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Design, methodology, and baseline data of the Personalized Addition Lenses Clinical Trial (PACT)

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Abstract

Background: The aim of this study was to describe the design, methods, and baseline characteristics of children enrolled in the Personalized Addition lenses Clinical Trial (PACT). PACT aims to test the myopia control efficacy of progressive addition lenses (PALs) with personalized addition values compared with standard (+2.00 D) addition PALs and single vision lenses (SVLs).

Methods: PACT is a randomized, controlled, double-masked clinical trial. Two hundred eleven myopic Chinese children (7–12 years) were enrolled and randomized into 1 of the 3 following groups: personalized addition PALs; +2.00 addition PALs; and SVLs. Personalized addition values were determined based on the highest addition that satisfied Sheard criterion. Axial length and other biometric data were also recorded.

Results: At baseline, no differences were found between the right and left eyes for any of the main parameters. The enrolled children were 9.7 ± 1.1 years' old with cycloplegic autorefraction (right eye [OD]: −2.36 ± 0.64 D), near phoria (1.0 ± 5.0 prism diopter esophoria), lag of accommodation (1.40 ± 0.50 D) and axial length (OD: 24.58 ± 0.74 mm). The personalized addition values ranged from +0.75 to +3.00 (average ± SD: 2.19 ± 0.73 D).

Conclusion: PACT is a clinical trial evaluating whether myopia progression in children can be slowed by wearing personalized addition PALs compared with fixed addition PALs and SVLs as measured by cycloplegic autorefraction and axial length. Baseline data were comparable with those of previous myopia control studies in children. Subjects will be followed up every 6 months for 2 years.

Abbreviations: ADD = addition power, COMET = Correction of Myopia Evaluation Trial, FPALs = fixed addition PALs, PACT = Personalized Addition lenses Clinical Trial, PALs = progressive addition lenses, PD = prism diopter, PPALs = personalized addition PALs, SE = spherical equivalent, SOP = standard operating procedure, SVLs = single vision lenses, VA = visual acuity, WEIRC = Wenzhou Medical University-Essilor International Research Center.

Keywords: myopic children, phoria, progressive addition lenses

1. Introduction

Myopia is one of the most common disorders of the eye, with increasing prevalence in school-age children in Asia, the Americas, and Europe.[1] A recent epidemiological study found a myopic shift in the youngest Chinese generation with a prevalence of high myopia similar to that in the elderly population.[2] High myopia is often associated with various ocular pathologies, for example, vitreoretinal pathologies,[3,4] a higher prevalence of dense nuclear cataract,[5] and idiopathic focal subretinal neovascularization.[6] It is therefore important and worthwhile to slow the progression of myopia in school-age children.

Near addition lenses have been prescribed for myopic children to slow the progression of myopia.[7]The effects of addition lenses on myopia progression have often been inconclusive when considering all children: the difference in the progression of myopia between the progressive addition lenses (PALs) and the single vision lenses (SVLs) groups was small in the COMET (Correction of Myopia Evaluation Trial) study,[8,9] as well as in other studies.[10,11]The accommodative and phoria statuses of children were found to be related to myopic progression with progressive addition lenses. Children with larger accommodative lags and near esophoria had better myopia progression control with PALs[9,12,13] (average 0.6 D for 3 years) than those of the overall cohort (0.2 D) in the COMET study.[9] However, later clinical trials that recruited only children with high accommodative lag and mainly near esophoria failed to confirm those fidings.[14,15]

Animal model evidence has shown that peripheral defocus influences eye growth,[16,17] although the basic hypothesis that a relatively hyperopic peripheral refractive error can induce the development of myopia in humans remains unproven.[17]

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Peripheral defocus may also be involved in the effect of PALs on myopia progression. A clinical trial found that superior myopic defocus caused by PALs was significantly associated with slower myopia progression.[18] Bifocal soft contact lenses and contact lenses designed with progressive relative positive power were found to slow myopia progression in children by reducing hyperopic defocus in the peripheral retina and/or inducing myopic defocus in the central retina.[19,20]

An obvious exophoric shift while wearing near addition spectacle lenses was observed, which would be expected to reduce the positive-lens treatment effect,[21,22] potentially because of lack of use of the near vision zone.[23] An attempt has been undertaken to correct this effect with prismatic bifocal lenses (3 BI prism diopter, pd) on both eyes in near vision and a +1.50 D addition).[24,25] Incorporating near base-in prisms was found to reduce the addition lens-induced exophoria,[26] which led to better usage of the near addition. A significant effect of prismatic bifocal lenses on myopia progression was found at the 2-year (0.85D treatment effect) and 3-year (1.05 D treatment effects) follow-ups compared with that of SVLs.[24,25] However, this study used a fixed prism and did not consider the children's phoria status.

Several studies failed to find an association between the accommodative lag and myopia progression in children.[27,28] It is therefore plausible that the myopia control effect with PALs or bifocals may not be only because of a reduction of accommodative lag. Previous studies have suggested that a reduction of the peripheral defocus in the upper retina by PALs or bifocals may also contribute to the observed myopia control.[18–20] We hypothesized that the inconsistent effects of PALs on myopia control in children may be because of the inconsistent usage of the near vision zone of PALs, which could be caused by the use of a standard near addition value, instead of a personalized or suitable for the patient's binocular vision, in previous studies. Our preliminary study found that the optimal addition value determined by satisfying Sheard criterion was correlated with the phoria status at near; most of the children with exophoria had near addition values <+2.00D, whereas most of the children with esophoria had addition values higher than +2.00D. With these values, compared with the standard +2.00 D addition values, patients, especially exophoric children, should obtain reasonable phoria and should gain better binocular balance.[29]

1.1. Study rationale and objectives

The PACT study arose from three distinct lines of research: addition lenses for myopia control, addition lenses with vergence compensation, and personalized addition lenses with a balance of accommodation and vergence. Based on our pilot study, the determination of near additions for myopic children can be achieved to obtain reasonable phoria. The addition value thus determined by the pilot study is the highest addition value that satisfies a binocular vision comfort criterion (e.g., Sheard Criterion, fusional amplitudes/phoria = 2) without inducing any lead of accommodation (over-accommodation). These customized near addition values can be tolerated by the wearer, especially by children with orthophoria and exophoria.[29] The objective of this 2 years of follow-up research is to evaluate whether myopia progression, defined by cycloplegic autorefraction and axial length, is slowed in children by the wearing of personalized addition PALs (PPALs), compared with fixed addition PALs (FPALs) and SVLs.

This article describes the study design, methodology, and baseline data for refractive error and ocular components of the 211 children enrolled in PACT. Follow-up data will show whether myopia progression is slowed in the group with PPALs in these school-aged Chinese children.

