Prevalence, Risk Factors, and Impact of Myopic Macular Degeneration on Visual Impairment and Functioning Among Adults in Singapore

Yee-Ling Wong,[1–3] Charumathi Sabanayagam,[1,4,5] Yang Ding,[1,6] Chee-Wai Wong,[1,4] Anna Chwee-Hong Yeo,[3] Yin-Bun Cheung,[4] Gemmy Cheung,[1,4,5] Audrey Chia,[1] Kyoko Ohno-Matsui,[7] Tien-Yin Wong,[1,2,4,5] Jie Jin Wang,[4] Ching-Yu Cheng,[1,4,5] Quan V. Hoang,[1,4] Ecosse Lamoureux,[1,4] and Seang-Mei Saw[1,2,4,5]

[1]Singapore Eye Research Institute, Singapore National Eye Centre, Singapore
[2]Saw Swee Hock School of Public Health, National University of Singapore, Singapore
[3]R&D Vision Sciences AMERA, Essilor International, Singapore
[4]Office of Research, Duke-NUS Medical School, Singapore
[5]Yong Loo Lin School of Medicine, National University of Singapore and National University Health System, Singapore
[6]School of Optometry and Ophthalmology, Wenzhou Medical College, Wenzhou, China
[7]Department of Ophthalmology and Visual Science, Tokyo Medical and Dental University, Tokyo, Japan

Correspondence: Seang-Mei Saw, Singapore Eye Research Institute, The Academia, 20 College Road, Discovery Tower Level 6, Singapore 169856, Singapore; ephssm@nus.edu.sg.

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Purpose. To determine the prevalence, risk factors, and impact of myopic macular degeneration (MMD) on visual impairment and functioning among adults in Singapore.

Methods. A comprehensive eye examination, including subjective refraction, axial length, and visual acuity (VA) measurements, was performed in adults aged ≥40 years in the Singapore Epidemiology of Eye Diseases (SEED) study. From fundus photographs, MMD was graded using the International META-PM classification. Vision-specific functioning (VSF) was assessed with a validated visual-functioning questionnaire (VF-11) using Rasch analysis.

Results. A total of 8716 phakic subjects were included in this analysis. The mean age (± SD) was 57.2 ± 9.5 years (33.5% Malays, 33.2% Indians, and 33.3% Chinese). The prevalence of myopia (spherical equivalent [SE] ≤ −0.5 diopters [D]) and high myopia (SE ≤ −5.0 D) was 35.7% and 6.0%, respectively. The age-standardized prevalence of MMD was 3.8% (95% confidence interval [CI], 3.4–4.3%). The prevalence of MMD was 7.7% among low to moderate myopes, and 28.7% among high myopes. The prevalence of MMD increased nonlinearly with SE and age. MMD was associated with older age, more myopic SE, and lower education. Subjects with Meta-PM categories 3 or 4 in the better-seeing eye had worse best-corrected VA (β, 0.19; 95%CI, 0.16–0.23) and poorer VSF (β, −9.7; 95%CI, −17.6 to −1.8) than those without MMD after multivariate adjustments.

Conclusions. Approximately 1 in 26 phakic adults in Singapore has MMD. Older age and myopic SE are major risk factors of MMD. Severe MMD has a substantial impact on visual impairment and functioning.

Keywords: epidemiology, quality of life, vision-specific functioning, pathologic myopia

Myopia is a major public health problem worldwide.[1–3] It has been estimated that nearly 23% (1406 million) and 3% (163 million) of the world population had myopia (spherical equivalent [SE] ≤ −0.5 diopters [D]) and high myopia (SE ≤ −5.0 D) in 2000.[1] Individuals with high myopia are at increased risk of developing myopia-related blinding complications, such as myopic macular degeneration (MMD), posterior staphyloma, and retinal detachment, all of which can cause irreversible vision loss.[1,2,4,5]

Several population studies worldwide, including in Australia,[6] China and Taiwan,[7–9] Japan,[10] and India,[11] have assessed the prevalence of MMD in adult populations, reporting estimates ranging from 0.2% in rural India to 3.1% in China. However, there were varying definitions of MMD in these previous studies.[4,12] The same definition of MMD by Curtin[13] that included posterior staphyloma was used by the Blue Mountains Eye Study ($N = 3583$),[6] the Beijing Eye Study ($N = 4319$),[7] and the Handan Eye Study ($N = 6603$).[8] In contrast, a slightly different definition of MMD that did not account for posterior staphyloma was adopted by the Shihpai Eye Study ($N = 1058$)[9] and the Hisayama Study ($N = 1892$).[10] Recently, the International Photographic Classification and Grading System for Myopic Maculopathy (META-PM) classification was proposed. Among these population-based studies, only the Central India Eye and Medical Study conducted in rural India ($N = 4561$)[11] employed the International META-PM classification.[14] Therefore, the use of inconsistent definitions of MMD has led to limited comparability of findings, highlighting the need to use a standardized international definition of MMD.[4,12] Most studies

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were also conducted in ethnically homogenous populations, and interethnic comparisons of MMD were limited.

MMD can result in irreversible loss of central vision and is one of the leading causes of blindness in countries worldwide.[15–18] Ranked as a more important cause of visual impairment (VI) in Asian populations (second to third) than in Western populations (third to ninth), the burden of VI due to MMD appears to be greater in Asian countries.[4] However, studies on the impact of MMD on VI in Asia have been limited to Chinese[18] and Japanese[16] populations. MMD was also associated with poorer vision-specific functioning (VSF)[19,20] in clinic-based studies,[19–21] but the association may be overestimated in selective clinic samples with more severe MMD cases. Furthermore, the impact of MMD on VSF has yet to be assessed in detail in population-based studies.

Using the International META-PM classification, we aimed to examine the prevalence of MMD among population-based samples of Chinese, Indians, and Malays living in Singapore and its impact on vision and VSF.

Methods

Study Population

The Singapore Epidemiology of Eye Diseases (SEED) study is a population-based study conducted in Singapore from 2004 to 2011, comprising three major ethnic groups: Malays (recruitment conducted in 2004–2006), Indians (2007–2009), and Chinese (2009–2011). The study methodologies have been described elsewhere.[22,23] In brief, an age-stratified random sampling frame selected 5600 Malays, 6350 Indians, and 6752 Chinese aged 40 to 80 years from the Ministry of Home Affairs. Of these, 4168 Malays, 4497 Indians, and 4605 Chinese were eligible to participate. Persons who had moved from the residential address, not lived there in the past 6 months, deceased, or terminally ill were ineligible. A total of 3280 Malays, 3400 Indians, and 3353 Chinese participated (response rates of 78.7%, 75.6%, and 72.8%, respectively; mean total response rate of 75.6%). Participants were slightly older than nonparticipants ($P < 0.001$), but there was no sex difference ($P = 0.68$). Written informed consent was obtained from all participants. The study adhered to the Declaration of Helsinki, and ethics approval was obtained from the Singapore Eye Research Institute Institutional Review Board.

