



Association between Axial Length and Myopic Maculopathy

The Hisayama Study

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Purpose: To assess the association between axial length (AL) and the prevalence of myopic maculopathy in a general Japanese population.

Design: Population-based cross-sectional study.

Participants: A total of 2790 Hisayama residents 40 years of age or older who consented to participate and had available data of AL and fundus photographs for the right eyes were enrolled in this study.

Methods: Myopic maculopathy was defined as the presence of diffuse chorioretinal atrophy, patchy chorioretinal atrophy, or macular degeneration. The optimal cutoff values of axial length for identifying myopic maculopathy were estimated from the receiver operating characteristic curve. The odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using a logistic regression analysis.

Main Outcome Measures: Odds ratios of AL for prevalent myopic maculopathy and the optimal cutoff values of AL for detecting myopic maculopathy.

Results: Longer AL was associated significantly with prevalence of myopic maculopathy in both genders. The optimal cutoff values of AL for identifying myopic maculopathy were 25.9 mm in men and 25.3 mm in women. Participants with ALs of these values or longer showed a significantly higher OR for myopic maculopathy than those with AL of less than these values (men: OR, 21.23; 95% CI, 8.74–51.57; women: OR, 38.49; 95% CI, 18.03–86.49).

Conclusions: The present study found that there was a positive association between AL and the likelihood of myopic maculopathy, and the cutoff levels of AL for identifying myopic maculopathy were 25.9 mm in men and 25.3 mm in women. Our findings suggest that patients with AL close to or longer than these values should undergo intensive treatment and detailed ophthalmic follow-up. *Ophthalmology Retina* 2019;3:867–873 © 2019 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).



Supplemental material available at www.ophtalmologyretina.org.

Myopic maculopathy is a major cause of visual impairment and blindness around the world.^{1–7} This is especially true in East and Southeast Asian countries, where myopic maculopathy has been reported to be the second or third most frequent cause of vision loss and blindness and where the prevalence of high myopia or myopic maculopathy continues to increase very rapidly.^{8–11} Longer axial length (AL) has been reported to be a risk factor for myopic maculopathy progression,^{8,12,13} and degeneration of the retina reflects the loss of retinal pigment epithelium and photoreceptor cell layers and the thinning of the choroid and sclera, followed by eye globe elongation in highly myopic eyes.¹⁴ Because myopic maculopathy frequently is progressive and irreversible,^{12–15} early detection and early treatment of this disorder by eye examination are clinically valuable to

reduce the disease burden. Therefore, we should examine patients preferentially with the potential for myopic maculopathy development using a certain AL threshold, because continuous detailed ophthalmic monitoring of every myopic patient is inefficient in terms of both time and cost. In addition, some randomized controlled trials in Taiwan and Singapore and experimental studies in Asian countries have demonstrated that several strategies (e.g., outdoor activities under low light intensity,¹⁶ use of atropine,¹⁷ and riboflavin and ultraviolet A radiation with or without scleral cross-linking^{18,19}) are effective in slowing the extension of ALs in childhood. Although some studies have reported an association between AL values and the presence of myopic maculopathy, the cutoff values of AL for detecting myopic maculopathy have not been investigated in a general

population. Thus, there is need of an optimal threshold of AL for prevalent myopic maculopathy. The purpose of this study was to determine an AL cutoff level for identifying myopic maculopathy using receiver operating characteristic (ROC) curve analysis in a community-dwelling Japanese population.

Methods

Study Population

A population-based study of cardiovascular disease and its risk factors has been underway since 1961 in the town of Hisayama, a suburb of the Fukuoka metropolitan area on Kyushu Island, Japan.²⁰ As a part of the study, we performed an eye examination among 2874 Hisayama residents older than 40 years in 2012. None of them had undergone keratorefractive surgery. After excluding 84 persons without available data of AL, with ungradable photographs of the right eye, or both, 2790 individuals (1217 men and 1573 women) were enrolled in the present study.