2. Methods

2.1. Study design

PACT is a randomized clinical trial aiming to determine whether the progression of myopia is different between children wearing PPALs versus +2.00 D FPALs and SVL. Changes from baseline measurements in cycloplegic autorefraction and axial length will be assessed to evaluate the progression of myopia and will be reported at the conclusion of the study. The study is being conducted at the Wenzhou Medical University-Essilor International Research Centre (WEIRC) in Wenzhou city, China. PACT and its protocol followed the tenets of the Declaration of Helsinki and were approved by the institutional review board of the Eye Hospital of Wenzhou Medical University. Informed assent was obtained from the children and consent was obtained from children and their parents after verbal and written explanations of the objectives and possible consequences of the study

2.2. Subjects

The inclusion criteria of the study were as follows: age 7 to 12 years (inclusive); a refractive error of the spherical equivalent (SE) between −0.75 and −4.0, measured using cycloplegic autorefraction in both eyes; astigmatism of no >1.5; no anisometropia (<1.0 D of difference between the eyes in SE); a best corrective visual acuity of 0.05 LogMAR (Snellen 0.9) or better; no strabismus with corrective lenses or with the +2.0 D near addition lenses; within 10.0 PD exophoria, measured by modified Thorington test at 33 cm; the ability to comply with the protocol and remain in the study for at least 2 years; and myopia progression of at least 0.50 D of cycloplegic autorefraction or prescription in the preceding year (cycloplegic autorefraction compared to the previous cycloplegic autorefraction, or subjective refraction compared to the previous subjective refraction if the cycloplegic autorefraction was not available).

The exclusion criteria included the following: anisometropia of >1.0 D in SE; strabismus with corrective lenses or +2.0 D near addition lenses; >10.0 D exophoria at 33 cm; a history of wearing contact lenses or PALs; an ocular disease or systemic condition that might influence refractive development; or myopia progression of <0.50 D or no definition of the myopia progression in the preceding year.

We chose the specific age range (7–12 years) so that the myopia of these children would be likely to progress throughout the follow-up phase of the trial. The maximum enrollment was −4.00 D so that the refraction would not exceed −6.00 D over the 2 years of the study, which has been suggested to be associated with pathologic changes in the eyeball.[30] The enrollment criteria of myopia progression of >0.5 D in the previous year was determined based on the subjective refraction or cycloplegic autorefraction, which was collected by our department for most of the subjects and from other eye care providers outside our hospital. The children were asked to wear their prescribed glasses during all waking hours and not to wear contact lenses during the study.

2.3. Sample size

A total sample size of 210 subjects (70 per group) was required for this study, based on the following considerations: an expected

25% reduction in mean myopia progression compared with SVLs; mean myopia progression of 1.50 D over 2 years in Chinese children wearing SVLs; and an overall standard deviation of 0.60 D.[11] Statistical power was set at 90% with a type 1 error probability (α) of 0.05, based on a 2-tailed *t* test. The theoretical sample size was 56, with a 1:1:1 sample ratio. To allow for a maximum drop-out rate of 20%, the sample size for each group was estimated at 70.

2.4. Recruitment

All subjects were recruited from the Optometry Clinic of the Eye Hospital of Wenzhou Medical University from July 1, 2014 to February 1, 2015. Recruitment strategies included recommendations from clinical optometrists and advertisements in the public areas of the hospital, as well as advertising through WeChat. Two hundred and twenty-nine subjects were screened to be included in the baseline assessment for recruitment.

2.5. Randomization

Children were randomized to 1 of 3 groups (i.e., PPAL, FPAL, or SVL). A dynamic randomization technique (minimization process) was used for subject assignment in PACT. Age, sex, phoria, and myopia degree were considered to ensure the sequential balance of the distribution of the patients' characteristics and potential prognostic factors among the 3 study groups. Minimization assigns patients sequentially to treatment by attempting to minimize total imbalance between treatment groups with consideration of all important prognostic factors. A given patient assignment probability to experimental treatment is a function of the patient's stratification variables and the stratification variables of previously randomized patients.[31] Once a child was determined to be eligible after collection of the baseline data, the randomization assignment was then run using the MINIM software (www.sghms.ac.uk/depts/phs/guide/randser.htm), and a study number was issued. The child then received the assigned lenses.

2.6. Implementation

Dynamic randomization software was used by the clinical coordinator to generate the random allocation sequence. The ophthalmologist and optometrist enrolled the participants, and the clinical coordinator assigned the participants to the interventions.

2.7. Study visits

PACT included initial visits (recruitment, a baseline visit, and a randomization /dispensing visit), 6-, 12-, 18-, and 24-month follow-up visits with clinically based comprehensive examinations, and scheduled telephone calls at 1, 3, 9, 15, and 21months after randomization. Unscheduled visits could be scheduled when children had any questions about wearing glasses that need clinical management after judgement by a consulting optometrist over the telephone (Fig. 1). During the recruitment and baseline

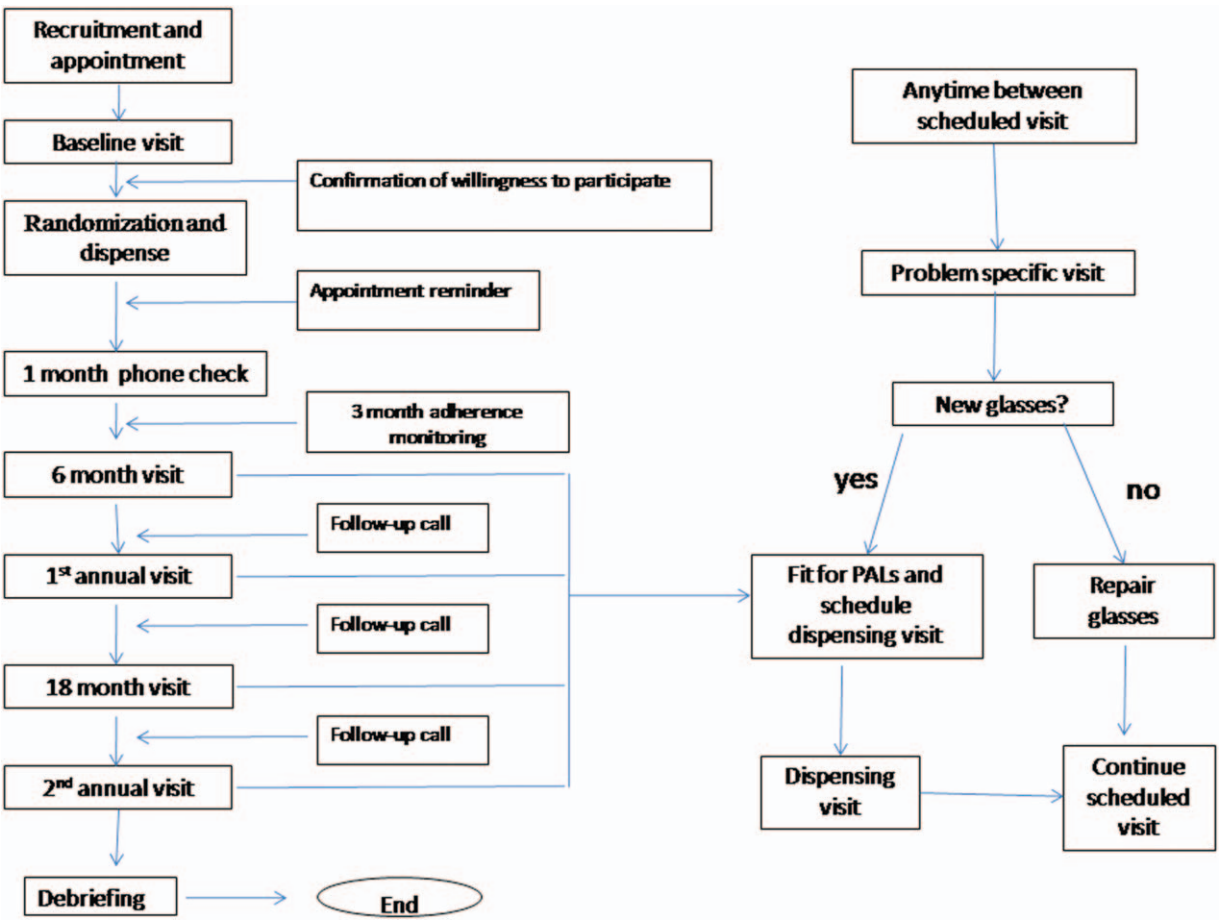

Figure 1. Overall workflow schematic of the Personalized Addition lenses Clinical Trial follow-up plan.