Inclusion/Exclusion Criteria

Subjects with the following conditions were excluded from this study: (1) history of cataract surgery, aphakic or pseudophakic, and/or self-reported refractive surgery in both eyes ($n = 765$); (2) missing refraction data in both eyes ($n = 90$); and (3) combination of cataract surgery in one eye and missing refraction data in the other eye ($n = 110$). Of the 9068 eligible participants, 352 participants had missing or ungradable fundus photographs in both eyes. A total of 8716 phakic subjects comprising 2926 Malays, 2890 Indians, and 2900 Chinese were included in this study.

Visual Acuity Assessment

The monocular presenting visual acuity (PVA) was measured using the logarithm of the minimal angle of resolution (logMAR) chart (Lighthouse International, New York, NY, USA) at 4 m, with the participants wearing their habitual correction. If the largest number could not be read at 4 m, the chart was moved closer to the participant; then counting fingers, hand motion, or light perception was assessed. Subjective refraction and best-corrected visual acuity (BCVA) measurements were conducted on the same day by a trained optometrist. Blindness and VI were defined based on BCVA (to account for only unavoidable vision loss) of the better-seeing eye. In the US definition, the presence and severity of VI was categorized as no VI (BCVA 20/40 or better, logMAR ≤ 0.30), VI (BCVA worse than 20/40 but better than 20/200, $0.30 <$ logMAR < 1.00), and blindness (BCVA of 20/200 or worse, logMAR ≥ 1.00).

Refraction, Biometry Measurements, and Ocular Examination

Noncycloplegic autorefraction was performed using an autorefractometer (model RK5; Canon, Inc., Ltd., Tochigiken, Japan). Refraction was then subjectively refined by the study optometrists until the BCVA was obtained. The results from subjective refraction were used in the analysis. SE of refractive error was defined as sphere plus half cylinder. Myopia was defined as SE ≤ -0.5 D in at least one eye. Low, moderate, and high myopia were defined as -3.0 D $<$ SE ≤ -0.5 D, -5.0 D $<$ SE ≤ -3.0 D, and SE ≤ -5.0 D, respectively. Axial length (AL) was measured using noncontact partial coherence interferometry (IOL Master V3.01; Carl Zeiss Meditec AG, Jena, Germany). Intraocular pressure was measured in mm Hg with a Goldmann applanation tonometer (Haag-Streit, Konig, Switzerland).

Fundus Photography and Grading

After cycloplegia, color fundus photographs of Early Treatment Diabetic Retinopathy Study (ETDRS) standard field 1 (centered on the optic disc) and ETDRS standard field 2 (centered on the fovea) were captured for each eye using standardized settings with a nonmydriatic retinal camera (Canon CR-DGi with 10D SLR back; Canon, Inc., Tokyo, Japan). Detailed fundus photograph grading was performed for all phakic subjects. The subjects were graded by one of three trained graders (Y-LW, YD, C-WT). The fundus photographs of both eyes were graded using a standardized protocol, and the graders were masked to the subjects' characteristics. Adjudication was performed by a retinal specialist (C-WW). Gradings of pathologic lesions by the retinal specialist (C-WW) and three trained graders were compared; the κ statistics showed high intergrader agreement (diagnosis of Meta-PM categories were 0.94 [C-WW, Y-LW] and 0.94 [C-WW, YD], and 0.88 [C-WW, C-WT]). Intergrader reliability was also high (κ coefficient of 0.88 [Y-LW, YD], 0.94 [Y-LW, C-WT], and 0.94 [YD, C-WT]).

Definition of MMD

Based on the International META-PM classification,[14] the presence of MMD was defined and classified into the following categories: no macular lesions (category 0); tessellated fundus only (category 1); diffuse chorioretinal atrophy (category 2); patchy chorioretinal atrophy (category 3); and macular atrophy (category 4). "Plus" lesions, which supplemented the Meta-PM categories, comprised lacquer cracks, choroidal neovascularization (CNV), and Fuchs spot. Based on fundus photograph grading, an eye was considered to have MMD if Meta-PM category 2, 3, 4, or any "plus" lesion, was observed.[24] The presence of optic disc abnormalities (optic disc tilt, peripapillary atrophy [PPA], and peripapillary intrachoroidal cavitation [ICC]) was also graded, although they are not part of the META-PM classification. Optic disc tilt was defined by an oval optic disc with a tilt ratio (minimum diameter to maximum diameter) of less than 0.75. PPA was defined using the classification by Curtin and Karlin.[25] Peripapillary ICC was observed as an elevated, well-circumscribed, dome-shaped, yellow-orange lesion inferior to the optic disc along the inferior margin of the PPA.[26]

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Risk Factor Assessment

Detailed questionnaires, administered by trained research staff through face-to-face interviews, were used to collect demographic information (age, sex, and race), socioeconomic characteristics (education level), general medical history, and lifestyle-related factors (smoker or nonsmoker) from participants in their preferred language (English or mother tongue). Education level was classified as primary/below education and secondary/above education. Body mass index was calculated as body weight (in kilograms) divided by body height (in meters) squared. Hypertension was defined as systolic blood pressure $\geq$ 140 mm Hg, diastolic blood pressure $\geq$ 90 mm Hg, physician-diagnosed hypertension, or self-reported history of hypertension. Diabetes mellitus was defined as random glucose of $\geq$ 11.1 mM, diabetic medication use, or a physician-diagnosed history of diabetes. Hyperlipidemia was defined as total cholesterol $\geq$ 6.2 mM or self-reported use of lipid-lowering drugs. Cardiovascular disease was defined as history of previous myocardial infarction, angina, or stroke.

Assessment of Vision-Specific Functioning

The VSF scale[27,28] consists of 11 questions (VF-11) about different aspects of vision-dependent activities to assess the level of difficulty in performing daily tasks involving near and distance vision.

Statistical Analysis

MMD grade and myopic refractive error in the worse eye were used in the analysis. The age-standardized prevalence rates of MMD were calculated by direct standardization of the study samples to the Singapore population, using the 2010 Singapore census. Associations of demographic and socioeconomic factors with MMD were assessed using multivariable-adjusted logistic regression models including covariables of age, ethnicity, sex, SE, and education, selected using stepwise backward methods. To determine optimal SE and age thresholds to detect individuals at risk of MMD, the sensitivity and specificity values were calculated for each predetermined cutoff. Simple practical thresholds were used.

