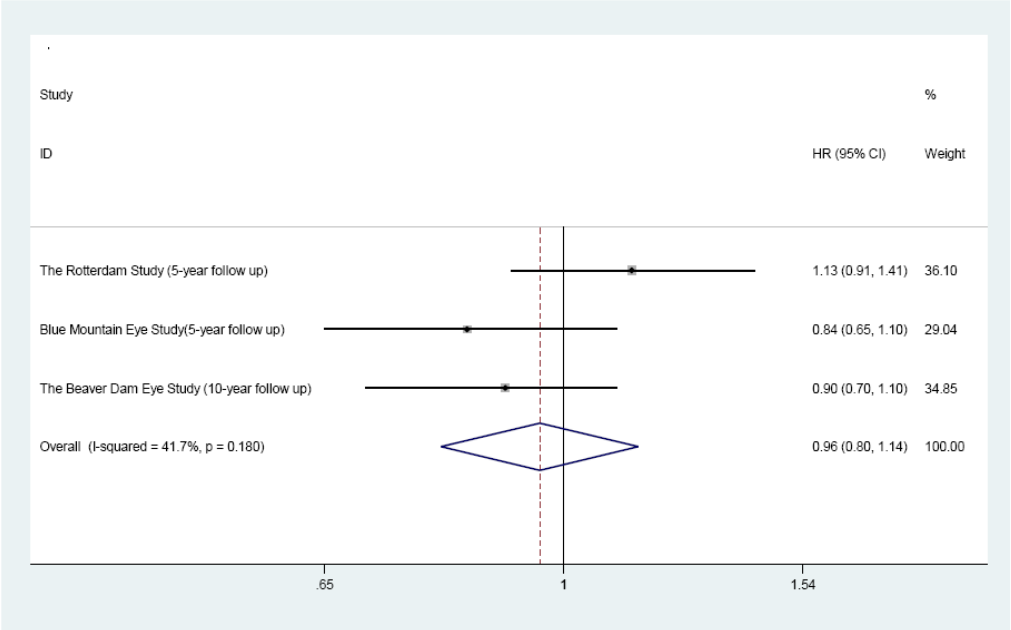

Figure 3. Forest Plot of Risk Estimates of the Association between Hyperopia and Incident Age-Related Macular Degeneration

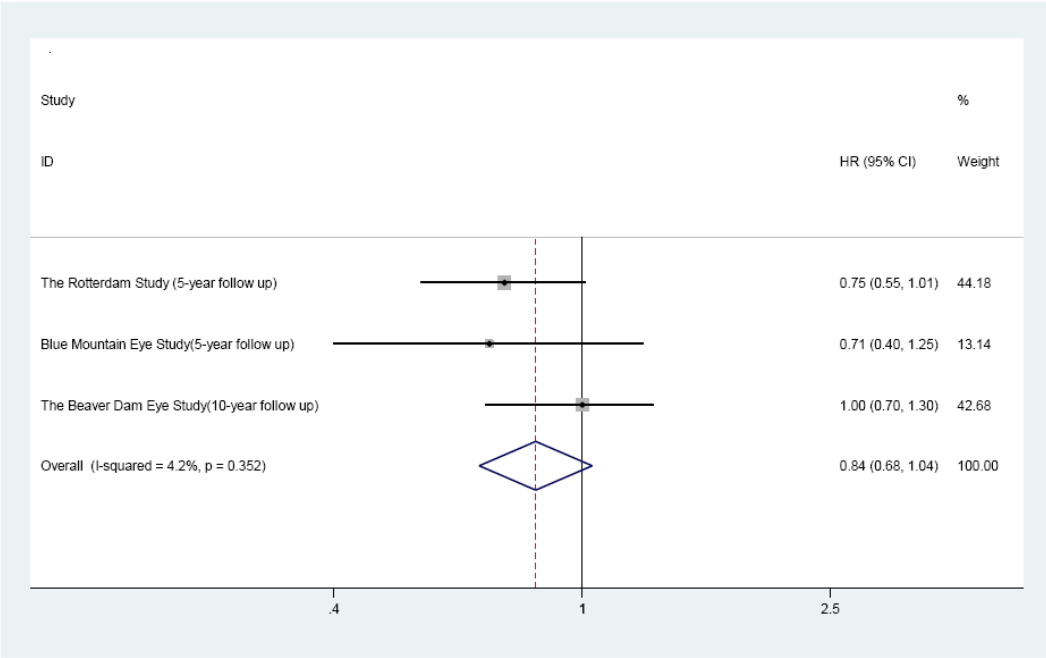

Figure 4. Forest Plot of Risk Estimates of the Association between Myopia and Incident Age-Related Macular Degeneration

Appendix 7

Questionnaire of the Singapore Indian Eye Study (SINDI)