Table 1

Summary of data collection procedures at each study visit.

Procedure	Initial visits: Baseline	Initial visits: Randomization/ dispensing	Scheduled visits (6, 12, 18, 24 mo)	Unscheduled visits
Review of study protocol/PACT commitment	√	√	√	√
Consent form signed	√			
Case history	√		√	√
Lensometry/existing prescriptions	√		√	√
Visual acuity (i.e., unaided and habitual)	√		√	√
Autorefraction noncyclopegic	√		√	*
Subjective refraction	√		√	*
Cover test-distance and near	√		√	*
Phoria (modified Thorington test)	√	√	√	*
Stereopsis	√		√	*
Accommodation measurement	√	√	√	*
Definition of optimal addition lens	√		√	*
Slit lamp examination	√		√	*
Eye drops (i.e., anesthetic, cycloplegia, fluorescein)	√		√	*
Autorefraction cycloplegic	√		√	
Lenstar (i.e., axial length, keratometry, anterior chamber depth, crystalline thickness, vitreous chamber depth)	√		√	
OCT (i.e., retinal and choroidal thickness)	√		√	*
Ophthalmoscopy	√		√	*
Frame selection	√		√	*
Inter-pupillar distance measurement	√		√	*
Fitting height measurement	√		√	*
Fitting frames and lenses		√	√	
Measurement of reading distance		√	√	
Reading parameter study		√	√	
Survey (i.e., outdoor activity, reading time, time of wearing, quality of vision and symptoms with wearing glasses)		√	√	*
Dispensing glasses		√	√	*
Appointment reminder	√	√	√	*
Wearing Instruction		√	√	*

OCT = Optical Coherence Tomography, PACT = Personalized Addition lenses Clinical Trial.
* Procedures done as needed.

examination at the clinical center, we explained the study, collected the baseline data, and evaluated the eligibility of the children (Table 1). If any of the exclusion criteria were identified at any time during the baseline visit, the visit would be continued as usual, but these children would not be invited to be enrolled in the study. Frames were selected for the children who met eligibility criteria and were willing to participate in PACT; measuring and fitting of the study glasses occurred at the end of the visit. The randomization visits were also scheduled during this visit.

Baseline forms were sent to the coordinating center for independent confirmation of eligibility and randomization. An unmasked investigator (clinical coordinator) ordered the study lenses based on the measurements and selected frames obtained during the baseline visit. After study group assignments were made and an identification numbers were issued by the coordinating center, the randomization visit was held. During the visit, the study glasses were dispensed, reading distance was collected, and the "Wearing Instructions" were administered to all groups. Upon this visit, the child was enrolled officially in PACT.

Follow-up visits were scheduled every 6 months for at least 2 years. The main outcome data (i.e., cycloplegic autorefraction and axial length), accommodation and phoria measures, assessment of adherence to the study glasses, and the reading parameters were collected at each visit. The need for a prescription change was evaluated at all visits based on the criteria detailed in the glasses section (see below). Outdoor activity, reading time, time of wearing spectacles, and quality of vision and symptoms while wearing glasses were surveyed at each follow-up visit and telephone contact.

2.8. Masking

PACT was designed as a double-masked trial to minimize observer and experimenter biases. Masking was achieved with the following steps

1. All children were identified by an identifying number that was not related to treatment assignment on all study documents.
2. At the baseline visit and all follow-up visits, measurements for glasses were performed for each child as if they were wearing personalized PALs. All children and their parents were given the same "Wearing Instructions" as if they were all wearing PALs.
3. Randomization assignments were made by the clinical coordinator using dynamic randomization software. The clinical coordinator kept this information and subsequent information related to the glasses separate from other PACT records.

4. At each follow-up visit, the study optometrists and the children and their parents were masked as to which group the child belonged. All children in the 3 groups were measured wearing trial frames (except for the posture measurements).
5. At an un-scheduled visit, the study measurements were masked as during follow-up visits if the child needed a new prescription.
6. During data collection, the forms and protocols were standardized and utilized for all children regardless of group assignment. Data collection forms and examination protocols were standardized and identical for all children regardless of treatment assignment.
7. If any significant symptoms were reported during the study, the clinical coordinator or ophthalmologist would be contacted to address the problem and maintain the mask of the assignment group of the child.
8. If some children and their parents discovered their lens assignment, steps were developed to minimize the effect of observation bias, including emphasizing that the patients not discuss the glasses with the study optometrist/ophthalmologist and reminding the children using the assigned glasses of the instructions.

2.9. Glasses

2.9.1. Lenses. All PACT lenses were polycarbonate lenses (index 1.59) to ensure maximum safety for the children; lenses had Essilor Crizal coating for optimal transparency and easy cleaning. Myopilux Pro (Polycarbonate Crizal Essilor International, Charenton-le-Pont, France) was utilized in the treatment groups, and the addition values depended on each treatment group (+2.00 D in the FPAL group and personalized addition in the PPAL group). Children in the SVL group wore single vision lenses (Polycarbonate, Airwear Crizal, Essilor International, Charenton-le-Pont, France).

2.9.2. Frame selection. The height of the frame was a minimum of 26 mm with a minimum pupil height of at least 16 mm. The frames were physically comfortable, attractive in appearance, and met the expectations of the subjects.

2.9.3. Fitting glasses. The frame was closely fitted with a vertex distance 10 to 12 mm to not touch the eye lashes; a pantoscopic angle of 6 to 8 degrees was used to not touch the wearer's cheeks and provided adequate depth (≥16 mm) beneath the center of the pupil to accommodate the reading zone of the lens.

2.9.4. Verification of PALs. The power of the lenses was verified by an optometrist before the lenses were mounted. When the lenses were mounted, the powers of the lenses and the progression heights were verified by an optician.

2.9.5. Guideline for changing the prescription, lenses, and frames. During visits, prescriptions were changed whenever the refraction changed by 0.5D or more or the visual acuity (VA) with glasses was less than 0.9 (0.05 LogMAR). Glasses were changed for any change of addition of 0.50D or more for the PPAL group (even without change in prescription or VA). Broken or damaged frames and lenses were replaced. During half-year visits, if the frame had become too small or the parents demanded a change, the frame was changed.