Rasch analysis was performed for VSF using the Andrich rating scale model[29] with Winsteps software version 3.68 (Chicago, IL, USA)[30] to transform the raw ordinal VF-11 scores into interval-level measurements (in logits).[31] To examine the impact of MMD on vision and VSF, participants with ocular comorbidities, including cataract, glaucoma, age-related macular degeneration, and diabetic retinopathy, were excluded from the following analyses. The association between MMD and each endpoint (BCVA and VSF score) was assessed by two multivariable-adjusted linear regression models. Model 1 adjusted for age, race, sex, education, and SE. Model 2 adjusted further for PVA to account for uncorrected refractive errors and determine if the impact of MMD on each endpoint extended beyond the changes in refractive error in eyes with MMD. Additionally, MMD severity (no MMD, Meta-PM category 2, and Meta-PM category 3 or 4) was also analyzed as an ordinal variable against each endpoint. Statistical software (Stata, version 13.1; StataCorp LP, College Station, TX, USA) was used.

Results

Of the 9068 eligible participants, 352 (3.9%) participants were excluded due to missing or ungradable fundus photographs in both eyes. A total of 8716 (96.1%) phakic subjects comprising 2926 Malays, 2890 Indians, and 2900 Chinese were included in this study. The mean age ($\pm$ standard deviation [SD]) of the participants was 57.2 $\pm$ 9.5 years, and comprised 49.6% males and 50.4% females. Myopia was present in 3108 (35.7%) participants, and high myopia was present in 523 (6.0%) participants. Participants excluded due to missing or ungradable fundus photographs were older, more likely to be Malays, and to have lower education ($P < 0.001$), compared to the participants included in this study.

The crude and age-standardized prevalence of MMD among phakic adults was 4.0% (95% confidence interval [CI], 3.6%–4.4%) and 3.8% (95%CI, 3.4%–4.3%), respectively (Table 1). Chinese participants had the highest age-standardized prevalence of MMD (4.6%), followed by Malays (3.7%) and Indians (2.3%; $P < 0.001$). The prevalence of MMD among persons with low, moderate, and high myopia was 7.0% ($n = 144$), 10.4% ($n = 56$), and 28.7% ($n = 150$), respectively. The prevalence of MMD increased significantly with greater myopic SE ($P < 0.001$), longer AL ($P < 0.001$), and older age ($P < 0.001$). Meta-PM category 2 (diffuse chorioretinal atrophy), Meta-PM category 3 (patchy chorioretinal atrophy), and Meta-PM category 4 (macular atrophy) were present in 3.8%, 0.1%, and 0.05% participants, respectively. Among 350 participants with MMD, the occurrence of "plus" lesions was rare, present in only 23 (6.6%) participants. Lacquer cracks, Fuchs spot, and CNV were found in 22 (6.3%), 1 (0.3%), and 0 (0.0%) participants, respectively. Of the 23 participants with "plus" lesions, 18 (78.2%) had high myopia (SE $\leq$ –5.0 D) and 15 (65.2%) had severe myopia (SE $\leq$ –8.0 D).

Risk Factors of MMD

The prevalence of MMD increased in a nonlinear pattern with increasing age, SE, and AL (Fig. 1). Each curve was obtained using the logistic function, and there were no evident natural thresholds seen. Specifically, a gradual nonlinear increase in prevalence of MMD with older age was observed (Fig. 1A), and the prevalence of MMD increased gradually at lower myopic SE and shorter AL levels and plateaued at higher myopic SE and longer AL levels (S-shaped trend; Figs. 1B, 1C). Among the 350 participants with MMD, 41.1% had low myopia (-3.0 D $<$ SE ≤ -0.5 D), 16.0% had moderate myopia (-5.0 D $<$ SE ≤ -3.0 D), and 42.9% had high myopia (SE ≤ -5.0 D). Within each age group, there was an increasing trend in prevalence of MMD with higher myopia severity (Fig. 2). Similarly, the prevalence of MMD increased with age within each myopia category. In participants with no, low, moderate, and high myopia, the prevalence of MMD was higher among those aged $\geq$ 70 years (0.0%, 31.1%, 47.7%, and 65.0%, respectively) than in those aged <70 years (0.0%, 3.5%, 7.1%, and 25.7%, respectively).

To determine optimal SE and age cutoff points for detection of MMD in the population, different predetermined cutoff points of SE (≤ -1.0, ≤ -3.0, and ≤ -5.0) and of age ($\geq$50, $\geq$60, and $\geq$70 years) were compared. For various SE cutoff points, the corresponding sensitivity and specificity values were 87.7% and 26.6% at -1.0 D, 58.7% and 68.9% at -3.0 D, and 42.7% and 86.5% at -5.0 D. As the SE cutoffs became more myopic, sensitivity dropped and specificity increased. There was no optimal cutoff for SE. For various age cutoff points, the corresponding sensitivity and specificity values were 94.9% and 17.8% at 50 years, 73.4% and 56.6% at 60 years, and 43.7% and 84.3% at 70 years. With increasingly older age cutoffs, sensitivity decreased and specificity increased, but with no optimal age cutoff.

After adjusting for age, ethnicity, sex, SE, and education (Table 2), the odds of MMD increased significantly with older age, more myopic SE, and primary/below education. After adjusting for age, ethnicity, sex, and education but not SE, the odds of MMD increased with longer AL (odds ratio [OR] of 3.6/mm; 95%CI, 3.2–4.0, $P < 0.001$). Intraocular pressure, body

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Table 1. Prevalence of Any Myopic Macular Degeneration (MMD), Meta-PM Categories, Bilateral MMD, and Unilateral MMD in Adults Aged 40 to 80 Years in the Singapore Epidemiology of Eye Diseases (SEED) Study Stratified by Age, Racial Groups, Sex, Myopia, and Axial Length Levels ($N = 8716$)