Ophthalmic Examination and Other Risk Factor Measurements

Each participant underwent a comprehensive ophthalmic examination, including measurements of objective refraction and AL, noncontact tonometry, and color fundus photography. Although both eyes were examined for each participant, only the findings from right eyes were used in the present analysis. Objective refraction was measured by automatic refractometry (Auto Refractometer AR-660; Nidek, Aichi, Japan) without cycloplegia. A spherical equivalent (SE) was used for the calculations of refractive error. The SE was defined as a sphere plus half of the cylindrical refraction. In the analysis using SE refraction, the participants with a history of cataract surgery in the right eyes (207 eyes for men and 265 eyes for women) were excluded. Axial length was measured with noncontact partial coherence laser interferometry (IOL Master; Carl Zeiss, Hennigsdorf, Germany). Axial length levels were divided into 4 groups using gender-specific quartiles (Qs; for men: Q1, <23.1 mm; Q2, 23.1–23.8 mm; Q3, 23.9–24.7 mm; and Q4, ≥24.7 mm; for women: Q1, <22.7 mm; Q2, 22.7–23.2 mm; Q3, 23.3–24.2 mm; and Q4, ≥24.3 mm). Fundus photographs (45°) were obtained from both eyes of each participant using a Topcon digital TRC NW-6SF fundus camera (Topcon Corporation, Tokyo, Japan) after pupil dilatation with 1.0% tropicamide and 10% phenylephrine. The photographs were obtained in 1 field per eye, centered on the macula. Body height and weight were measured in light clothing without shoes, and the body mass index (BMI) was calculated as the weight in kilograms divided by the height in square meters.

Definition of Myopic Maculopathy

The presence of myopic maculopathy was determined based on the grading of the color fundus photographs. All photographs were evaluated independently by 2 experienced ophthalmologists (S.H. and E.U.). When their judgments conflicted, the photographs were re-examined by 3 retinal specialists (SH, EU, and MY), and the final judgment was determined after discussion. Investigators were blinded to the clinical data of participants during photograph evaluation. According to the Meta-Analysis for Pathologic Myopia classification system, myopic maculopathy was defined as the presence of at least 1 of the following lesions derived from myopic changes: diffuse chorioretinal atrophy at the posterior pole, patchy

chorioretinal atrophy, macular atrophy, or plus lesions (lacquer cracks, Fuchs spot, or myopic choroidal neovascularization).²¹

Statistical Methods

The distributions of age, body height, BMI, AL, and SE refraction in men and women were compared by Student's *t* test. The distributions of age, body height, BMI, and SE refraction across the ALs in men and women were compared by using the linear regression model. Because the distributions of AL and SE refraction were skewed, median values and interquartile ranges were demonstrated in the tables and log-transformed values were applied in the test of difference. The 95% confidence intervals (CIs) of the prevalence of myopic maculopathy were estimated using the binomial distribution. The odds ratios (ORs) and their 95% CIs for myopic maculopathy across the ALs were estimated using a logistic regression analysis. In the logistic regression analysis, the combination of the Q1 and Q2 groups was used as a reference because of the small number of participants with myopic maculopathy. To estimate the discriminating ability of AL for identifying prevalent myopic maculopathy, ROC curves were plotted and the area under the ROC curves was calculated. The cutoff levels of AL that optimize the discriminating ability for identifying prevalent myopic maculopathy were determined as the point closest to (0, 1) on the ROC curve ($= \min \{ [1 - \text{sensitivity}]^2 + [1 - \text{specificity}]^2 \}$). The sensitivity of a cutoff level of AL was defined as the ability of the cutoff level to identify correctly individuals with myopic maculopathy, whereas the specificity was defined as the ability of the cutoff level to identify correctly individuals without myopic maculopathy. SAS software version 9.4 (SAS Institute, Cary, NC) was used to perform all statistical analyses. A 2-sided *P* value of less than 0.05 was considered statistically significant.

Ethical Considerations

This study was approved by the Kyushu University Institutional Review Board for Clinical Research and was carried out in accordance with the Declaration of Helsinki. Informed consent was obtained from all participants.

Results

Table 1 shows the characteristics of the study population by gender. Men demonstrated significantly higher distributions of height, BMI, and AL than women ($P < 0.001$ for all). There was no difference in the distributions of age or SE refraction between the genders.

Supplemental Table 1 (available at www.opthalmologyretina.org) shows the characteristics of the study participants according to the ALs of right eyes. The ALs showed significant inverse correlations with age and SE refraction and a significant positive correlation with body height in both genders ($P < 0.001$ for trend for all).