2.10. Variables measured

The main outcome measurement in PACT is progression of myopia assessed by cycloplegic autorefraction and axial length measured by Lenstar. Additional outcome measurements include other ocular components.

2.10.1. Visual acuity (VA). Uncorrected VA, VA with previous glasses, and best corrective VA were tested in both eyes in all subjects using a Snellen visual acuity chart at 4 m. Snellen acuity was converted to the LogMar scale for enrollment criteria and statistical analysis.

2.10.2. Subjective refraction. Subjective refraction was assessed before cycloplegia, starting with the mean of 5 noncycloplegic autorefractor measurements. Autorefraction with a Canon RK-F1 (Canon Inc., Tokyo, Japan), known for its accuracy and repeatability,[32] was evaluated in both eyes by experienced optometrists who were trained and certified on study protocols. Subjective refraction included measurement of the monocular best sphere, cylinder power and axis, binocular balance, and binocular best sphere.

2.10.3. Phoria and vergence fusion. As previously described,[29] near phoria was measured using the modified Thorington test (average of 3 measurements) at 33 cm through 6 near addition lenses (+3.00 D, +2.50 D, +2.00 D, +1.50 D, +1.00 D, and 0 D). Base-out fusional amplitudes were measured with a phoropter and a 0 D near addition, followed by base-in fusional amplitudes. The blur point, break point, and recovery point were recorded during the measurements. Fusional amplitudes were defined as the average of three measurements with the "blur point" records or recovery points (for children without blur points). Eighteen subjects reported no "blur points" for BO measurements, as well as 10 subjects for BI measurements.

2.10.4. Accommodative lag. Accommodative responses were binocularly measured with a Grand Seiko WAM-5500 (Grand Seiko Co. Ltd., Hiroshima, Japan) open field autorefractor (10 static measurements). Measurements taken with the Grand Seiko WAM-5500 have been shown to be accurate and repeatable.[33] During the measurements, the subjects wore their distance refraction lenses mounted in a trial frame with a vertex distance of 12 mm, and the accommodative response was measured with fixation on a Maltese cross at 33 cm, which is a distance commonly used for near refraction in children.[9] The accommodative response without any near addition was measured in both eyes. Additionally, the right eye's accommodative response was measured with near additions of +2.50 D, +2.0D, +1.50 D, and +1.00 D. To avoid accommodative adaptation, we tested the near addition lenses in order from highest to lowest as described in a previous study.[34] The calculation of the lag of accommodation on the subject's corneal plane was calculated as previously described (see Supplemental digital content 1, http://links.lww.com/MD/B552).[35]

2.10.5. Autorefraction. After corneal anesthesia induced with proparacaine (0.5% Alcaine, Alcon Laboratories, Ft. Worth, TX), 3 drops of 1% cyclopentolate (Alcon Laboratories, Ft. Worth, TX) were administered at 5 minutes a part to induce cycloplegia. Five consecutive, reliable autorefraction measurements were obtained 30 minutes after the third drop was administered. The child was asked to sit in front of the autorefractor (Canon RK-F1) and to look at the fixation target, which was designed to obtain the smallest accommodative response.[36] Both before and after cycloplegia, the right eye was measured (in 0.25 D steps) first and then the left eye.

2.10.6. Ocular component measurements. Ocular components were measured by Lenstar LS900 (Haag-StreitInterna-

tional, Koeniz, Switzerland) after cycloplegic autorefraction, including axial length, anterior-chamber depth, lens thickness, vitreous-chamber depth and keratometry. The Lenstar LS900 was suggested for its accuracy and repeatability as evaluated by a previous study.[37] Three individual measurements were obtained per eye and averaged. Keratometry was recorded as the greatest keratometry (K1) and the least keratometry (K2). Mean keratometry was calculated as the mean of K1 and K2.

2.10.7. Definition of personalized near addition value. As described previously,[29] personalized addition power was determined by analyzing the variation of fusional amplitude (FA)/phoria (Ph) ratios with addition power (ADD). The data were fitted by the following function: $|FA/Ph| = a/(Addition + b)$, where a represents a form factor that determines the amplitude of the response of the subject, and b the addition value for which the Ph is null. Personalized addition power was determined by this function for the highest ADD that satisfied FA/Ph = 2 (Sheard criterion) and induced the smallest accommodative error. The next highest 0.25 D value was selected (see Supplemental digital content 2, Supplemental Table 1, Supplemental Figure 1, http://links.lww.com/MD/B552). Accommodative response was then measured with this ADD. If an accommodative lead was measured, the ADD was decreased, and the accommodative response was measured again until a lag or null accommodation was attained. If the ADD was >+3.00 D (some children had high esophoria), the ADD was set at +3.00 D. This ADD was then considered the personalized addition value.

2.11. Quality assurance

The following elements were included for quality assurance: development of a standard protocol to perform all data collection and follow-up, development of and adherence to a detailed standard operation procedure (SOP), standards for training and certification of staff, use of standardized forms and consistent study conditions, uniform patient recruitment criteria, and regular communications between the study investigators. Data assurance was performed by the PACT investigators, clinical coordinator, and statistics specialist.

2.12. Data management

The investigator ensured that each study member followed the SOP to obtain reliable results. The clinical coordinator was also responsible for the data. Additionally, there were 2 levels for monitoring the data. The 1st level was that both the electronic files and the hard copy were well-kept and were backed up at each study visit. The 2nd level was the input of the data with required double keyboarding. A set of spreadsheets were prepared to store the data.

2.13. Statistical analysis

2.13.1. Baseline data analyses. The refraction data, defined as sphere with negative cylinder power and axis, were analyzed by decomposition of the power profile.[38] The refractive error was composed of 3 components: spherical equivalent (SE) and 2 Jackson-cross-cylinders—J0 (with meridian of maximum converging power set horizontally) and J45 (with meridian of maximum converging power setobliquely).[36] Continuous variables were summarized for right and left eyes using means ± SDs. The t test was used for continuous variables in univariate analyses and the χ^2 test for categorical variables. One-way analysis of variance (ANOVA) was used for comparisons among 3 groups. Pearson correlation coefficients were used to evaluate the correlations among refractive error, ocular components, and age. All of the statistical analyses were performed using SPSS software, version 13.0 (SPSS Inc, Chicago, IL).

2.13.2. Progression analyses. Progression in PACT was child-based and evaluated by the myopic change magnitude in spherical equivalent cycloplegic autorefraction between the follow-up and baseline data. The change of axial length measured by Lenstar was also evaluated as a parameter of myopia progression. Rate of myopic and axial length change was evaluated by determining the slope for the 3 study groups based on the measurements from baseline and examinations of each follow-up visit. Standard parametric tests (e.g., t test) or nonparametric approaches (e.g., Wilcoxon rank-sum test) for independent samples were used for comparisons of the distribution of myopia progression between groups. A multiple regression model would be used to explore the predictor variables for myopia progression, such as age, sex, baseline refractive error, accommodative lag, phoria level, and reading parameters.

