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Axial Length to Corneal Curvature Ratio is Insufficient for Detecting Pseudomyopia in Children: A Multi-Cohort Study

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PURPOSE: Pseudomyopia is an accommodative disorder that can be identified by the difference between pre- and post-cycloplegic refractive error. The current study aimed to evaluate whether the axial length to corneal curvature (AL/CR) ratio, in conjunction with non-cycloplegic refractive error, can reliably identify pseudomyopia in children, thus avoiding the need for cycloplegia.

METHODS: Refractive error and biometry data from longitudinal studies based in Denmark ($n = 645$; age 7–17 years) and China (Anyang Childhood Eye Study; $n = 2487$; age 6–13 years) were used to train separate linear mixed models for children of European or East Asian ancestry, respectively, with AL/CR ratio as outcome and cycloplegic spherical equivalent refractive error (SER), age and sex as predictors. The models could be used to calculate the AL/CR 95% prediction interval in a child of known age, sex and *non-cycloplegic* SER; if the child's AL/CR fell below the lower limit of the AL/CR 95% prediction interval, then the child was classified as pseudomyopic. The European and East Asian models were externally validated using data from participants of the Ireland Eye Study (IES; $n = 92$) and Sydney Myopia Study (SMS; $n = 686$) cohorts, and the Hong Kong Children Eye Study (HKCES; $n = 9519$) and Vietnam ($n = 1165$) cohorts, respectively.

RESULTS: The European model demonstrated moderate detection accuracy for pseudomyopia: sensitivity = 0.82 (IES) and 0.81 (SMS); specificity = 0.75 in both cohorts. By contrast, the East Asian model performed poorly: sensitivity = 0.22 (HKCES) and 0.13 (Vietnam); specificity = 0.99 in both cohorts.

CONCLUSIONS: Despite moderate diagnostic performance in European samples, the current AL/CR-based models lacked sufficient accuracy for screening and performed poorly in East Asian children, suggesting that AL/CR is not a reliable non-cycloplegic marker of pseudomyopia. Further studies incorporating additional ocular biometric parameters and employing a more rigorous definition of pseudomyopia may build on these initial findings.

Keywords: Axial length; Corneal curvature; Myopia; Non-cycloplegic screening; Pseudomyopia; Refractive error

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INTRODUCTION

By 2050, myopia is expected to affect almost half of the world's population, with around 10% developing high myopia [1]. Over the past few decades, the prevalence of myopia has increased rapidly among children, particularly in highly urbanised regions of East and Southeast Asia, where up to 80% of older school-aged children are affected [2–9]. Myopia is associated with an increased risk of several sight-threatening ocular diseases, including cataract, glaucoma, myopic maculopathy and retinal detachment [10–15], which not only diminishes the quality of life at the individual level but also places a growing socioeconomic burden on society [16, 17]. Hence, timely and accurate diagnosis of myopia in children is essential for effective myopia control interventions and for preventing vision-threatening complications.

Pseudomyopia is a subtype of excessive accommodation that poses a diagnostic challenge, as it can result in myopia

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KEY POINTS

- This study introduced models tailored to European and East Asian children that use axial length and corneal curvature to screen for pseudomyopia without cycloplegic refraction.
- When tested in four independent datasets, the European pseudomyopia screening model performed moderately, whereas the East Asian model performed poorly, limiting their clinical usefulness.
- Models based mainly on axial length and corneal curvature were insufficiently accurate for pseudomyopia screening, supporting research combining additional eye measurements and stricter diagnostic criteria.

misdiagnosis with clinical and public health consequences [18]. Pseudomyopia is distinct from secondary myopia, which can be induced by medications, ocular diseases, systemic syndromes or systemic conditions [18, 19]. Kang et al. [20] defined pseudomyopia as a spherical equivalent refractive error (SER) of ≤ -0.50 dioptres (D) before cycloplegia and > -0.50 D after cycloplegia. Pseudomyopia is often a persistent condition and should ideally be distinguished from instrument myopia, a transient accommodative response induced by viewing through optical instruments that may temporarily overestimate myopia during autorefraction [21–23]. However, definitions such as those proposed by Kang et al. [20] will inevitably group instrument myopia with less transitory forms of pseudomyopia. Pseudomyopia has a high prevalence among school-aged children in several East Asian countries [20, 24]. Sun et al. [24] reported that pseudomyopia was associated with an increased risk of incident myopia, indicating that early detection of pseudomyopia may help identify children at high risk of myopia who require earlier monitoring or preventive interventions.

Cycloplegic refraction is considered the gold standard method for measuring refractive error in children [25], but is limited by time requirements, cost and patient discomfort. Non-cycloplegic autorefraction is therefore commonly used in vision screening, despite its tendency to overestimate myopia and underestimate hyperopia in children [25–30]. Consequently, children with pseudomyopia may be misclassified as myopic when diagnoses rely solely on non-cycloplegic measurements, potentially leading to unnecessary myopia control interventions.

The axial length to corneal radius of curvature (AL/CR) ratio correlates strongly with refractive error [31–34]; therefore, it may accurately reflect the actual cycloplegic SER when cycloplegia is unavailable. Additionally, the AL/CR ratio reflects ocular biometric structure rather than accommodative state, because axial length and corneal curvature remain relatively stable during accommodation. Thus, we hypothesised that the AL/CR ratio may be a useful clinical parameter for screening for pseudomyopia in children classified as myopic using non-cycloplegic autorefraction. Hence, the current work evaluated whether the AL/CR ratio could detect pseudomyopia reliably in children classified as being myopic by non-cycloplegic autorefraction.

METHODS

This study followed a prespecified Analysis Plan, consisting of two phases: Phase 1 trained predictive models using data from Denmark and China, while Phase 2 evaluated the models' performance on external validation datasets from three cohorts of the Consortium for Refractive Error and Myopia Research in Children (CREAM-Kids) and additional data from Vietnam. Figure 1 shows the workflow of the study. After completing the analyses according to the prespecified Analysis Plan, a series of six sensitivity analyses was performed. The sensitivity analyses were not included in the prespecified Analysis Plan.

Training Datasets

Training Dataset for the European Model. The European model was trained using publicly available longitudinal data for myopic children who attended an ophthalmology clinic in Denmark between 2000 and 2021 [35]. The children were aged 7–15 years at baseline and follow-up duration varied between participants, ranging from 11 months to 9 years. Refractive error was measured using a Retinomax autorefractor (Nikon, nikon.com) 30 min after one drop of 1% cyclopentolate. Axial length and corneal curvature were determined using an IOL-Master (Carl Zeiss Meditec AG, zeiss.com/med). The data were exempted from formal ethical approval by the Danish Ethics Committee and the study adhered to the tenets of the Declaration of Helsinki.