		Any MMD, $n = 350$		Any MMD Meta-PM Category 2, $n = 334$		Any MMD Meta-PM Category 3 or 4, $n = 16$		Bilateral MMD, $n = 237$		Unilateral MMD, $n = 113$	
Factor	***N***	***n***	**% (95%CI)**	***N***	**% (95%CI)**	***n***	**% (95%CI)**	***n***	**% (95%CI)**	***n***	**% (95%CI)**
Crude rate	8716	350	4.0 (3.6–4.4)	334	3.8 (3.4–4.2)	16	0.2 (0.1–0.3)	237	2.7 (2.4–3.1)	113	1.3 (1.1–1.5)
Age-standardized rate (95%CI)*			3.8 (3.4–4.3)		3.6 (3.3–4.1)		0.2 (0.1–0.3)		2.6 (2.3–3.0)		1.2 (1.0–1.5)
Age group, y											
40–49	2437	35	1.4 (0.9–1.9)	29	1.2 (0.8–1.6)	6	0.2 (0.0–0.4)	16	0.7 (0.3–1.0)	19	0.8 (0.4–1.1)
50–59	3016	80	2.7 (2.1–3.2)	77	2.6 (2.0–3.1)	3	0.1 (0.0–0.2)	41	1.4 (0.9–1.8)	39	1.3 (0.9–1.7)
60–69	2195	106	4.8 (3.9–5.7)	103	4.7 (3.8–5.6)	3	0.1 (0.0–0.3)	74	3.4 (2.6–4.1)	32	1.5 (1.0–2.0)
70+	1068	129	12.1 (10.1–14.0)	125	11.7 (9.8–13.6)	4	0.4 (0.0–0.7)	106	9.9 (8.1–11.7)	23	2.2 (1.3–3.0)
P value for trend			<0.001		<0.001		0.70		<0.001		0.001
Race											
Chinese											
Crude rate	2900	140	4.8 (4.0–5.6)	134	4.6 (3.9–5.4)	6	0.2 (0.0–0.4)	89	3.1 (2.4–3.7)	51	1.8 (1.3–2.2)
Standardized rate (95%CI)*			4.6 (3.9–5.5)		4.4 (3.7–5.3)		0.2 (0.0–0.5)		3.0 (2.4–3.7)		1.7 (1.2–2.2)
Malay											
Crude rate	2926	143	4.9 (4.1–5.7)	135	4.6 (3.9–5.4)	8	0.3 (0.1–0.5)	102	3.5 (2.8–4.2)	41	1.4 (1.0–1.8)
Standardized rate (95%CI)*			3.7 (3.1–4.5)		3.4 (2.9–4.1)		0.3 (0.1–0.6)		2.5 (2.0–3.1)		1.2 (0.9–1.7)
Indian											
Crude rate	2890	67	2.3 (1.8–2.9)	65	2.2 (1.7–2.8)	2	0.1 (0.0–0.2)	46	1.6 (1.1–2.0)	21	0.7 (0.4–1.0)
Standardized rate (95%CI)*			2.3 (1.7–3.0)		2.2 (1.7–2.9)		0.0 (0.0–0.0)		1.5 (1.1–2.1)		0.8 (0.4–1.2)
P value for between-race comparison			<0.001		<0.001		0.16		<0.001		0.002
Sex											
Male											
Crude rate	4323	177	4.1 (3.5–4.7)	171	4.0 (3.4–4.5)	6	0.1 (0.0–0.2)	120	2.8 (2.3–3.3)	57	1.3 (1.0–1.7)
Standardized rate (95%CI)*			3.5 (3.0–4.1)		3.4 (2.9–3.9)		0.1 (0.1–0.3)		2.3 (1.9–2.8)		1.2 (0.9–1.6)
Female											
Crude rate	4393	173	3.9 (3.3–4.5)	163	3.7 (3.2–4.3)	10	0.2 (0.1–0.4)	117	2.7 (2.2–3.1)	56	1.3 (0.9–1.6)
Standardized rate (95%CI)*			4.1 (3.5–4.8)		3.9 (3.3–4.6)		0.2 (0.1–0.5)		2.9 (2.4–3.5)		1.2 (0.9–1.6)
P value for between-sex comparison			0.71		0.55		0.45		0.68		0.86
Myopia levels											
No myopia, SE > −0.5 D	5608	0	0.0 (0.0–0.0)	0	0.0 (0.0–0.0)	0	0.0 (0.0–0.0)	0	0.0 (0.0–0.0)	0	0.0 (0.0–0.0)
Low myopia, −3.0 D < SE ≤ −0.5 D	2045	144	7.0 (5.9–8.2)	144	7.0 (5.9–8.2)	0	0.0 (0.0–0.0)	106	5.2 (4.2–6.1)	38	1.9 (1.3–2.4)
Moderate myopia, −5.0 D < SE ≤ −3.0 D	540	56	10.4 (7.8–12.9)	54	10.0 (7.5–12.5)	2	0.4 (0.0–0.9)	41	7.6 (5.3–9.8)	15	2.8 (1.4–4.2)
High myopia, −8.0 D < SE ≤ −5.0 D	356	61	17.1 (13.2–21.1)	57	16.0 (12.2–19.8)	4	1.1 (0.0–2.2)	41	11.5 (8.2–14.9)	20	5.6 (3.2–8.0)
Severe myopia, SE ≤ −8.0 D	167	89	53.3 (45.6–60.9)	79	47.3 (39.7–55.0)	10	6.0 (2.4–9.6)	49	29.3 (22.4–36.3)	40	24.0 (17.4–30.5)
P value for trend			<0.001		<0.001		<0.001		<0.001		<0.001
Axial length, mm											
<26.5 mm	8217	219	2.7 (2.3–3.0)	217	2.6 (2.3–3.0)	2	0.0 (0.0–0.5)	159	1.9 (1.6–2.2)	60	0.7 (0.5–0.9)
≥26.50 mm	280	110	39.3 (33.5–45.0)	101	36.1 (30.4–41.7)	9	3.2 (1.1–5.3)	65	23.2 (18.2–28.1)	45	16.1 (11.7–20.4)
P value			<0.001		<0.001		<0.001		<0.001		<0.001

* Age-standardized rate (95%CI) compared with the 2010 Singapore population by direct standardization.

mass index, smoking, hypertension, diabetes, hyperlipidemia, and cardiovascular disease were not associated with MMD.

Disc Lesions Associated With MMD

Figure 3 shows the fundus photographs of eyes with various Meta-PM categories and associated disc lesions. The prevalence of optic disc tilt, PPA, and peripapillary ICC was 12.5%, 79.6%, and 0.1%, respectively, and the corresponding prevalence rates were 19.3%, 88.2%, and 0.4% among participants with myopia ($N = 3108$) and 61.5%, 96.2%, and 1.7% among participants with high myopia ($N = 523$). The prevalence of MMD was significantly higher among eyes with optic disc lesions than eyes without these lesions (all P values < 0.001; Fig. 4), and this association remained statistically significant in subgroups with low and moderate myopia ($N = 2582$) and with high myopia ($N = 523$). Among participants with MMD ($N = 405$), the prevalence of optic disc tilt, PPA, and peripapillary ICC was 43.1%, 100.0%, and 2.6%, respectively.

Impact of MMD

In the whole study population ($N = 8716$), there were 16 subjects with both MMD and bilateral VI or blindness. After excluding 3624 participants with ocular comorbidities, 5092 participants without ocular comorbidities were included for