3. Results

3.1. Basic characteristics of children in the three groups

Table 2 shows the basic data of the 211 children enrolled in the study. Of the 211 subjects, 115 (52%) were male. Sixty (28%) subjects had no myopic parent, 78 (37%) subjects had 1 myopic parent, and 73 (35%) subjects had 2 myopic parents. Eighty-nine (42%) children had near esophoria (2.0~16 Pd), 52 (25%) had orthrophoria (−1.5~1.5 PD), and 70 (33%) had near exophoria (−9.0~−2.0 PD).

3.2. Refractive data

There were no significant differences between the SE of the right and left eyes measured by cycloplegic autorefraction ($t = 0.80$, $P = 0.47$) or subjective refraction ($t = 1.40$, $P = 0.17$). Therefore, we analyzed and present the data of the right eyes only. Figure 2 shows the distribution of SE determined by cycloplegic autorefraction in the right eyes of the 211 children, with a mean of −2.36 ± 0.64 D. Most of the subjects (191, 90.2%) had an SE between −1.50 and −3.50 D.The SE of cycloplegic autorefraction was not correlated to age ($r = 0.09$, $P = 0.21$).

Table 2

Basic characteristics of the children enrolled in the study.

	Mean ± SD
Age, y	9.7 ± 1.1
Age at first glasses, y	8.5 ± 1.1
SE of cycloplegic autorefraction (right eye, D)	−2.36 ± 0.64
Axial length, mm	24.58 ± 0.74
Vitreous chamber depth, mm	17.25 ± 0.73
Anterior chamber depth, mm	3.28 ± 0.20
Lens thickness, mm	3.33 ± 0.13
AL/CR	3.14 ± 0.06
Phoria at near (pd)	0.97 ± 5.0
Accommodative lag (D)	1.40 ± 0.50
Accommodative lag with near addition lenses (D)	0.77 ± 0.69
FA/Ph with near addition lenses	6.00 ± 7.67

AL/CR = axial length/corneal radius, FA/Ph = fusional amplitude/phoria, SE = spherical equivalent.

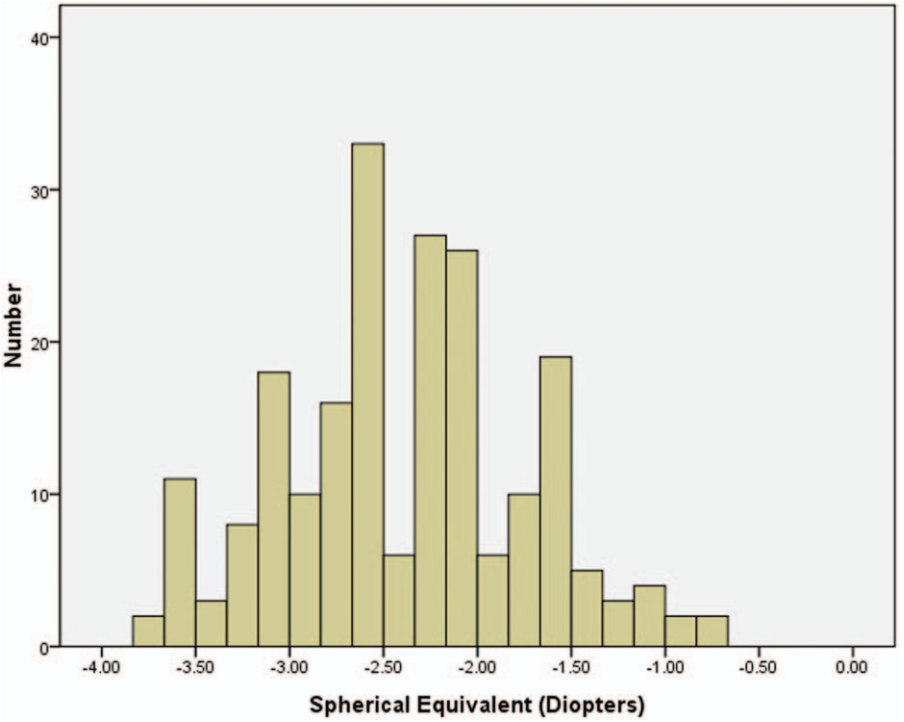

Figure 2. Baseline distribution of the spherical equivalent of cycloplegic refraction in right eyes.

There was little astigmatism in this group of children: J0 and J45 were mostly close to zero within a ±0.25D range (90% for J0 and 85% for J45; Fig. 3). The axis of the cylinder was classified according to a previous study: with the rule (WTR) was defined as between 0 and 22.5 degree or between 157.5 and 180 degree; against the rule (ATR) was defined as between 67.5 and 112.5 degree; and oblique was defined as the intermediate values.[23] Eighty-one percent of the astigmatism was WTR, 14% was oblique, and 5% was ATR in the right eyes of our sample.

The mean difference between the SE of the distance prescription determined by subjective refraction and the cycloplegic autorefraction was minor (0.10 ± 0.29 D, with 95% limits of agreement of 0.06–0.14 D) but significant ($t = 5.1$, $P < 0.001$), with the distance prescription being slightly less myopic. Forty-seven percent of children were found to be more myopic by 0.25 to 0.5D through cycloplegic autorefraction than subjective refraction, and only 4% of the children had more than a 0.5-D myopic difference (Fig. 4). Figure 5 shows good correlation between the distance prescription and cycloplegic autorefraction ($r = 0.90$, $P < 0.001$).

3.3. Ocular components

The axial length of the right eyes (24.58 ± 0.74 mm) was similar to that of the left eyes (24.58 ± 0.75 mm) in the 211

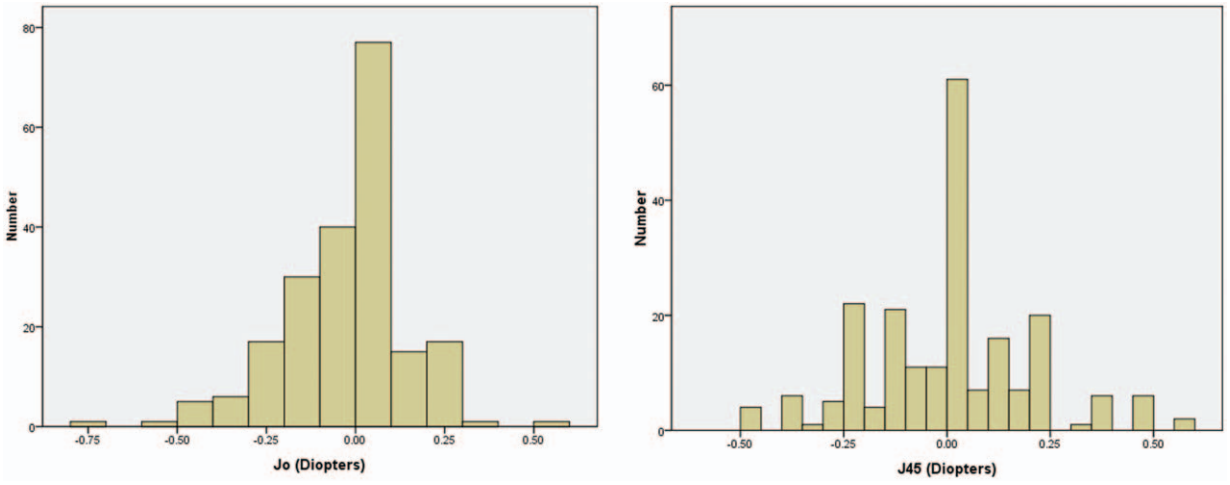

Figure 3. Baseline distribution of J0 (left) and J45 (right) in right eyes.