Training Dataset for the East Asian model. The Anyang Childhood Eye Study (ACES) is a school-based longitudinal study conducted in urban Anyang, Henan Province, China, which followed 6-year-old children for 5 years and 13-year-old children for 3 years, beginning in 2011. The methodology of the ACES study has been described elsewhere [36]. Refractive error was measured using cycloplegic autorefraction (HRK-7000A; Huvitz Co., Ltd, huvitz.com) 30 min after two drops of 1% cyclopentolate and one drop of 0.5% tropicamide. Axial length and corneal curvature were measured using an IOL-Master (Carl Zeiss Meditec AG, zeiss.com/med). The study was approved by the Institutional Review Board of Beijing Tongren Hospital, Capital Medical University and adhered to the tenets of the Declaration of Helsinki. Parents or guardians provided informed consent for their child to participate. The East Asian model was trained using 5-year longitudinal data from ACES participants who were aged 6 years at baseline.

Validation Datasets

Ireland Eye Study (IES). The IES is a population-based, stratified random sampling study of schoolchildren aged 6–7 years and 12–13 years, conducted in Ireland between 2016 and 2018. The methodology has been reported previously [37]. Refractive error was measured before and after cycloplegia (one drop of 1% cyclopentolate) using an autorefractor (Dong Yang Rekto ORK-11 Auto Ref-Keratometer; Everview Corp., everview.kr). An IOL-Master (Carl Zeiss Meditec AG, zeiss.com/med) was used to measure axial length and corneal curvature [38]. Ethical approval was obtained from the Technological University Dublin Research Ethics Committee. The study adhered to the tenets of the Declaration of Helsinki. Parents or guardians provided informed consent for their child to participate.

Sydney Myopia Study (SMS). The SMS is a cross-sectional, population-based study that involved a random cluster sample of 55 schools across the Sydney metropolitan region between 2003 and 2005. The methodology has been published [39]. A subset of 12-year-old children who underwent both cycloplegic and non-cycloplegic autorefraction was included in this study, recruited from 21 secondary schools across the Sydney metropolitan area. Refractive error was assessed using an autorefractor (RK-F1; Canon Inc., canon.com), both before and after cycloplegia (two cycles of one drop each of 1% cyclopentolate and 1% tropicamide). An IOL-Master (Carl Zeiss Meditec AG, zeiss.com/med) was used to measure axial length and corneal curvature. Ethical approval was provided by the Human Research Ethics Committee, University of Sydney, the New South Wales Department of Education and Training and Catholic Education Office. The study adhered to the tenets of the Declaration of Helsinki. Parents or guardians provided informed consent for their child to participate.

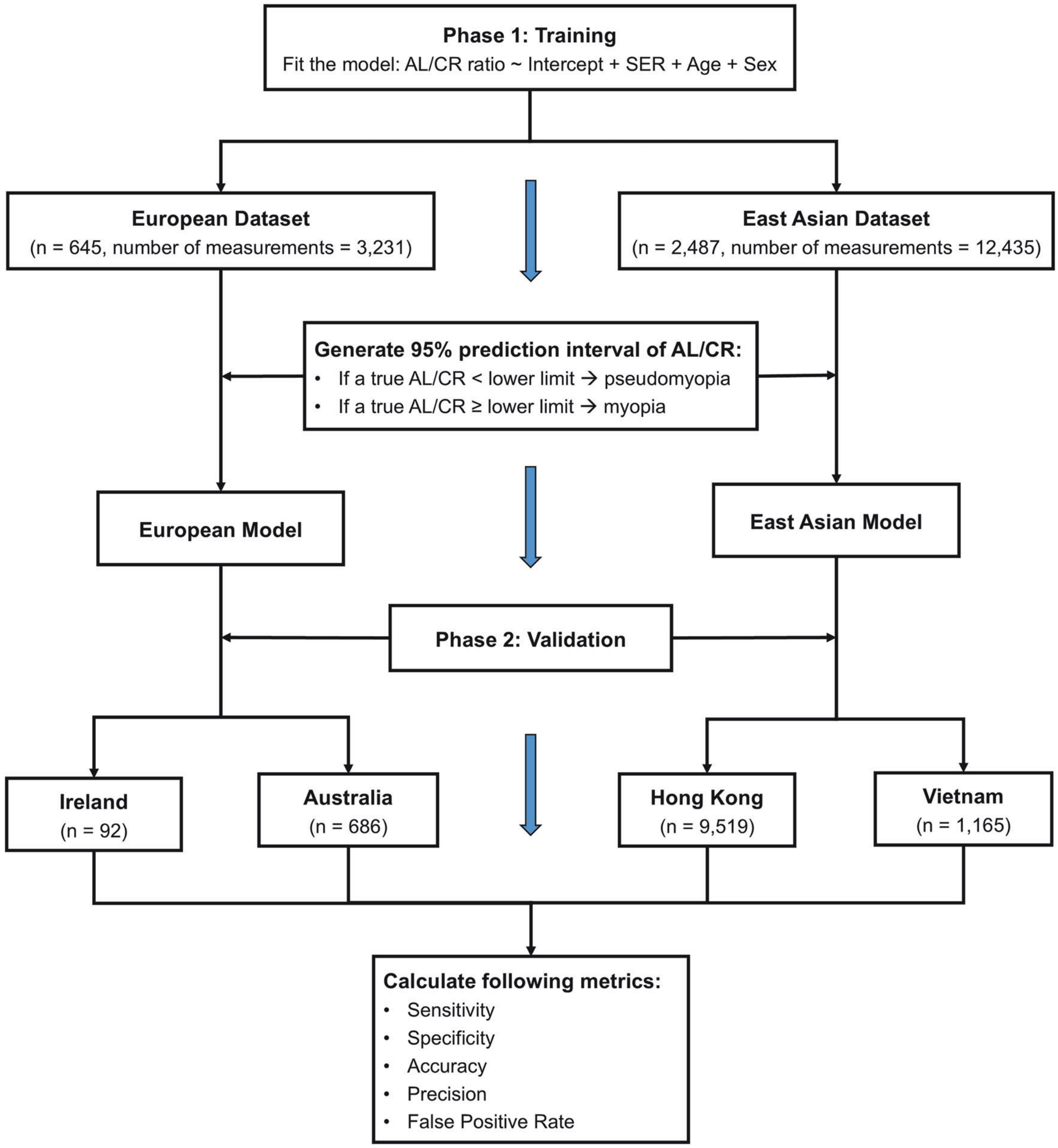

Fig. 1 Overview of the data analysis process. AL axial length, CR corneal radius of curvature, SER spherical equivalent refraction.

Hong Kong Children Eye Study (HKCES). The HKCES, initiated in 2015, is a population-based, stratified random sampling study of primary school children primarily aged 6–8 years in Hong Kong [40–42]. Non-cycloplegic refraction was measured using an autorefractor (ARK-510A; NIDEK Co., Ltd, nidek-intl.com), followed by cycloplegic autorefraction (after two cycles of one drop each of 1% cyclopentolate and 1% tropicamide). Axial length and corneal curvature were measured using an IOL-Master (Carl Zeiss Meditec AG, zeiss.com/med) [42, 43]. Ethical approval was obtained from the Institutional Review Board of the Chinese University of Hong Kong. The study adhered to the tenets of the Declaration of Helsinki. Parents or guardians provided informed consent for their child to participate.