Myopic maculopathy in the right eyes was observed among 74 participants (30 men and 44 women). As shown in Figure 1, individuals with longer AL showed a significantly higher prevalence of myopic maculopathy in both genders ($P < 0.001$ for trend for both). Myopic maculopathy was observed in participants with ALs of 23.0 mm or longer in men and 22.0 mm or longer in women, although myopic maculopathy was not observed in participants with ALs less than these values.

Table 1. Characteristics of the Study Population by Gender in the 2012 Hisayama Study

Variables	Men (n = 1217)	Women (n = 1573)	P Value
Age (yrs), mean ± SD	63±12	63±13	0.51
Height (cm), mean ± SD	165.1±6.7	152.4±6.8	<0.001
BMI (kg/m ²), mean ± SD	23.6±3.1	22.8±3.6	<0.001
Axial length (mm), median (IQR)*	23.9 (23.1–24.7)	23.3 (22.7–24.3)	<0.001
SE refraction (D), median (IQR)*,†	−0.13 (−1.88 to 0.88)	−0.25 (−2.13 to 1.00)	0.74

BMI = body mass index; D = diopter; IQR = interquartile range; SD = standard deviation; SE = spherical equivalent.

*Data from right eyes.

†Participants with a history of cataract surgery in the right eye (207 men and 265 women) were excluded.

Supplemental Table 2 (available at www.opthalmologyretina.org) shows the characteristics of 74 participants with myopic maculopathy and its subtypes (diffuse chorioretinal atrophy [n = 30], patchy chorioretinal atrophy [n = 31], macular atrophy [n = 6], and plus disease [n = 7]). The most prevalent subtype of myopic maculopathy was diffuse chorioretinal atrophy in men (23.0%) and patchy choroidal atrophy in women (31.1%).

Table 2 demonstrates the association of AL with myopic maculopathy in right eyes. Longer AL was associated significantly with greater OR of prevalent myopic maculopathy after adjusting for age and height in both genders ($P < 0.05$ for trend in both genders). The participants with the Q3 level of AL showed significantly greater age- and height-adjusted ORs than the reference group (the combination of the Q1 and Q2 levels) in both genders (men: OR, 5.55; 95% CI, 1.07–28.76; women: OR, 9.62; 95% CI, 1.83–50.69), and the participants in the Q4 group showed much higher ORs (men: OR, 54.71; 95% CI, 11.78–254.09; women: OR, 119.27; 95% CI, 26.92–528.42).

Finally, we investigated the cutoff values of ALs that optimize the discriminating ability for the presence of myopic maculopathy by using a ROC curve (Fig 2). The optimal cutoff levels of AL

were 25.9 mm in men (sensitivity, 0.80, specificity, 0.76; area under the receiver operating characteristic curve, 0.86; 95% CI, 0.81–0.90), and 25.3 mm in women (sensitivity, 0.88, specificity, 0.72; area under the receiver operating characteristic curve, 0.87; 95% CI, 0.83–0.92). Participants with AL of these values or longer showed significantly higher age- and height-adjusted ORs than those with AL less than the values in both genders (men: OR, 21.23; 95% CI, 8.74–51.57; women: 38.49; 95% CI, 18.03–86.49).

Discussion

In the present study, we observed a positive association between AL and the presence of myopic maculopathy. The optimal cutoff levels of AL for identifying myopic retinopathy, derived from ROC curve analysis, were 25.9 mm in men and 25.3 mm in women. To the best of our knowledge, this is the first time population-based data have been used to determine the cutoff values of AL for detecting myopic maculopathy in an older Asian population.