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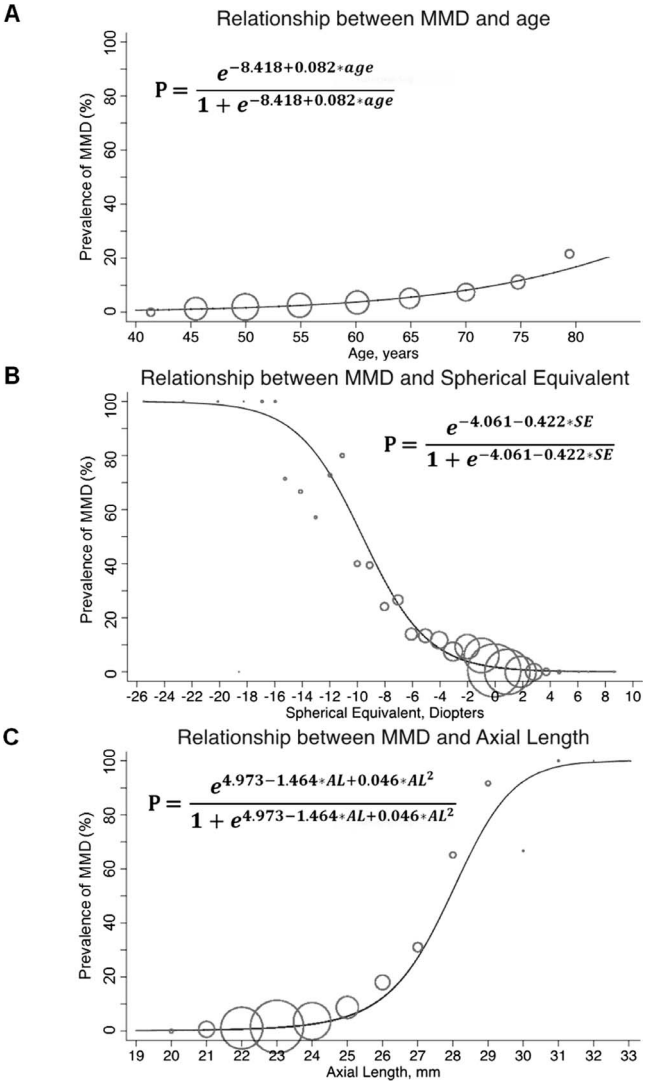


Figure 1. Prevalence of any myopic macular degeneration (MMD) in adults aged 40 to 80 years in the Singapore Epidemiology of Eye Diseases (SEED) study with age, spherical equivalent, and axial length (N = 8716). For each graph (**A**–**C**), the size of the data points (represented by *circles*) is proportional to the sample size of the particular group.

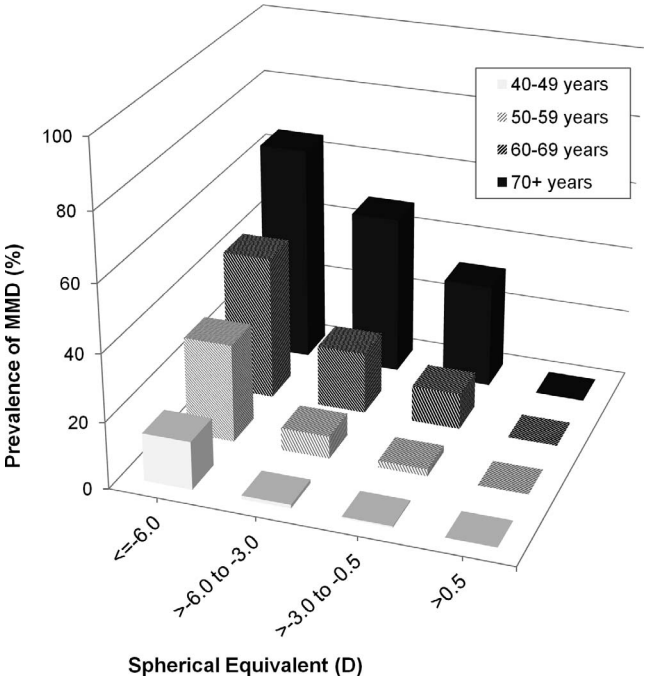


Figure 2. Prevalence of any myopic macular degeneration (MMD) in adults aged 40 to 80 years in the Singapore Epidemiology of Eye Diseases (SEED) study stratified by age group and myopia level (N = 8716).

the following analyses. Of the 5092 participants, 119 (2.3%) were identified as having MMD, of whom 26 (21.8%) had blindness or VI in at least one eye, and 93 (78.2%) had normal vision in both eyes, based on the US definition (Fig. 5). Among the 26 participants with blindness or VI in at least one eye, 23 had high myopia and the remaining 3 participants had low or moderate myopia.

The presence of any MMD was associated with poorer BCVA, but the presence of MMD in general was not significantly associated with poorer VSF, compared to persons without MMD (Table 3). The mean BCVA of the better-seeing eye of participants with MMD was significantly worse (0.11; 95%CI, 0.1–0.12) than that of participants without MMD (0.016; 95%CI, 0.015–0.016; $P < 0.001$), after multivariate adjustments with PVA in model 2. Additionally, the mean BCVA of the better-seeing eye of participants with Meta-PM categories 3 or 4 was significantly worse (0.33; 95%CI, 0.30–0.36) than that of participants with Meta-PM category 2 (0.10; 95%CI, 0.09–0.11; $P < 0.001$). The presence of Meta-PM categories 3 or 4 in the better-seeing eye was found to be significantly associated with worse BCVA ($P < 0.001$) and poorer VSF ($P = 0.02$) compared to individuals with no MMD in the better-seeing eye. An independent association with Meta-PM categories 3 or 4 in the better-seeing eye was observed for 3 of 11 items in the VF-11, after multivariable adjustments in both models 1 and 2. In model 2, the presence of Meta-PM categories 3 or 4 had the largest effect on difficulty in playing games (β coefficient of −20.2; 95%CI, −39.6 to −0.8, $P = 0.04$), followed by difficulty in recognizing friends (β coefficient of −14.6; 95%CI, −22.2 to −7.0, $P < 0.001$), and difficulty in seeing stairs (β coefficient of −7.6; 95%CI, −14.7 to −0.4, $P = 0.03$).

Discussion

The age-standardized prevalence of MMD was 3.8% in a phakic adult population in Singapore, and was higher in those of older age, higher myopic SE, and lower education level. There was a dose–response relationship between MMD and SE, and MMD was present even in low and moderate myopes. The detrimental impact of advanced grades of MMD on VI and VSF presents a potential public health issue.

Prevalence of MMD

The prevalence of MMD among adults in Singapore (3.8%) is one of the highest to be reported in recent studies, that is, the Beijing Eye Study (3.1%, $N = 4319$; aged $\geq$ 40 years), Handan Eye Study (0.9%, $N = 6603$; aged $\geq$ 30 years), Hisayama Eye Study in Japan (1.7%, $N = 1892$; aged $\geq$ 40 years), Central India Eye and Medical study in Rural India (0.2%, $N = 4561$; aged $\geq$ 30 years), Blue Mountains Eye Study in Australia (1.2%, $N = 3583$; aged $\geq$ 49 years), and Shihpai Eye Study in Taiwan (3.0%, $N = 1058$, aged $\geq$ 65 years).[6–8,10,11] Our high prevalence of MMD could be related to the higher prevalence rates of myopia

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Table 2. Univariate and Multivariate Analyses of Risk factors for Any Myopic Macular Degeneration (MMD) Among Adults Aged 40 to 80 Years in the Singapore Epidemiology of Eye Diseases (SEED) Study ($N = 8716$)