Data from Vietnam. The Vietnamese children's data were cross-sectional, involving children under 18 years of age who visited a paediatric eye clinic in Hanoi, Vietnam, between February and May 2025. Refraction was assessed using retinoscopy both before and after cycloplegia (two drops of 1% cyclopentolate). Axial length was measured using an AL-Scan (NIDEK Co., Ltd, nidek-intl.com), while corneal curvature was measured with an autorefractor (ARK-1A; NIDEK Co., Ltd, nidek-intl.com). The study was approved by the University of Bradford Biomedical, Natural, Physical and Health Sciences Research Ethics Panel and adhered to the tenets of the Declaration of Helsinki. Data were obtained as part of routine care; therefore, informed consent to participate was not applicable.

Methodological Considerations Across Cohorts

Measurement protocols, including autorefractors, cycloplegia regimens and ocular biometry devices, differed across cohorts in accordance with established study-specific procedures. All measurement approaches have been validated previously and are consistent with those used in large population-based paediatric eye studies. While such heterogeneity may contribute to between-cohort variability in refractive and biometric measures, it reflects real-world clinical and epidemiological settings and enhances the generalisability of the findings across diverse clinical and research settings.

Statistical Analysis

The AL/CR ratio was defined as axial length (mm) divided by corneal radius of curvature (mm). SER was calculated as the spherical power plus half the cylindrical power. Myopia was defined as a cycloplegic SER ≤ −0.50 D [19] and pseudomyopia was defined by a SER of ≤ −0.50 D before cycloplegia and > −0.50 D after cycloplegia [20]. This operational definition of pseudomyopia may include instrument myopia, which is unavoidable in non-cycloplegic screening contexts. For both the training and validation datasets, only SER and AL/CR measurements from the right eye were included in the analysis. All statistical analyses were performed using R version 4.4.2 (r-project.org).

Phase 1: Model Training. Linear mixed models (LMM) were used to examine the association between the AL/CR ratio and cycloplegic SER. This approach accommodated participants with missing data at one or more time points, while also accounting for the correlation of measurements across adjacent clinic visits. Children with fewer than three completed clinic visits were excluded from the analysis. Separate models were constructed for the European sample and for the East Asian sample. Each model included fixed effects for sex, polynomial terms of age at visit (first, second and third order) and SER, with the AL/CR ratio as the outcome. Individual effects were treated as random (random intercepts and random slopes on age-at-visit by individual). LMM were performed using the 'lme4' package with the 'lmer' function [44].

The 'predictInterval' function of the 'merTools' package was applied to the LMM to generate the AL/CR 95% prediction interval for any child of known age, sex and cycloplegic SER, using either the European LMM or the East Asian LMM. For use as a predictive tool, the AL/CR 95% prediction interval was calculated for a child of known age, sex and *non-cycloplegic* SER. If the child's clinically measured (true) AL/CR ratio fell below the lower limit of the AL/CR 95% prediction interval, then the child was predicted to be pseudomyopic; otherwise, the child was predicted to be myopic (Fig. 2).

Phase 2: Model Performance Evaluation (External Validation). The European model was validated using the IES and SMS cohorts, while the East Asian model was validated using the HKCES and Vietnam cohorts. The sensitivity, specificity, accuracy, precision and false positive rate were calculated to assess the performance of the models in detecting pseudomyopia. For each performance metric, 95% confidence intervals were estimated using the Wilson score method. The external validation adhered to the prespecified Analysis Plan.

Sensitivity Analysis. Six sensitivity analyses were conducted to evaluate the robustness of the findings to specific modelling assumptions. First, since the East Asian model showed poor accuracy (see below), a sensitivity analysis was performed in which a new East Asian model was trained using data from the HKCES cohort and then validated using data from the Vietnam cohort. Second, the analysis was repeated using AL/CR prediction intervals ranging from 50% to 100% to assess the robustness of model performance to the prediction interval level. Third, the prediction models were validated in cross-population cohorts to evaluate the generalisability of the European model in East Asian validation datasets and vice versa. Fourth, new European and East Asian models were trained while relaxing the original assumption of a linear relationship between SER and AL/CR to assess whether model performance improved when non-linear models were fitted. Fifth, sex-stratified models were fitted separately for male or female participants in the European and East Asian samples to compare their predictive accuracy with that of the original models in which sex was included as a fixed effect. The sex-stratified models allowed the relationship between AL/CR ratio and SER to vary with age in a different pattern in male and female participants. Finally, a sixth sensitivity analysis was performed, in which new European and East Asian models were trained using participants with the same age range (7–13 years) to examine whether the performance discrepancy between the two models (see below) was age-related.

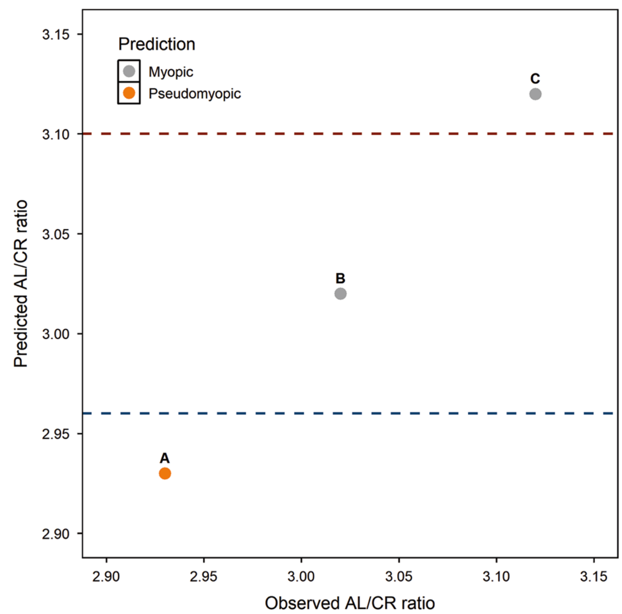

Fig. 2 Predicted myopic and pseudomyopic classification based on 95% prediction interval of AL/CR ratio for three hypothetical European male children aged 7 years with non-cycloplegic SER = −1.00 D. **A** This child has an observed AL/CR below the lower limit and is therefore predicted to be pseudomyopic. **B** This child has an observed AL/CR within the 95% prediction interval and is therefore predicted to be myopic. **C** This child has an observed AL/CR above the upper limit and is therefore predicted to be myopic. Grey symbols indicate children predicted to be myopic; orange symbols indicate children predicted to be pseudomyopic. The blue dashed line represents the lower 95% prediction limit and the red dashed line denotes the upper 95% prediction limit. AL axial length, CR corneal radius of curvature, SER spherical equivalent refraction.