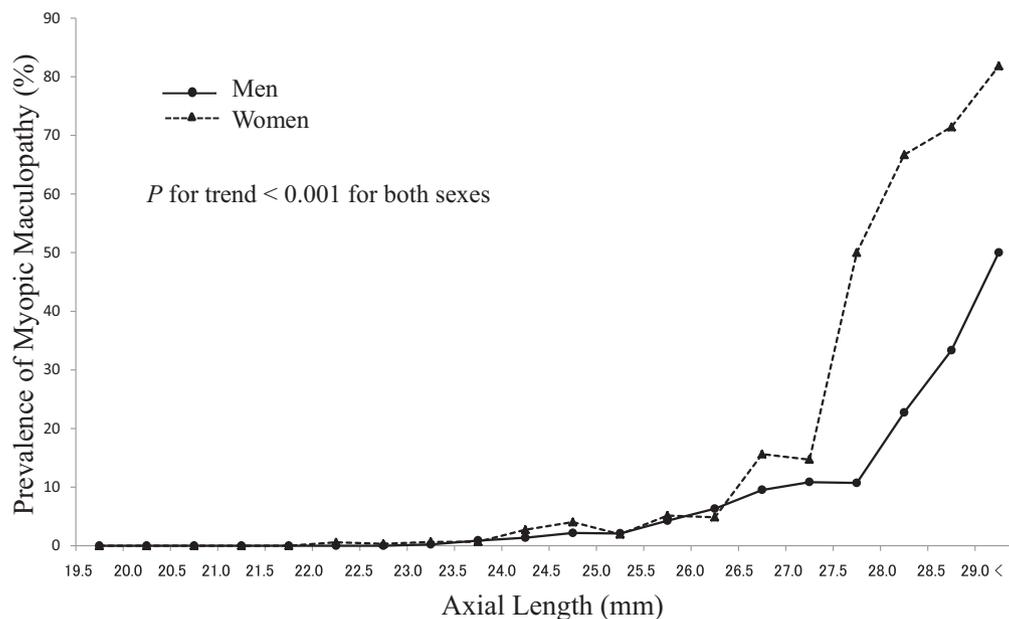


Figure 1. Graph showing the prevalence of myopic maculopathy according to the axial length levels by gender in the 2012 Hisayama Study.

Table 2. Association between Axial Length and Myopic Maculopathy in Right Eyes in the 2012 Hisayama Study

	Axial Length				P Value for Trend
	Quartile 1*	Quartile 2*	Quartile 3*	Quartile 4*	
Men					
Range of axial length (mm) [†]	<23.1	23.1–23.8	23.9–24.6	≥24.7	
No. of participants	305	302	313	296	
No. of eyes with myopic maculopathy	0	2	4	23	
Crude OR (95% CI)	1.00 (reference)		4.91 (0.95–25.46)	25.39 (5.95–108.46) [‡]	0.10
Adjusted OR (95% CI) [†]	1.00 (reference)		5.55 (1.07–28.76) [§]	39.99 (9.59–166.79) [‡]	0.04
Women					
Range of axial length (mm) [†]	<22.7	22.7–23.2	23.3–24.2	≥24.3	
No. of participants	378	424	365	406	
No. of eyes with myopic maculopathy	2	4	9	65	
Crude OR (95% CI)	1.00 (reference)		6.29 (1.20–33.02) [§]	54.71 (11.78–254.09) [‡]	<0.001
Adjusted OR (95% CI) [†]	1.00 (reference)		9.62 (1.83–50.69) [§]	119.27 (26.92–528.42) [‡]	<0.001

CI = confidence interval; OR = odds ratio.

The combination of quartile 1 and 2 groups was used as a reference group.

*For men: quartile 1, <23.1 mm; quartile 2, 23.1–23.8 mm; quartile 3, 23.9–24.7 mm; and quartile 4, ≥24.7 mm. For women: quartile 1, <22.7 mm; quartile 2, 22.7–23.2 mm; quartile 3, 23.3–24.2 mm; and quartile 4, ≥24.3 mm.

[†]Adjusted for age and body height.

[‡]P < 0.01 vs. the reference.

[§]P < 0.05 vs. the reference.

The present study found that the AL cutoff levels for detecting myopic retinopathy were 25.9 mm in men and 25.3 mm in women. These values are approximately in accordance with the lengths of 26.0 mm^{22,23} or 25.0 mm,^{24,25} which are used as the definition of high myopia in Japanese clinical reports. A retrospective study among elderly participants in Japan demonstrated that the slight

change of AL in a high myopia group with myopic choroidal neovascularization (AL ≥26.0 mm) was significantly greater than the axial length change in a group that was not highly myopic.²² Another hospital-based study reported that inflammatory cytokines (interleukin 10 and monocyte chemoattractant protein 1) in the anterior chamber were elevated significantly among myopic patients with