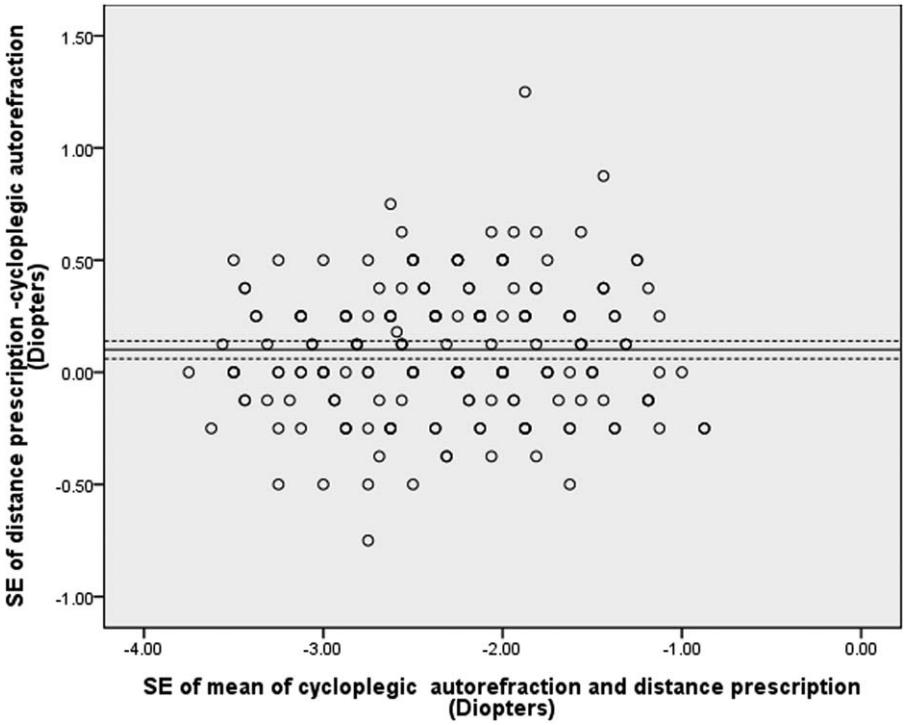

Figure 4. Differences and means of distance prescriptions and cycloplegic autorefraction in right eyes. Solid line: the mean; dashed lines: the 95% limits of agreement.

children ($t=0.27$, $P=0.79$).Vitreous-chamber depth was the main cause of the axial length difference and was significantly correlated with axial length ($r=0.95$, $P<0.001$). Both axial length (Fig. 6, $r=0.25$, $P<0.01$) and vitreous-chamber depth ($r=0.23$, $P<0.001$) were positively correlated with age. However, both lens thickness and anterior chamber depth were not significantly correlated with age ($r=0.03$, $P=0.73$; $r=0.07$, $P=0.29$).

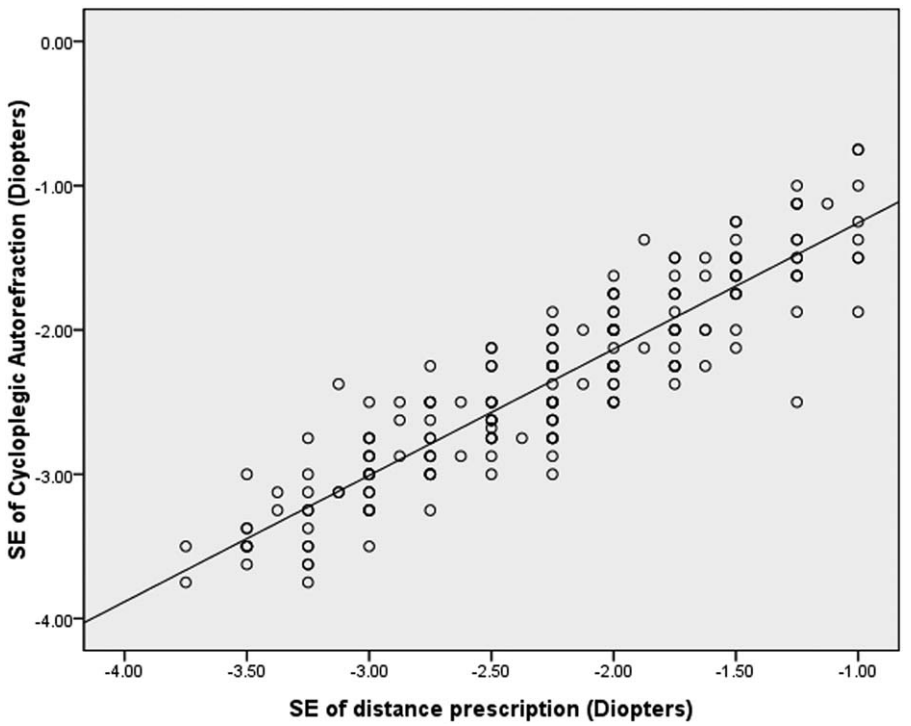

Figure 5. Spherical equivalent of distance prescriptions in right eyes as a function of cycloplegic autorefraction ($r=0.90$, $P<0.001$).

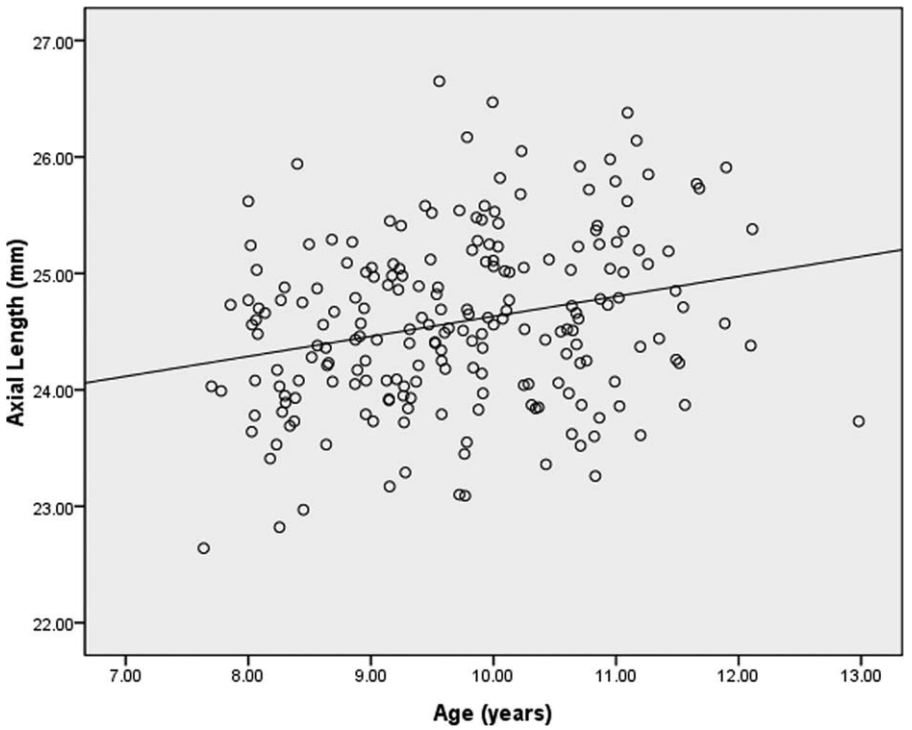

Figure 6. Axial length in right eyes as a function of age ($r=0.25$, $P<0.001$).