		Any MMD				
Risk Factor	*N*	*n*	Unadjusted OR* (95%CI)	*P* Value	Multivariate-Adjusted OR† (95%CI)	*P* Value
Age group, y						
40–49	2437	35	1.0 (reference)	–	1.0 (reference)	–
50–59	3016	80	1.9 (1.3–2.8)	0.002	4.9 (2.9–8.3)	<0.001
60–69	2195	106	3.5 (2.4–5.1)	<0.001	16.4 (9.5–28.4)	<0.001
70+	1068	129	9.4 (6.4–13.8)	<0.001	58.2 (32.8–103.4)	<0.001
P value for trend			<0.001		<0.001	
Race						
Indian	2890	67	1.0 (reference)	–	1.0 (reference)	–
Non-Indian	5826	283	2.2 (1.6–2.8)	<0.001	1.3 (1.0–1.8)	0.10
Sex						
Male	4323	177	1.0 (reference)	–	1.0 (reference)	–
Female	4393	173	1.0 (0.8–1.2)	0.71	1.0 (0.8–1.3)	0.96
Spherical equivalent, D	8716	350	1.5 (1.5–1.6)	<0.001	1.8 (1.7–1.9)	<0.001
Education level						
Secondary/above education	3689	130	1.0 (reference)	–	1.0 (reference)	–
Primary/below education	5027	220	1.3 (1.0–1.6)	0.04	1.7 (1.3–2.4)	<0.001

* Univariate analysis.

† Multivariate analysis, adjusted for age, race, sex, spherical equivalent, and education level.

and high myopia (35.7% and 6.0%, respectively), compared to that in the Blue Mountains Eye Study (16.8% and 2.7%, respectively) and Handan Eye Study (26.6% and 2.1%, respectively).[6,8] However, the differences between prevalence rates among populations may also be due to varying definitions of MMD adopted, and different age compositions in each study population.[32]

Risk Factors of MMD

The age-related trend with MMD is well established in previous studies and is consistent with our findings, which places MMD as another important age-related eye disease.[7,8,10] The MMD lesions are primarily degenerative and worsen with age.[12,33] The age-related association with MMD may denote an

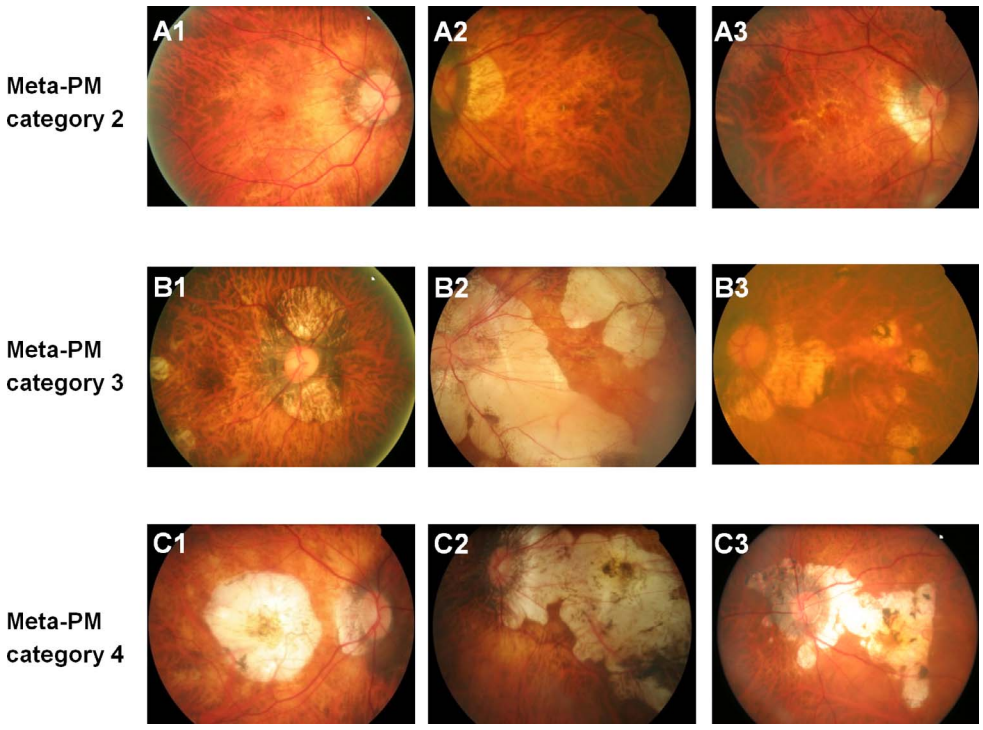


Figure 3. Fundus photographs of eyes with myopic macular degeneration (MMD) Meta-PM categories and associated disc lesions. *Top row* (**A1–A3**) shows the photographs of eyes with Meta-PM category 2 (diffuse chorioretinal atrophy). *Middle row* (**B1–B3**) shows the photographs of eyes with Meta-PM category 3 (patchy chorioretinal atrophy). *Bottom row* (**C1–C3**) shows the photographs of eyes with Meta-PM Category 4 (myopic macular atrophy). Peripapillary atrophy was present in all eyes. (**A2**, **C1**, **C2**) show eyes with optic disc tilt. (**A3**) shows an eye with peripapillary intrachoroidal cavitation and lacquer crack.

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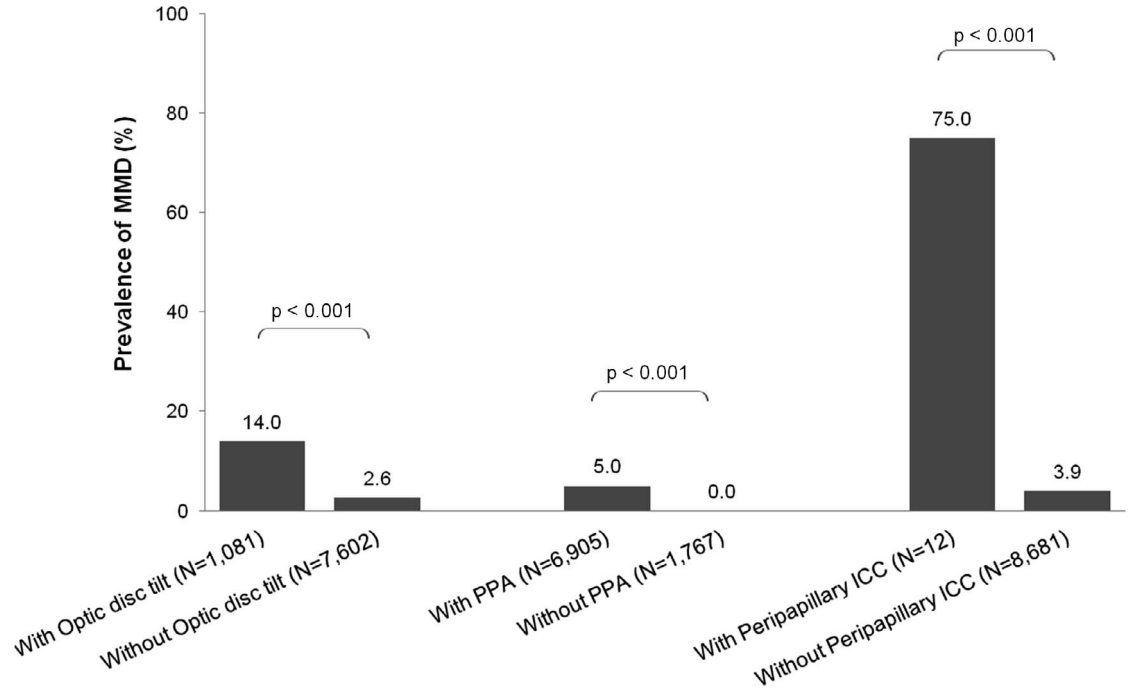