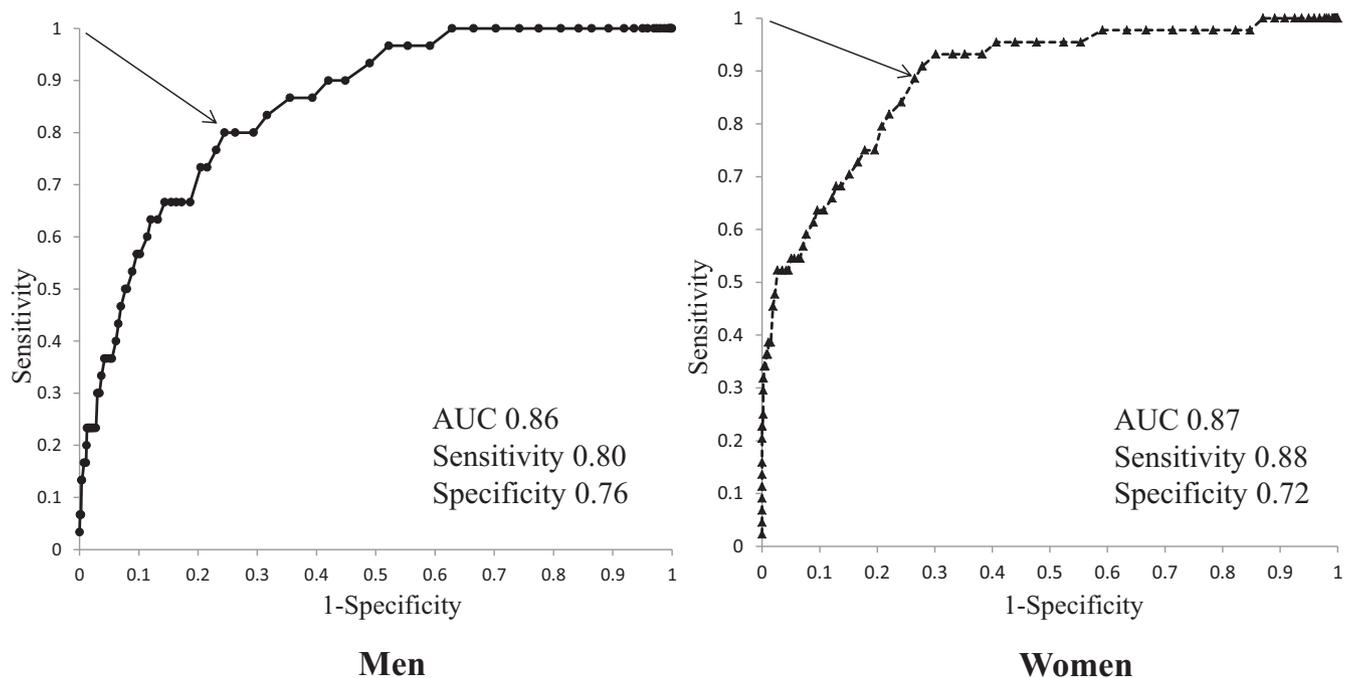


Figure 2. Receiver operating characteristic (ROC) curve analysis for identifying the cutoff values of axial length that optimize the discriminative ability for the presence of myopic maculopathy in men and women in the 2012 Hisayama Study. The optimal cutoff values of axial length were 25.9 mm for men and 25.3 mm for women. Arrows indicate the sensitivity and specificity values estimated using the optimal cutoff values. AUC = area under the receiver operating characteristic curve.

myopic choroidal neovascularization (AL ≥ 25.0 mm), compared with controls without myopia.²⁴ These findings suggest that changes in AL or intraocular cytokine concentrations, which are related to myopic maculopathy progression¹² or angiogenesis,²⁶ may be more common among patients with myopia-related fundus than ALs in the range of 25.0 to 26.0 mm. Thus, it would be reasonable to consider that our results demonstrated the optimal thresholds of AL for the presence of myopic maculopathy and that these values could be used as a cutoff to indicate therapies for preventing axial length elongation.