3.4. Corneal radii

There were small but significant differences in corneal radii between the right (42.7 ± 1.3 D) and left eyes (42.6 ± 1.3D) in K2 ($t=2.37$, $P=0.018$) but not in K1 (right eye: 43.6 ± 1.5 D, OS: 43.7 ± 1.5D, $t=1.77$, $P=0.078$). Keratometry was negatively correlated with age (Fig. 7, $r=-0.18$, $P=0.01$).

There was no significant difference in AL/CR ratio (axial length over corneal radius) between right and left eyes ($t=0.67$, $P=0.51$). The average AL/CR ratio was 3.14 ± 0.06, which was >3.0 in 99.5% of the right eyes of the 211 children. The correlation between age and AL/CR ratio was not significant ($r=0.088$, $P=0.20$).

3.5. Near addition, FA/Ph, and accommodative lag

In 82.5% of the subjects, lags of accommodation were >1.0 D when measured with their distance prescriptions. Figure 8 shows the near addition values of the 71 children in the PPAL group, which ranged from 0.75 to 3.0 D (2.19 ± 0.73 D).

4. Discussion

We reported the design, methodology, baseline refraction, and ocular component data of 211 children enrolled in the PACT study. This population had a mild to moderate level of myopia (90% of −1.50 to −3.50 D) and an average axial length of 24.58 mm in the right eyes. The results reflected the eligibility criteria for this clinical trial, which enrolled children with progressive myopia who will be followed up for at least 2 years. These data will be used as baseline measurements for later analyses of the progression of myopia during the follow-up of PACT.

The SE of cycloplegic autorefraction in the right eyes of the 211 children was an average of −2.36 D. Because it was a selected population, it does not reflect the actual refraction level for a similar age group. In a school-based cohort study conducted in China,[39] myopia was reported to be, on average,-1.43 D and -2.58 D in 7- and 14-year-old Chinese children, respectively. Similar to a study by Hasebe et al in Japanese school children,[40] no significant correlation was found between refraction and age in our study.

SE determined by cycloplegic autorefraction was in good agreement with distance prescription, based on subjective refraction. Subjective refraction required longer procedure times and sustained attention both from the child and the examiner, whereas cycloplegic autorefraction only required brief fixation on a target.[36] The agreement between subjective refraction and cycloplegic autorefraction ensured that the control of the end point of the subjective refractive measurements was properly achieved in PACT because it has been suggested that the spherical end point determination might be difficult in children because of a lower sensitivity to lens-induced blur in myopes.[35,36,41] Subjective refraction was slightly less myopic than cycloplegic autorefraction, with 4% of children having a difference of >0.5 D. Previous studies also found that few subjects had less myopia with subjective refraction than with cycloplegic autorefraction, particularly in myopes. This difference may be because of changes in higher order aberrations with cycloplegia, in particular the increase in positive spherical error with dilated pupils during cycloplegic autorefraction.[42,43]

Younger children had higher corneal power than older children, but no difference in lens thickness was noted. This finding differed from previous epidemiological studies, which reported that lens thickness decreased with age, whereas corneal power remained stable.[44–47] This difference might be because of the subjects enrolled in our study, based on specific criteria, unlike the subjects of population-based cohort studies.

An AL/CR ratio >3.0 has been suggested to be related to an increased risk of myopia development.[48,49] Of the subjects in

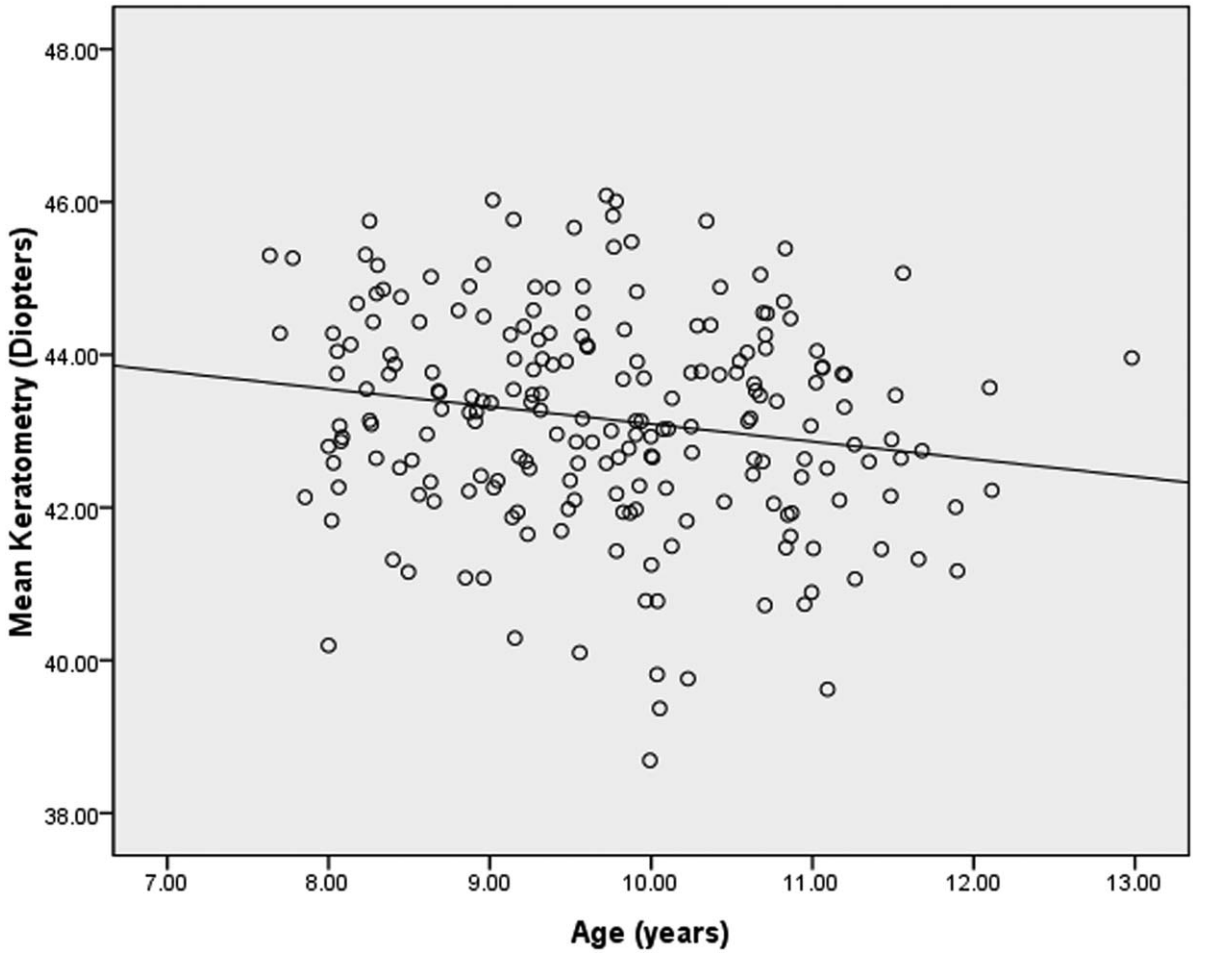

Figure 7. Mean keratometry in right eyes as a function of age ($r = -0.178$, $P = 0.01$).