RESULTS

European and East Asian Predictive Models

Data for 645 Danish children (age at baseline: 11.1 ± 2.9 years; median ± IQR) and 2487 Chinese children from the ACES study (age at baseline: 7.1 ± 0.6 years) were used to train the European and East Asian models, respectively. The age range of participants used to train the European model was 7–17 years, whereas for the East Asian model, the age range was 6–13 years. The median baseline AL/CR ratio was 3.11 in Danish children and 2.91 in Chinese children. Male children in ACES exhibited a higher AL/CR ratio than female children (Mann–Whitney U test; $p < 0.001$). By contrast, the AL/CR ratio was similar between sexes in Danish children (Mann–Whitney U test; $p = 0.27$). Baseline participant demographics of the training datasets are summarised in Table 1.

Table 2 presents the coefficients of the European and East Asian models. In both models, all fixed effects, sex, age and cycloplegic SER, were significantly associated with the AL/CR ratio (all $p < 0.05$). Each 1D shift towards a more myopic SER was associated with an increase in the AL/CR ratio of 0.04 (95% CI: 0.040 to 0.038; $p < 0.001$) in Danish children and 0.05 (95% CI: 0.051 to 0.049; $p < 0.001$) in Chinese children.

Based on the two models, the AL/CR 95% prediction intervals could be generated for European and East Asian children across a range of ages, sex and cycloplegic SER (Figs. 3 and 4). A child with

Table 1. Baseline demographic characteristics of the European and East Asian training datasets.

Cohort	Danish cohort (European)				ACES cohort (East Asian)			
	Total	Female	Male	*p*-value	Total	Female	Male	*p*-value
Sample size	645	325	320		2487	1066	1421	
Age (Years) #1	11.14 ± 2.93	11.23 ± 2.83	11.00 ± 3.00	0.63	7.11 ± 0.55	7.10 ± 0.51	7.13 ± 0.53	0.01*
Cycloplegic SER (D) #1	−1.88 ± 2.00	−2.00 ± 2.00	−1.88 ± 2.03	0.40	1.00 ± 0.88	1.00 ± 0.88	0.88 ± 0.88	0.25
AL (mm) #1	24.41 ± 1.21	24.16 ± 1.27	24.64 ± 1.14	<0.001*	22.73 ± 0.96	22.43 ± 0.86	22.97 ± 0.86	<0.001*
CR (mm) #2	7.82 ± 0.26	7.76 ± 0.25	7.89 ± 0.26	<0.001*	7.80 ± 0.24	7.73 ± 0.23	7.85 ± 0.23	<0.001*
AL/CR #1	3.11 ± 0.13	3.11 ± 0.12	3.11 ± 0.14	0.27	2.91 ± 0.09	2.90 ± 0.09	2.92 ± 0.09	<0.001*

ACES Anyang Childhood Eye Study, *AL* axial length, *CR* corneal radius of curvature, *IQR* inter-quartile range, *SD* standard deviation, *SER* spherical equivalent refraction.
#1: Values are the median ± IQR. *P*-values were derived from the Mann–Whitney U test.
#2: Values are the mean ± SD. *P*-values were derived from the *t*-test.
*$p < 0.05$.

Table 2. Fixed effect parameters for linear mixed models in the European and East Asian training samples.

Variable	Beta	95% CI	*p*-value
European sample			
Male sex (vs. female)	0.010	0.000 to 0.019	0.04*
Age (polynomial order 1) (Years)	1.478	1.410 to 1.547	<0.001*
Age (polynomial order 2) (Years)	−0.371	−0.398 to −0.344	<0.001*
Age (polynomial order 3) (Years)	0.048	0.027 to 0.069	<0.001*
SER (D)	−0.039	−0.040 to −0.038	<0.001*
East Asian sample			
Male sex (vs. female)	0.015	0.011 to 0.019	<0.001*
Age (polynomial order 1) (Years)	2.325	2.228 to 2.421	<0.001*
Age (polynomial order 2) (Years)	−0.275	−0.337 to −0.214	<0.001*
Age (polynomial order 3) (Years)	0.166	0.101 to 0.231	<0.001*
SER (D)	−0.050	−0.051 to −0.049	<0.001*

CI confidence interval, *SER* spherical equivalent refraction.
*$p < 0.05$.

a *non-cycloplegic* SER ≤ −0.50 D whose clinically measured (true) AL/CR ratio fell below the lower limit of the 95% prediction interval would be classified as pseudomyopic (Fig. 2).

Accuracy of Predictive Models for Detecting Pseudomyopia

To test the performance of the models, a total of 11,462 participants with non-cycloplegic SER ≤ −0.50 D from four cross-sectional cohorts were assessed: 92 Irish children (13.00 ± 0.25 years; median ± IQR), 686 Australian children (13.00 ± 1.00 years), 9519 Hong Kong children (7.84 ± 1.62 years) and 1165 Vietnamese children (8.00 ± 3.00 years). The initial age ranges of the validation cohorts were as follows: IES, 6−14 years; SMS, 11−14 years; HKCES, 3−12 years and Vietnam, 2−18 years. However, the age range of participants in the European training dataset was 7−17 years; therefore, only children from the IES and SMS cohorts who were within this age range were analysed. Likewise, the age range of the East Asian training dataset was 6−13 years; therefore, only children from the HKCES and Vietnam cohorts who were within this age range were analysed.

Table 3 compares the demographic characteristics of participants from the four validation cohorts included in Phase 2 of the study. Among children with non-cycloplegic SER ≤ −0.50 D, the prevalence of pseudomyopia was highest in the SMS cohort (60%), followed by HKCES (43%), IES (12%) and the Vietnam cohort (4%). The median AL/CR ratio in pseudomyopic children was 2.94, 3.00, 2.96 and 2.98 in the IES, SMS, HKCES and Vietnam cohorts, respectively, whereas the corresponding values in myopic children exceeded 3.0 in all cohorts.

Table 4 presents the sensitivity, specificity, accuracy and false positive rates in the validation datasets. The European model was partially effective in detecting children with pseudomyopia, yielding a sensitivity of 0.82 in IES children and 0.81 in SMS children. The model also demonstrated moderate specificity of 0.75 in both the IES and SMS cohorts. By contrast, the East Asian model exhibited a low sensitivity of 0.22 in the HKCES and 0.13 in the Vietnam cohort, although it achieved a high specificity of 0.99 in both cohorts. Thus, the European model demonstrated a better trade-off between sensitivity and specificity in identifying pseudomyopia, compared with the East Asian model. The accuracy of the European model was 0.76 in the IES cohort and 0.78 in the SMS cohort, while the East Asian model achieved accuracies of 0.65 and 0.96 in the HKCES and Vietnam cohorts, respectively. The high accuracy value in the Vietnam cohort should be interpreted with caution, because it was likely driven by class imbalance (Fig. 5) and accompanied by a low precision (0.46), indicating that a substantial proportion of participants predicted to be pseudomyopic were false positives.