Figure 4. Prevalence of any myopic macular degeneration (MMD) among participants with and without disc lesions in adults aged 40 to 80 years in the Singapore Epidemiology of Eye Diseases (SEED) study ($N = 8716$).

association between the duration of myopia and MMD. The relatively high prevalence of MMD in subjects with low myopia suggests that age may be a surrogate for duration of myopia in an individual.

A higher risk of MMD was associated with greater myopic SE among adults in other studies.[6–10] Similarly, our findings indicate that individuals with severe myopia levels have a high risk of MMD development, but MMD can develop in individuals with low and moderate myopia as well. The prevalence of MMD increased with severity of myopia in a dose–response pattern, which is similar to the results from the Handan Eye Study.[8]

The prevalence of MMD was highest in Chinese compared to Malays and Indians in Singapore, which may be due to the higher prevalence of high myopia in Chinese (9.7%) compared to Malays (4.1%), and Indians (4.3%). Given a certain SE distribution after adjustments in the multivariate regression model, the risk of MMD was not significantly different in Indians compared to Chinese and Malays. Further investigations on the ethnic differences in prevalence of MMD are warranted.

Previous studies found no association between MMD and education,[7–9,11] but we found one with lower education level. Low socioeconomic status and education levels were related to other age-related eye diseases, such as cataract and age-related

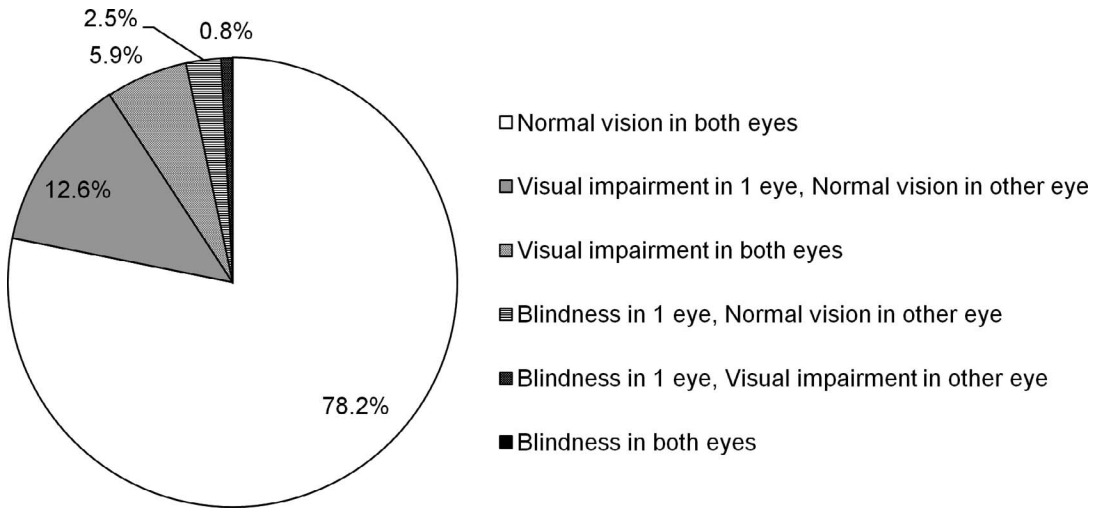


Figure 5. Proportion of participants with visual impairment and blindness in adults with both myopic macular degeneration (MMD) and absence of ocular comorbidities ($N = 119$) using best-corrected visual acuity following US definition. In the US definition, the presence and severity of visual impairment was categorized into normal vision (BCVA 20/40 or better, logMAR $\leq$ 0.30), visual impairment (BCVA worse than 20/40 but better than 20/200, 0.30 $<$ logMAR $<$ 1.00), and blindness (BCVA of 20/200 or worse, logMAR $\geq$ 1.00).

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Table 3. Differences in Best-Corrected Visual Acuity and Vision-Specific Functioning Scores From the Modified VF-11 Questionnaire With Myopic Macular Degeneration (MMD) and Corresponding Meta-PM Categories in Adults Without Ocular Comorbidities Aged 40 to 80 Years in the Singapore Epidemiology of Eye Diseases (SEED) Study ($N = 5092$) Using Linear Regression Models

		BCVA, logMAR				Vision-Specific Functioning Score			
		Model 1		Model 2		Model 1		Model 2	
Variable	*N*	β Coefficient (95%CI)	*P* Value	β Coefficient (95%CI)	*P* Value	β Coefficient (95%CI)	*P* Value	β Coefficient (95%CI)	*P* Value
MMD in the better-seeing eye									
No MMD	5008	Reference	–	Reference	–	Reference	–	Reference	–
MMD	84	0.06 (0.04–0.07)	<0.001	0.04 (0.03 to 0.06)	<0.001	−1.80 (−4.39 to 0.80)	0.18	−0.96 (−3.52 to 1.61)	0.46
MMD in the worse-seeing eye									
No MMD	4986	Reference	–	Reference	–	Reference	–	Reference	–
MMD	106	0.14 (0.10–0.17)	<0.001	−0.01 (−0.04 to 0.02)	0.43	−2.24 (−4.63 to 0.15)	0.07	0.30 (−2.70 to 2.10)	0.81
Severity of MMD in the better-seeing eye									
No MMD	5008	Reference	–	Reference	–	Reference	–	Reference	–
Meta-PM category 2	76	0.04 (0.03–0.05)	<0.001	0.03 (0.02 to 0.04)	<0.001	−1.34 (−4.08 to 1.40)	0.34	−0.56 (−3.26 to 2.14)	0.69
Meta-PM category 3 and 4	8	0.23 (0.19–0.27)	<0.001	0.19 (0.16 to 0.23)	<0.001	−13.64 (−21.68 to −5.61)	0.001	−9.71 (−17.64 to −1.79)	0.02
Severity of MMD in the worse-seeing eye									
No MMD	4986	Reference	–	Reference	–	Reference	–	Reference	–
Meta-PM category 2	98	0.12 (0.08–0.16)	<0.001	−0.02 (−0.05 to 0.01)	0.17	−2.28 (−4.73 to 0.17)	0.07	−0.49 (−2.94 to 1.97)	0.70
Meta-PM category 3 and 4	8	0.40 (0.27–0.52)	<0.001	0.13 (0.03 to 0.22)	0.008	−1.67 (−9.49 to 6.16)	0.68	2.36 (−5.43 to 10.16)	0.55