General Questionnaire

Singapore Consortium of Cohort Studies
Interview booklet (translated to both Tamil and Mandarin)

Questionnaire

PART 1

{date1} *Date* _____/_____/_____(eg 01 / Jan / 2009)

{qtime1} *Questionnaire Time* _____

{intcode1} *Interviewer Code*: ☐☐☐

{loc1} *Interview Location*:
SERI.....☐1
Home.....☐2
Community centre.....☐3
Pilgrimage.....☐4
Mobile clinic.....☐5
{locoth1} Others.....☐6
Please specify _____

{lang1} *Language of interview*:

Chinese.....☐1
English.....☐2
Others.....☐3
Please specify _____

{deaf} Is participant deaf? {mute} Is participant mute?

Yes.....☐1 Yes.....☐1
No.....☐0 No.....☐0

{status} Status of the patient if abnormal: _____

Allergies

1-1 {allergy} *Do you have any allergies to any medications or eye drops?*

Yes	☐1
No	☐2
Don't know	☐88
Unobtainable	☐99

If yes, please specify:

1-2 {allergy1} *Allergy 1*_____

1-3 {allergy2} *Allergy 2*_____

1-4 {allergy3} *Allergy 3*_____

1-5 {allergy4} *Allergy 4*_____

1-6 {allergy5} *Allergy 4*_____

A.DEMOGRAPHY

A1 {race} *Race (as in IC)*:

Indian	☐1
Chinese	☐2
Others	☐3

{raceoth}Please specify_____

A2 {hsehold} *Number of individuals living in the house?* _____

A3 {yrslive} *How long have you lived in Singapore?*

_____ yrs

Don't know	☐88
Unobtainable	☐99

A4 {cob} *Where were you born?*

China	☐1
Singapore	☐2
Malaysia	☐3
Indonesia	☐4
Pakistan	☐5
Thailand	☐6
India	☐7
Philippines	☐8
Brunei	☐9
Others	☐10

{coboth} Please specify _____

A4.1{chipart} *Which Part of China are you from?*

Shanghai ☐1
Beijing ☐2
Guangzhou ☐3
Shenzhen ☐4
Hongkong ☐5
Tianjin ☐6
Wuhan ☐7
Shenyang ☐8
Changchun ☐9
Harbin ☐10
Chengdu ☐11
Jinan ☐12
Chongqing ☐13
Hangzhou ☐14
Handan ☐15
Taiyuan ☐16
Nanjing ☐17
Xi'an ☐18
Lanzhou ☐19
Dalian ☐20
Zhengzhou ☐21
Wulumuqi ☐22
Qingdao ☐23
Others ☐24

{chioth} Please specify _____

A4.2{fachipa} Which Part of China is your Father from?

Shanghai ☐1
Beijing ☐2
Guangzhou ☐3
Shenzhen ☐4
Hongkong ☐5
Tianjin ☐6
Wuhan ☐7
Shenyang ☐8
Changchun ☐9
Harbin ☐10
Chengdu ☐11
Jinan ☐12
Chongqing ☐13
Hangzhou ☐14
Handan ☐15
Taiyuan ☐16
Nanjing ☐17
Xi'an ☐18
Lanzhou ☐19
Dalian ☐20
Zhengzhou ☐21
Wulumuqi ☐22
Qingdao ☐23
Others ☐24

{fachioth} Please specify _____

A4.3{mochipa} *Which part of China is your Mother from?*

Shanghai	☐1
Beijing	☐2
Guangzhou	☐3
Shenzhen	☐4
Hongkong	☐5
Tianjin	☐6
Wuhan	☐7
Shenyang	☐8
Changchun	☐9
Harbin	☐10
Chengdu	☐11
Jinan	☐12
Chongqing	☐13
Hangzhou	☐14
Handan	☐15
Taiyuan	☐16
Nanjing	☐17
Xi'an	☐18
Lanzhou	☐19
Dalian	☐20
Zhengzhou	☐21
Wulumuqi	☐22
Qingdao	☐23
Others	☐24

{mochioth} Please specify _____

A5 {marital} *What is your current marital status?*

Never married	☐1
Married	☐2
Separated but not divorced	☐3
Divorced	☐4
Widowed	☐5
Don't know	☐88
Unobtainable	☐99

A6 {rel}*Religion*

Hindu	☐1
Islam	☐2
Christianity	☐3
Buddhism	☐4
Others	☐5

{reloth} Please specify _____

Don't know	☐88
Unobtainable	☐99

A7 {edu} *What is your highest completed educational level?*

No formal education ☐1
Primary education ☐2
O"/"N" levels ☐3
Levels/polytechnic/diploma/ITE/cert ☐4
University education ☐5
Others ☐6
{eduoth} Please specify_____