Sensitivity Analysis

The first sensitivity analysis, in which the East Asian model was trained with data from the HKCES cohort rather than the ACES cohort, demonstrated similarly poor performance in detecting

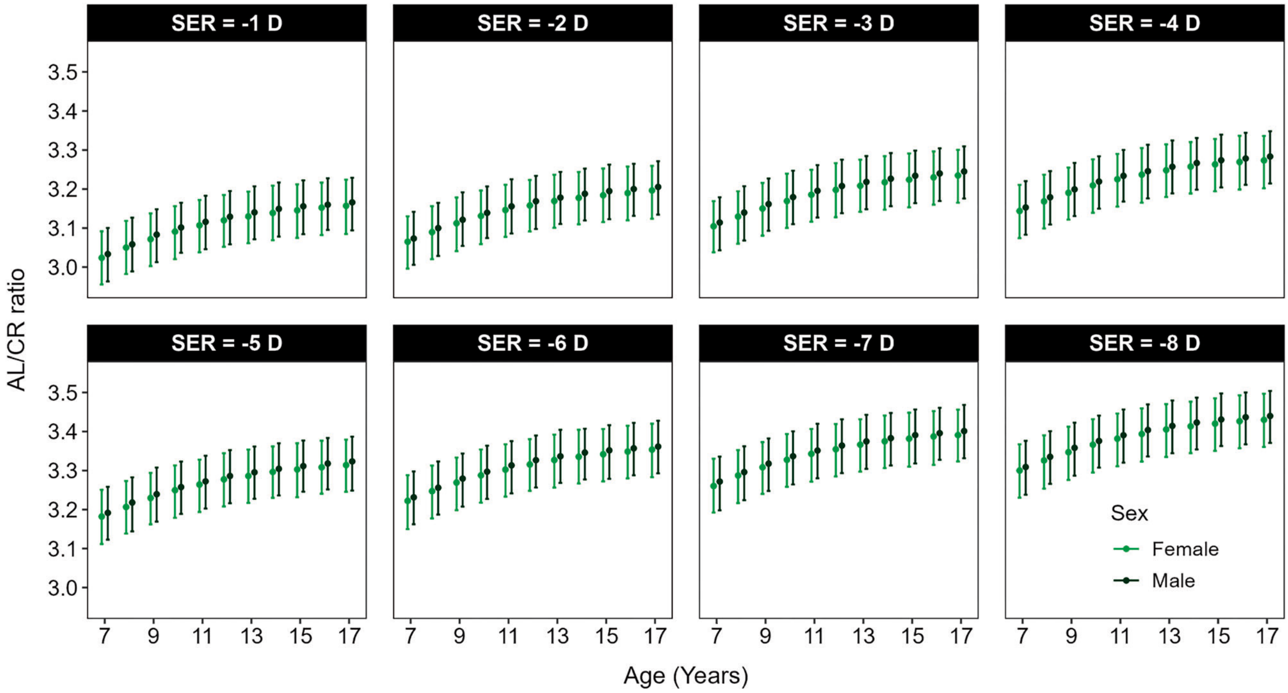

Fig. 3 Results of the training model in the European training sample ($n = 645$ Danish children followed longitudinally). The graph shows the 95% prediction interval of AL/CR ratio in children aged 7–17 years (*x*-axis), sex (colour) and cycloplegic SER (black panels). If a child's true AL/CR ratio falls below the lower limit of the AL/CR 95% prediction interval, given their age, sex and non-cycloplegic SER, then they are predicted to be pseudomyopic. AL axial length, CR corneal radius of curvature, SER spherical equivalent refraction.

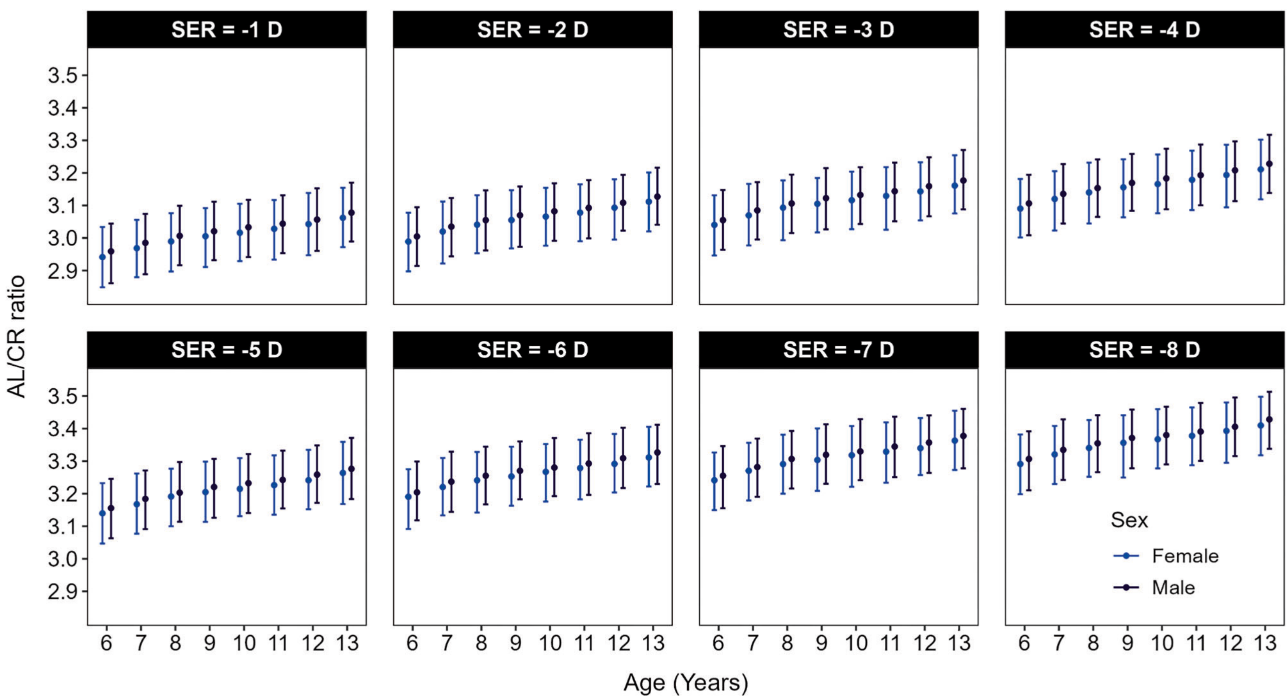

Fig. 4 Results of the training model in the East Asian training sample ($n = 2487$ Chinese children followed longitudinally). The graph shows the 95% prediction interval of AL/CR ratio in children aged 6–13 years (*x*-axis), sex (colour) and cycloplegic SER (black panels). If a child's true AL/CR ratio falls below the lower limit of the AL/CR 95% prediction interval, given their age, sex and non-cycloplegic SER, then they are predicted to be pseudomyopic. AL axial length, CR corneal radius of curvature, SER spherical equivalent refraction.

pseudomyopia. Specifically, the model had low sensitivity (0.24) despite high specificity (0.98) in Vietnamese children (Supplementary Fig. S1, and Supplementary Table S1). Second, the optimal AL/CR prediction interval was 95–100% for the European model, whereas it was 50–55% for the East Asian model (Supplementary Note S1). However, even at the optimal prediction interval, the East Asian model performed substantially worse than the European model (sensitivity ≤ 0.50, despite high specificity), consistent with the findings obtained using the 95% AL/CR prediction interval. Third, in the cross-population sensitivity

Table 3. Demographic characteristics of participants included in the analysis of the four cross-sectional validation cohorts.