The present study demonstrated that the distribution of ALs and cutoff values for myopic maculopathy were higher in men than in women. These results may be a reflection of the larger size of eyes in men than in women.²⁷ In addition, the present study found that AL was correlated significantly with body height (Spearman's correlation coefficient, 0.37; $P < 0.05$). The Shandong Children Eye Study in China also reported that there was a moderate correlation between body height and AL.²⁸ The present study showed that the median value of AL in men was 0.6 mm longer than in women, which is the same as the difference in the cutoff values between the genders. Moreover, choroidal thickness, which is related negatively to the presence of myopic maculopathy,²⁹ was reported to be thinner in women than men in a Chinese population-based study.³⁰ Although the mechanism underlying that difference is still unclear, it may involve estrogen and progesterone concentrations, because it has been reported that pregnancy and menstrual cycles are related to changes in choroidal thickness.^{31,32} Women could be more vulnerable to the development of myopic maculopathy. Therefore, it may be essential that the cutoff values of AL for prevalent myopic maculopathy are defined separately between the genders.

As shown in Figure 1, myopic maculopathy was observed in participants with ALs of 23.0 mm or longer in men and 22.0 mm or longer in women. These values were similar to those in Asian studies,^{33,34} but lower than those in a United States study¹⁵ and a population-based study in India.³⁵ In support of these findings, a population-based study in Singapore revealed that chorioretinal atrophy, the earliest stage of myopia-associated retinal changes, was more prevalent than an AL of 22.6 to 25.7 mm among participants 40 years of age or older, and the prevalence of myopic maculopathy significantly increased with increasing AL.³³ The Singapore study also demonstrated that myopia-related fundus change may depend on the duration of myopia rather than AL, because chorioretinal atrophy and staphyloma were not common, whereas peripapillary atrophy was more frequent in childhood and in teenagers with high myopia.^{33,36} This relationship between myopia-related fundus change and myopia duration could have some influence on our results as well, because the age of myopia onset has been lower in Japan.^{6,11} Similar to our findings, an observational case series among elderly Chinese workers found that all participants with AL shorter than 26.5 mm (AL range, 23.7–26.3 mm) showed chorioretinal atrophy and 50% of the participants showed posterior staphyloma.³⁵ The authors considered that this finding was

related not only to elongation of AL, but also to aging-related processes such as choroidal thinning, which is associated significantly with myopic maculopathy.²⁹ Our results also might have been affected by age-related changes in choroidal thickness.³⁰ However, in the 1970s, a clinic-based study among individuals 40 years of age or older in an urban area of the United States reported that chorioretinal atrophy was found in those with ALs longer than 24.5 mm (median AL range, 26.5–27.4 mm).¹⁵ A population-based study in a rural area of India demonstrated that myopic maculopathy appeared at an AL of more than 26.0 mm, and its prevalence was only 0.24% among individuals 30 years of age or older.³⁵ They also reported that the crude prevalences of myopia were 17.0% (< -0.5 diopter) and 0.9% (< -6.0 diopters),³⁷ which were considerably lower than those of the Japanese population (41.8% and 5.5%, respectively).¹¹ Such differences in AL or SE distributions could affect the relationship between AL and myopic maculopathy. It has been determined that elongation of AL is related significantly to the area of residence (urban vs. rural), time spent reading, and the interval of exposure to daylight.²⁸ Moreover, another European population-based study documented that the AL growth rate in childhood and adolescence differed according to gender (men vs. women), geographic region (East Asia vs. Europe or the United States), and era (2000–the present vs. before 1990).³⁸ In consideration of all these findings, the differences in eras, races, lifestyles, and environmental factors among these studies might have influenced the value of AL associated with the onset of myopic maculopathy.

Our study had some limitations. First, we used only nonstereoscopic, 45° fundus photographs to detect myopic maculopathy, whereas other studies used 30° stereoscopic fundus photographs or OCT. Thus, there is a possibility that we underestimated prevalence of myopic maculopathy by not detecting all the earliest stages of chorioretinal atrophy. Second, the cross-sectional design of this study might have affected the threshold measurements of AL. Further prospective investigations would help to clarify this issue.

In conclusion, we observed a positive association between AL and the likelihood of myopic maculopathy. Moreover, the cutoff values for myopic maculopathy in a general Japanese population were 25.9 mm in men and 25.3 mm in women. Our results may have the important implication that patients with AL close to or more than those values are indicated for intensive treatment and detailed ophthalmic management.

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Abbreviations and Acronyms:

AL = axial length; **BMI** = body mass index; **CI** = confidence interval; **OR** = odds ratio; **Q** = quartile; **ROC** = receiver operating characteristic; **SE** = spherical equivalent.

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