Don't know ☐88
Unobtainable ☐99

A8 {job} *What is your current job?*

Legislator/senior official ☐1
Professional ☐2
Technician & associated professional ☐3
Clerical worker ☐4
Service worker ☐5
Agricultural worker ☐6
Production craftsman ☐7
Plant and machine operator ☐8
Homemaker ☐9
Student ☐10
Retired ☐11
Unemployed ☐12
Others ☐13
{joboth} Please specify_____
Don't know ☐88
Unobtainable ☐99

A9 {home} *What sort of a place do you live in?*

1-2 room HDB flat ☐1
3-4 room HDB flat ☐2
5 room / executive HDB flat ☐3
其它 ☐4
{homeoth} Please specify_____
Don't know ☐88
Unobtainable ☐99

A10 {read} *Can you **read**?*

Yes ☐1
No ☐2
Don't know ☐88
Unobtainable ☐99

A11 {write} *Can you **write**?*

Yes ☐1
No ☐2
Don't know ☐88

Unobtainable..... ☐99

A12 {contact1} *For emergency, please contact*:

*Name:*_____
*Relationship:*_____
*Contact number(s):*_____
*Address:*_____
_____

{contact2} *Name:*_____
*Relationship:*_____
*Contact number(s):*_____
*Address:*_____
_____

C. LIFESTYLE FACTORS

C1. Smoking

C1.1 {smkyn} ***Have you ever*** *smoked cigarettes, cigars or a pipe regularly? (regularly being at least weekly)*

Yes ☐1
No ☐2 **(Go to C1.5)**
Don't know ☐88
Unobtainable ☐99

C1.2 {smkstop} *Have you **given up** smoking?*

Yes ☐1
No ☐2**(Go to C1.4)**
Don't know ☐88
Unobtainable ☐99

C1.3 *How much did you usually smoke per week just before you stopped?*

{smkpast1} _____ Packs of cigs (20/pack)
{smkpast2} _____ Cigars
{smkpast3} _____ Packets of pipe tobacco

C1.4 *How much do you smoke per week currently?*

{smkcurr1} _____ Packs of cigs (20/pack)
{smkcurr2} _____ Cigars
{smkcurr3} _____ Packets of pipe tobacco

C1.5 {smkhseyn} *Is there anyone else living with you in the same house who currently smokes?*

Yes ☐1
No ☐2**(Go to C2.1)**

C1.6 {smkhseno} *If yes, how many smokers are you exposed to at home?* _____ persons

C2. *Near Work*

C2.1 {nwread} *Currently, how many <u>hours per day</u> do you read and write?*

0 hour ☐0
0.1 – 1 hour ☐1
1 – 2 hours ☐2
3 – 4 hours ☐3
4 – 5 hours ☐4
More than 5 hours ☐5
{nwreadno} Please specify_____(hrs)
Don't know ☐88
Unobtainable ☐99

C2.2 {nwcomp} *Currently, how many <u>hours per day</u> do you spend using the computer?*

	0 hour	☐0
	0.1 – 1 hour	☐1
	1 – 2 hours	☐2
	3 – 4 hours	☐3
	4 – 5 hours	☐4
	More than 5 hours	☐5
{nwcompno}	Please specify_____ (hrs)	
	Don't know	☐88
	Unobtainable	☐99

C2.3 {nwtv} *Currently, how many <u>hours per day</u> do you spend watching television or playing games on the television screen?*

	0 hour	☐0
	0.1 – 1 hour	☐1
	1 – 2 hours	☐2
	3 – 4 hours	☐3
	4 – 5 hours	☐4
	More than 5 hours	☐5
{nwtvno}	Please specify_____(hrs)	
	Don't know	☐88
	Unobtainable	☐99

D. VF-14 MODIFIED VF-14

D1 {vfstair} *Do you have difficulty, even with glasses, seeing stairs?*

No	☐0
Yes, a little	☐1
Yes, moderate	☐2
Yes, a great deal	☐3
Yes, unable to do activity	☐4
NA	☐77
Don't know	☐88
Unobtainable	☐99

D2 {vfsign} *Do you have any difficulty, even with glasses, reading street signs or shop signs?*

No	☐0
Yes, a little	☐1
Yes, moderate	☐2
Yes, a great deal	☐3
Yes, unable to do activity	☐4
NA	☐77
Don't know	☐88
Unobtainable	☐99

D3 {vfrecog} *Do you have difficulty, even with glasses, recognizing your friends when you meet them while you are out shopping?*

No	☐0

Yes, a little ☐1
Yes, moderate ☐2
Yes, a great deal ☐3
Yes, unable to do activity ☐4
NA ☐77
Don't know ☐88
Unobtainable ☐99