Cohort	IES				SMS				HKCES				Vietnam			
	Total	Myopia	Pseudo	*p*-value	Total	Myopia	Pseudo	*p*-value	Total	Myopia	Pseudo	*p*-value	Total	Myopia	Pseudo	*p*-value
Sample size	92	81	11		686	274	412		9519	5412	4107		1165	1120	45	
Sex #1				0.19				0.01*				<0.001*				0.11
Female	41.3%	38.3%	63.6%		52.3%	58.4%	48.3%		48.7%	45.9%	52.3%		48.5%	49%	35.6%	
Male	58.7%	61.7%	36.4%		47.7%	41.6%	51.7%		51.3%	54.1%	47.7%		51.5%	51%	64.4%	
Age (Years) #2	13.00 ± 0.25	13.00 ± 0.00	13.00 ± 3.50	0.20	13.00 ± 1.00	13.00 ± 1.00	13.00 ± 1.00	0.51	7.84 ± 1.62	8.12 ± 1.51	7.44 ± 1.54	<0.001*	8.00 ± 3.00	9.00 ± 3.00	7.00 ± 2.00	<0.001*
Non-Cycloplegic SER (D) #2	−1.50 ± 1.53	−1.75 ± 1.38	−0.50 ± 0.06	<0.001*	−1.00 ± 1.24	−1.93 ± 2.00	−0.75 ± 0.50	<0.001*	−1.25 ± 1.50	−1.88 ± 1.62	−0.75 ± 0.62	<0.001*	−2.25 ± 2.38	−2.25 ± 2.25	−0.63 ± 0.50	<0.001*
Cycloplegic SER (D) #2	−1.75 ± 1.65	−2.00 ± 1.63	0.75 ± 0.88	<0.001*	−0.06 ± 1.81	−1.53 ± 2.01	0.62 ± 0.76	<0.001*	−0.62 ± 2.00	−1.62 ± 1.62	0.38 ± 0.88	<0.001*	−2.00 ± 2.25	−2.13 ± 2.25	0.13 ± 0.75	<0.001*
AL (mm) #2	24.25 ± 1.21	24.35 ± 1.14	23.27 ± 0.82	<0.001*	23.63 ± 1.25	24.32 ± 1.38	23.30 ± 0.93	<0.001*	23.53 ± 1.33	23.99 ± 1.16	22.94 ± 1.00	<0.001*	24.54 ± 1.31	24.56 ± 1.26	23.23 ± 0.88	<0.001*
CR (mm) #2	7.80 ± 0.47	7.79 ± 0.44	7.93 ± 0.42	0.36	7.76 ± 0.33	7.72 ± 0.34	7.77 ± 0.32	0.01*	7.74 ± 0.34	7.73 ± 0.34	7.76 ± 0.34	<0.001*	7.77 ± 0.33	7.77 ± 0.33	7.70 ± 0.42	0.61
AL/CR #2	3.11 ± 0.14	3.14 ± 0.12	2.96 ± 0.14	<0.001*	3.04 ± 0.14	3.14 ± 0.14	3.00 ± 0.08	<0.001*	3.03 ± 0.15	3.10 ± 0.11	2.96 ± 0.09	<0.001*	3.16 ± 0.14	3.16 ± 0.14	2.98 ± 0.09	<0.001*

AL axial length, *CR* corneal radius of curvature, *HKCES* Hong Kong Children Eye Study, *IES* Ireland Eye Study, *IQR* inter-quartile range, *Pseudo* pseudomyopia, *SER* spherical equivalent refraction, *SMS* Sydney Myopia Study.

#1: Values are percentages. *P*-values were derived from the Chi-squared test, except for IES (Fisher's exact test).

#2: Values are median ± IQR. *P*-values were derived from the Mann–Whitney U test.

*$p < 0.05$.

analyses, the European model generally outperformed the East Asian model in detecting pseudomyopia in both the European and East Asian validation datasets (Supplementary Note S2). However, performance in detecting East Asian participants with pseudomyopia was still limited (sensitivity ≤ 0.60, despite high specificity). Fourth, European and East Asian models trained assuming the relationship between SER and AL/CR to be non-linear showed generally similar performance to the original models that assumed a linear relationship between SER and AL/CR (Supplementary Note S3). Fifth, comparing the sex-stratified models to the original models, the female-specific models demonstrated slight improvements in the European cohorts and substantial improvements in the East Asian cohorts, whereas the male-specific models performed either more poorly or similarly (Supplementary Note S4). However, the general trend of results for the sex-stratified models mirrored those observed for the original models. The sixth sensitivity analysis, in which European and East Asian models were trained on participants with the same age range of 7–13 years, yielded similar findings to the original models. The European model demonstrated consistently better performance in detecting pseudomyopia than the East Asian model (Supplementary Note S5). In summary, the six sensitivity analyses suggested that modifying the training datasets, prediction interval levels, training data participant age-range, modelling approach (linear vs. non-linear, sex-stratified vs. including sex as a fixed effect) or use of cross-population validation did not materially enhance detection accuracy.

DISCUSSION

Two models were developed utilising AL/CR ratio prediction limits in combination with non-cycloplegic refractive error to identify pseudomyopia in European and East Asian children. Evaluation of the European model in two external validation datasets demonstrated moderate detection accuracy, with sensitivities of 0.82 and 0.81, respectively, and a specificity of 0.75 in both cohorts. By contrast, the East Asian model performed poorly in detecting pseudomyopia in two additional external validation datasets, exhibiting sensitivities of 0.22 and 0.13, respectively, despite a high specificity of 0.99. Consistent with previous studies reporting a relationship between the AL/CR ratio and SER [31, 45, 46], the present study found a significant negative association, with the AL/CR ratio increasing by 0.04-0.05 per 1D shift in SER towards more myopia (more negative SER). Although several prediction models based on the AL/CR ratio have been reported to show good performance in predicting myopia, they have not been tested for detecting pseudomyopia [31, 47–49].

The gold standard for diagnosing pseudomyopia is identifying the difference between non-cycloplegic and cycloplegic SER [20]. However, the use of cycloplegia is not always acceptable to children and their parents due to adverse effects such as stinging upon instillation, blurred vision and glare; the costly and time-consuming nature of the procedure is a further disadvantage. Rarely, children may suffer systemic adverse reactions with cycloplegia, such as headache, tachycardia, excessive sweating, skin rashes, delirium or high fever [50]. Consequently, cycloplegic refraction is not routinely included in eye screening programmes. The models described were designed to address this challenge, potentially enabling clinicians to identify pseudomyopia without the need for cycloplegia. However, with a sensitivity of 0.80 and a specificity of 0.75, even the better-performing European model remained below levels typically considered acceptable for screening [49, 51–53]. These findings suggest that the AL/CR ratio is well suited to detecting structural myopia, but is inherently limited for identifying pseudomyopia, which is driven by accommodative and lenticular mechanisms. The moderate performance observed in the European cohorts suggests that AL/CR may still contribute as one component of a multivariable screening strategy rather than as a standalone marker.