Ocular comorbidities include cataract, glaucoma, age-related macular degeneration, and diabetic retinopathy. Model 1 adjusted for age, race, sex, education, and spherical equivalent (SE). Model 2 adjusted for age, race, sex, education, SE, and presenting visual acuity in the better or worse eye accordingly. A high BCVA (logMAR) indicates poorer visual acuity, and a low BCVA better acuity. A high vision-specific functioning score indicates a high level of visual functioning, and a low score a low level of functioning.

macular degeneration[34,35]; thus low education level may act as a proxy for low socioeconomic status, rather than an indicator of the amount of near work. This is in contrast to the link between myopia and higher education level (a surrogate of cumulative near work), implying that MMD may not be linked to near work.[24] The mechanism underlying the association between socioeconomic status and MMD remains unknown, as it may reflect a wide variety of lifestyle differences or general health status. There may be a possibility of an interaction among socioeconomic status, general health status, and MMD. Although the stratified analyses showed that the association of education level (proxy for socioeconomic status) with MMD was unlikely to be affected by general health outcomes or lifestyle habits, for instance, smoking, there may be other unknown factors, and further studies are needed.

We found no clear optimal age and SE thresholds for detecting MMD. Although there are currently no effective treatments available for the atrophic component of MMD, efficient and safe algorithms to detect and refer suspected cases of MMD to a tertiary eye care center may facilitate early detection of other myopia-related complications, such as myopic CNV and myopic traction maculopathy (such as macular hole and foveoschisis), for monitoring, treatment, surgical management, and visual rehabilitation to improve visual functioning.[36,37] Currently, an optimal cutoff point for detection of MMD has not been established, and further studies are recommended.

Disc Lesions Associated With MMD

The prevalence of PPA was only slightly lower in myopic adolescents aged 12 to 16 years in Singapore (76.1%; $N = 850$) compared to our findings (88.2%).[38] This suggests that disc lesions occur early during childhood or adolescence, compared to MMD atrophic lesions that tend to develop later in adulthood. Similar to our findings, PPA was detected in majority of the eyes with MMD in the Blue Mountains Eye Study, Beijing Eye Study, and Central India Eye and Medical Study.[6,7,11] Approximately two in five participants with MMD in our study had disc tilt, which is a less common disc lesion compared to PPA. In our population-based study, the prevalence of peripapillary ICC was low among eyes with MMD. Peripapillary ICC was present in 4.9% of patients with high myopia in a case series from a Japanese High Myopia Clinic (N = 324, 632 eyes), but the prevalence of peripapillary ICC among eyes with MMD was not reported.[26]

Impact of MMD

The detrimental impact of MMD on vision was also observed in previous population-based studies, as the proportion of those with VI or blindness due to MMD ranged from 18% to 39%.[6–8] Morphologic changes in the posterior region of the eye, such as diffuse and localized chorioretinal atrophic lesions that are often associated with choroidal thinning, may have resulted in loss of central vision.[39] In our findings, a higher magnitude of vision deterioration was detected in eyes with severe MMD (Meta-PM categories 3 or 4), which may have implications for an individual's VSF that is influenced by the function of the better-seeing eye. Visual rehabilitation becomes a priority for those with advanced MMD stages experiencing poorer VSF, but of the study population, this group of individuals formed a very small proportion only.[40,41] In addition, the impact of advanced MMD grades on VSF may not be due to changes in VA alone, as VSF may be influenced by other factors, such as peripheral vision, contrast sensitivity, depth perception, and glare.[42]

Strengths

The strengths of this study include the large population-based sample with racial diversity (Malay, Indian, and Chinese ethnic origins), reasonable response rates (75%), and standardized methodology for data collection, refraction, ocular biometry assessment, fundus photography, and MMD grading. Lastly, Rasch analysis was used to validate the VF-11 questionnaire in the SEED population and to provide interval-level scoring for VSF.

Limitations

Our study has several limitations. Respondents could differ from nonrespondents, resulting in potential selection bias. The exclusion of subjects with previous cataract and cataract surgery may result in an underestimation of the prevalence of MMD in our population, as we may have excluded a greater proportion of myopic participants with past cataract surgery who have MMD. This is because individuals with myopia have increased risks of cataract (OR of 2.8, 95%CI, 1.9–4.1)[43] and cataract surgery (OR of 2.1, 95%CI, 1.1–4.2).[44] Furthermore, the risks of cataract and cataract surgery increase with more severe myopia levels.[44,45] However, previous prevalence studies on MMD also excluded subjects with history of cataract surgery[7,10] to reflect the true relationship between MMD and SE among phakic participants without cataract surgery. Posterior staphyloma is included in the definition of pathologic myopia, but such anatomic abnormalities were not investigated as optical coherence tomography images were not available in 7002 (80.3%) participants in this study. Therefore, the detection of other myopia-related complications, for instance, macular hole and macular schisis, was not possible. Subtle lacquer cracks might be missed in fundus photographs without the use of fluorescein angiography or indocyanine green angiography. Lens-induced myopia shifts due to cataracts may result in overestimation of negative SE values. The stratified analyses showed that the risk of MMD increased with SE in participants with cataract (OR of 1.6 per 1 D; 95%CI, 1.5–1.7), and this association was also present in participants without cataract (OR of 1.9 per 1 D; 95%CI, 1.8–2.1). As AL is not affected by cataract, the high correlation between SE and AL (r = 0.73) suggests that the effect of cataract-induced myopia shifts on the association between SE and MMD is not large, if present. Other risk factors of MMD, such as choroidal thickness and family history of myopia, were not available in all adults. Also, visual field data were not collected for all participants. In addition, due to the cross-sectional design of our study, the temporality of associations cannot be established and thus inference of causal relationships of MMD is limited.

Conclusions

In conclusion, the age-standardized prevalence of MMD among phakic adults in Singapore was one of the highest worldwide at 3.8%, and ranged between 2.3% and 4.6% across Chinese, Malays, and Indians. Contrary to the association between myopia and higher education level, MMD was associated with lower education level, which may act as a proxy for low socioeconomic status rather than an indicator of near work. The risk of MMD is present not only in high myopes, but in low and moderate myopes as well, especially in older age. These findings suggest that closer monitoring of those with advanced grades of MMD is crucial for appropriate management and for instituting timely visual rehabilitation.[46] Finally, the higher prevalence of MMD among individuals with more severe myopia levels highlights an urgent need for preventive myopia control strategies in early life to delay the onset and

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progression of myopia,[47,48] which in turn lowers the risk of myopia-related vision-threatening complications in adulthood.[49,50]

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