D4 {vftv} *Do you have difficulty, even with glasses, watching television?*

No ☐0
Yes, a little ☐1
Yes, moderate ☐2
Yes, a great deal ☐3
Yes, unable to do activity ☐4
NA ☐77
Don't know ☐88
Unobtainable ☐99

D5 {vfcook} *Do you have difficulty, even with glasses, cooking?*

No ☐0
Yes, a little ☐1
Yes, moderate ☐2
Yes, a great deal ☐3
Yes, unable to do activity ☐4
NA ☐77
Don't know ☐88
Unobtainable ☐99

D6 {vfgame} *Do you have difficulty, even with glasses, playing games such as chess or cards?*

No ☐0
Yes, a little ☐1
Yes, moderate ☐2
Yes, a great deal ☐3
Yes, unable to do activity ☐4
NA ☐77
Don't know ☐88
Unobtainable ☐99

D7 {vfpaper}*Do you have any difficulty, even with glasses, reading newspaper size print?*

No ☐0
Yes, a little ☐1
Yes, moderate ☐2
Yes, a great deal ☐3
Yes, unable to do activity ☐4
NA ☐77
Don't know ☐88
Unobtainable ☐99

D8 {vftoto} *Do you have any difficulty, even with glasses, filling out 4-D or Toto forms?*

No ☐0
Yes, a little ☐1
Yes, moderate ☐2
Yes, a great deal ☐3
Yes, unable to do activity ☐4
NA ☐77
Don't know ☐88
Unobtainable ☐99

D9 {vftelbk} *Do you have any difficulty, even with glasses, reading small print in the telephone book?*

No ☐0
Yes, a little ☐1
Yes, moderate ☐2
Yes, a great deal ☐3
Yes, unable to do activity ☐4
NA ☐77
Don't know ☐88
Unobtainable ☐99

D10 {vfdrcurr} *Do you currently drive a car or ride a motorbike ?*

Yes ☐1 **(Go to D-14)**
No ☐2
NA ☐3

D11 {vfdrpast}*In the past, did you drive a car or ride a motorbike?*

Yes ☐1
No ☐2 **FINISH**
NA ☐3

D12 {vfdrstop} *When did you stop driving?*

Less than 6 months ago ☐1
6-12 months ago ☐2
More than 12 months ago ☐3

D13 {vfdrwhy} *Why did you stop driving?*

Because of my vision ☐1
Because of another illness ☐2
For another reason ☐3

D14 {vfdrday}*How much difficulty do you have driving during the day because of your vision?*

No difficulty ☐1
A little difficulty ☐2
A great deal of difficulty ☐3

D15 {vfdrnt} *How much difficulty do you have driving in the night because of your vision?*

No difficulty ..... ☐1
A little difficulty ..... ☐2
A great deal of difficulty ..... ☐3

Myopia Questionnaire

H5. *Myopia*

H5.1 {myopia} *您是否曾经被任何医生告知您有**近视**?*
*Have you ever been told by a doctor that you have **myopia**?*

Yes ☐1
No ☐2
Don't know ☐88
Unobtainable ☐99

Use of glasses

H5.2 {gls} *Do you wear **glasses** of any kind?*

Yes ☐1
No ☐2 **(Go to H6)**
Don't know ☐88
Unobtainable ☐99

H5.3 {glstyp} ***If yes**, are they:*

Single vision distance glasses only ☐1
Single vision reading glasses only ☐2
Separate reading & distance glasses ☐3
Bifocals ☐4
Multifocals ☐5

H5.4 {glsage1} *How old were you when you first needed to wear glasses to see clearly in the distance?*

_____ yrs old

Don't wear distance glasses ☐77
Don't know ☐88
Unobtainable ☐99

H5.5 {glsage2} *How old were you when you first needed reading glasses, bifocals or multifocals?*

_____ yrs old

Don't wear reading glasses ☐77
Don't know ☐88
Unobtainable ☐99

H5.6 {glsvisit} *How often do you visit the optometrist / optician / ophthalmologist to check your glasses / contact lenses?*

Once or more a year ☐1
Once in two years ☐2
Once in three years ☐3
Once in four years ☐4
Once in five to ten years ☐5
Never see the eye care practitioner regularly ☐6
Don't know ☐88
Unobtainable ☐99

H5.7 {glsck} *When did you last have the strength of your glasses checked?*

~~(Please~~ specify year)

Don't know ☐88
Unobtainable ☐99

H5.9 {glsrs} *Have you ever had refractive surgery?*

Yes	☐1	
No	☐2	**(Go to H6)**
Don't know	☐88	
Unobtainable	☐99	

H5.11 {glshosp1} *Which hospital?*

Singapore General Hospital	☐1
National University of Singapore	☐2
Tan Tock Seng Hospital	☐3
Changi General Hospital	☐4
Others	☐5

{ glshosp2} Please specify _____