Table 4. Performance of the European and East Asian models in the validation datasets.

Cohort	Pseudomyopia (%)	Sensitivity (95% CI)	Specificity (95% CI)	Accuracy (95% CI)	Precision (95% CI)	FPR (95% CI)
European model (7–17 years)						
IES	12%	0.82 (0.52–0.95)	0.75 (0.65– 0.83)	0.76 (0.66– 0.84)	0.31 (0.17– 0.49)	0.25 (0.17–0.35)
SMS	60%	0.81 (0.77– 0.84)	0.75 (0.69– 0.80)	0.78 (0.75– 0.81)	0.83 (0.79– 0.86)	0.25 (0.20–0.31)
East Asian model (6–13 years)						
HKCES	43%	0.22 (0.20– 0.23)	0.99 (0.98– 0.99)	0.65 (0.64– 0.66)	0.93 (0.91– 0.94)	0.01 (0.01– 0.02)
Vietnam	4%	0.13 (0.06– 0.26)	0.99 (0.99– 1.00)	0.96 (0.95– 0.97)	0.46 (0.23– 0.71)	0.01 (0.00– 0.01)

CI confidence interval, *FPR* false positive rate, *HKCES* Hong Kong Children Eye Study, *IES* Ireland Eye Study, *SMS* Sydney Myopia Study.

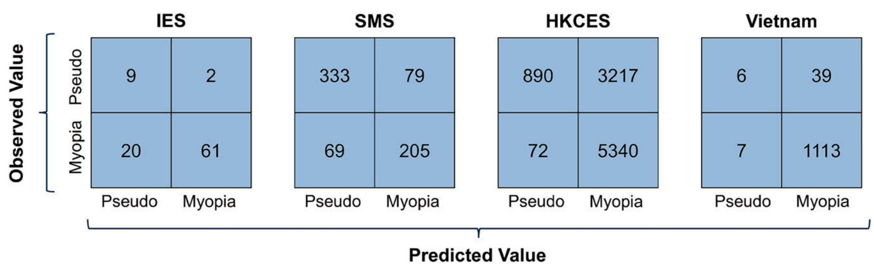

Fig. 5 Confusion matrices for predicting pseudomyopia across the validation datasets. HKCES Hong Kong Children Eye Study, IES Ireland Eye Study, Pseudo pseudomyopia, SMS Sydney Myopia Study.

Pseudomyopia is a common finding in many studies of children's refractive error. The ACES study reported a pseudomyopia prevalence of 24.1% among 2612 6-year-old children and 18.9% among 1984 13-year-old children [20]. Another longitudinal study of 2328 children aged 4–17 years in Shandong, China, revealed a baseline pseudomyopia prevalence of 37.2%, with more than 20% of these participants developing myopia after 6 months [24]. In the current work, the prevalence of pseudomyopia varied across European and East Asian countries, with a high prevalence reported in the SMS and HKCES cohorts and a much lower prevalence in the IES and Vietnam cohorts (Table 4). The mechanisms underlying pseudomyopia remain unclear, but they most likely relate to accommodative excess and ciliary spasm, which are commonly associated with prolonged near-work activities [18]. East Asian children are exposed to heavy academic workloads and limited outdoor activities, which may explain the high prevalence of pseudomyopia reported. However, the ACES study found no significant association between pseudomyopia and either near work or time spent outdoors during school days [20]. Together with the variability in pseudomyopia prevalence across cohorts in both European and East Asian populations in the present study, these findings suggest that additional factors may contribute to the development of pseudomyopia.

A striking finding of the current work was the substantially poorer performance of the East Asian prediction model compared with the European model. There are several potential reasons for this discrepancy. First, the AL/CR 95% prediction intervals were wider in the East Asian model than those in the European model (approximately 0.14 vs. 0.19 in the European and East Asian models, respectively), indicating greater variability in the AL/CR ratio within the East Asian cohorts. Additionally, a substantial number of children in the HKCES and Vietnam cohorts who were truly pseudomyopic exhibited AL/CR ratios greater than 3 (which is more typical of myopia [31–33]) compared with those in the IES and SMS cohorts (Fig. 6). Previous studies have demonstrated a significant association between crystalline lens power and refractive error across both East Asian and European populations [54–58]. By contrast, while a deeper anterior chamber was significantly associated with a more myopic SER in East Asian children [56, 59, 60], no such association was observed among Irish children [55]. Therefore, anterior chamber depth may exert a greater influence on SER in East Asian than European children, which could explain why the East Asian model performed poorly, as it did not account for differences in anterior-posterior segment proportion. Second, the East Asian samples may have had greater measurement error in SER, AL or CR, compared to the European samples. However, the first sensitivity analysis showed that both the ACES and HKCES models exhibited similarly poor performance (Supplementary Fig. S1, and Supplementary Table S1), suggesting this was an unlikely explanation. Third, the different age ranges used to train the European and East Asian models may have contributed to this discrepancy. However, the sixth sensitivity analysis showed that the European model trained on the overlapping age range consistently outperformed the East Asian model, suggesting that the observed discrepancy was not age-related (Supplementary Note S5).

Strengths of the present study were: (i) it is the first to develop a model using AL/CR ratio limits to detect pseudomyopia without the use of cycloplegia, (ii) separate models were trained for European and East Asian samples and (iii) each model was externally validated using two independent cohorts. The approach enhanced the generalisability of the findings by accounting for potential ethnic-specific variations in ocular biometry and demographic characteristics. Furthermore, the use of cohort-specific measurement protocols, while contributing to heterogeneity, reflects real-world practice and strengthens the external validity of the findings. However, the work had several limitations. First, the European training dataset included Danish children exposed to the caffeine metabolite 7-methylxanthine (7-MX). We assumed that 7-MX did not affect the association between the AL/CR ratio and SER, but were unable to verify this. Second, the models were limited to specific age ranges of 7–17 years in the European population and 6–13 years in the East Asian population, based on the age ranges of the training datasets. Third, the models did not account for ocular biometric parameters beyond AL/CR, such as anterior chamber depth, lens power and lens thickness. Models

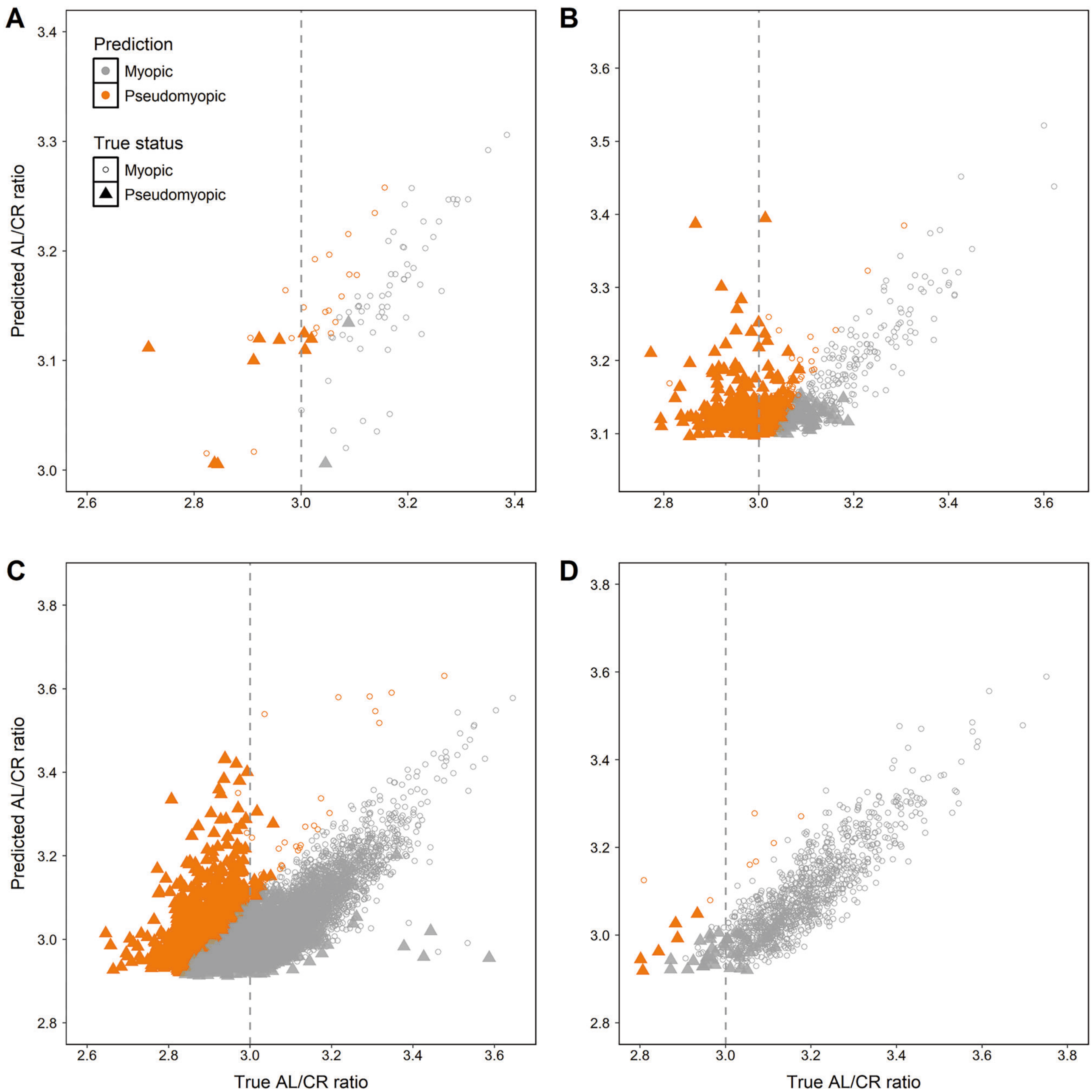

Fig. 6 Scatter plots of observed (true) vs. predicted AL/CR by true vs. predicted myopia/pseudomyopia classifications in the European and East Asian validation cohorts. **A** IES cohort. **B** SMS cohort. **C** HKCES cohort. **D** Vietnam cohort. Grey symbols indicate children predicted to be myopic orange symbols indicate children predicted to be pseudomyopic; circles represent children who were truly myopic and triangles represent children who were truly pseudomyopic. The grey dashed line denotes a true AL/CR ratio of 3.0. AL axial length, CR corneal radius of curvature, HKCES Hong Kong Children Eye Study, IES Ireland Eye Study, SMS Sydney Myopia Study.

incorporating additional biometric parameters may improve the detection of pseudomyopia. Fourth, the definition of pseudomyopia necessarily included instrument myopia. Factors such as the cycloplegia regimen and the amount of near work (and thus accommodative hysteresis) of participants prior to non-cycloplegic autorefraction could potentially influence instrument myopia. In the context of screening, AL/CR-based approaches may therefore have an intrinsic performance ceiling. Although it is challenging to measure instrument myopia accurately [23], future studies employing a more rigorous definition of pseudomyopia, by quantifying and excluding instrument myopia and by assessing the accommodation system, would be beneficial.

CONCLUSION

In summary, two separate models were developed using AL/CR ratio limits to detect pseudomyopia in children of known age, sex and non-cycloplegic SER from Europe or East Asia. Although the European model demonstrated moderate diagnostic performance when evaluated in external validation datasets (sensitivity of 0.80; specificity of 0.75), this level of accuracy would not be sufficient for routine screening purposes. Performance was even worse for the East Asian model. Further studies incorporating additional ocular biometric parameters and employing a more rigorous definition of pseudomyopia may be able to build on these initial findings.

DATA AVAILABILITY

The Danish 7-MX dataset is publicly available at: https://bjo.bmj.com/highwire/filestream/233815/field_highwire_adjunct_files/1/bjo-2021-320920supp002_data_supplement.csv. ACES: The data from the Anyang Childhood Eye Study cohort is available upon reasonable request to Prof. Shi-Ming Li (lishiming81@163.com). IES: Data supporting the findings of the Ireland Eye Study are not publicly available due to ethical and privacy restrictions regarding the inclusion of identifiable paediatric participant data. De-identified data may be available from Dr Síofra Harrington (siofra.harrington@tudublin.ie) upon reasonable request, subject to institutional ethical approval and data sharing agreements. SMS: The data from the Sydney Myopia Study may be available from the study team upon reasonable request. HKCES: The data pertinent to this study will be made available upon request for researchers whose proposed use of the data has been approved by the Department of Ophthalmology and Visual Sciences, The Chinese University of Hong Kong. The data from Vietnam is available upon reasonable request to Ms Hai-Yen Nguyen (n.t.haiyen@bradford.ac.uk).

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AUTHOR CONTRIBUTIONS

HTB: investigation (lead); methodology (equal); writing – original draft (lead); writing – review and editing (lead). DJVH: investigation (equal); methodology (equal); writing – review and editing (equal). TP, SY, HYTN, HN, SCH, SCMK, LAH, CSW: investigation (equal); writing – review and editing (equal). EM, MC, RCB, NGM, OP: supervision (equal); writing – review and editing (equal). LT, SML, ANF, JCY: supervision (equal); project administration (equal); resources (equal); writing – review and editing (equal). CCWK, JAG: conceptualization (equal); supervision (equal); project administration (equal); resources (equal); writing – review and editing (equal).

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COMPETING INTERESTS

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