our study, 99.5% had an AL/CR ratio >3.0, with an average of 3.14.These high AL/CR ratios reflected our inclusion criteria, which selected only children with myopia progression of at least 0.5D/year. The average value of AL/CR in our study was similar to that observed in the COMET study,[36] as well as that reported in a group of 14-year-old Chinese children, in which 74% of the 1786 children were myopic.[47]

Of the children in our study, 42% had esophoria, 25% had orthophoria, and 33% had exophoria at near, measured while wearing their distance correction lenses. This distribution was comparable to those in the previous studies shown in table 4, http://links.lww.com/MD/B552, except for the COMET 2 study, which enrolled only children with near esophoria. Fusional convergence was reported to decrease and phoria at near to shift toward more exophoria over a period of 10 years in myopic children.[50] Phoria and fusional vergence data, as well as the FA/Ph ratio, will be evaluated at each follow-up visit. As shown in Table 3, the average lag of accommodative at 33 cm in our study was comparable with that in the COMET2 study[15] but much higher than that measured in COMET.[8,36] This difference maybe because COMET2 only enrolled children with a high lag of accommodation and also implies that our subjects had a high accommodative lag. Another possible reason for this difference could be the measurement instrument. COMET 2 and our study used a Grand Seiko WAM-5500 autorefractor, whereas COMET used a Canon R-1. Addition values ranged from +0.75 to +3.00 D in the 71 children of the PPAL group, and they varied with near phoria (Fig. 8), as described in a previous study.[29] The personalized addition value will be determined at each follow-up visit, and the PAL lenses will be changed accordingly.

As we previously noted,[29] adaptation effects in the vergence system might be observed with the testing of near addition lenses from highest to lowest. The fusion and phoria measurement results would be affected by the adaptation for the subsequent lenses. Consequently, we measured the accommodation first and then phoria and fusional amplitudes. The phoria and fusional amplitudes measurements might be affected in some subjects by the lens-induced phoria adaptation during the proceeding accommodation testing. We used the general protocol for all subjects to minimize the intersubject effects, though there might be potential adaptation effects in a subject when using the near addition lenses order.

In summary, PACT is a randomized, double-masked study that aims to evaluate whether myopia progression can be slowed using PALs with personalized addition values, compared with PALs with a +2.00 D addition prescribed to all children, as well as single vision lenses. This study provides measurements of myopia using cycloplegic autorefraction and of ocular components using Lenstar measurements. The baseline data will be used to evaluate the progression of myopia in each treatment group of children.

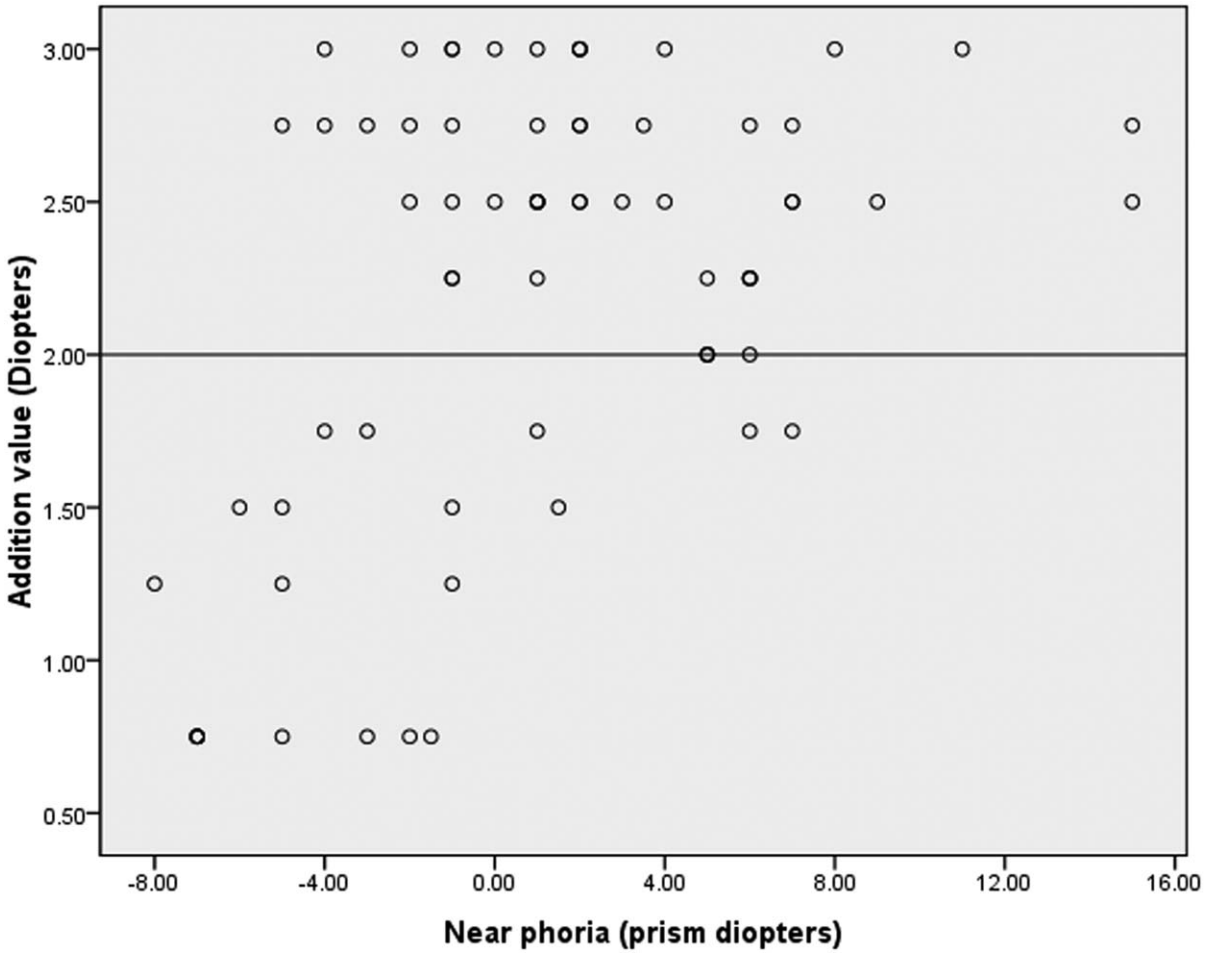

Figure 8. Distribution of addition values in children with personalized addition progressive addition lenses as a function of near phoria.

Table 3

Comparison of near phoria and lag of accommodation with similar studies.

	Near phoria			
	Average (pd)	Esophoric	Exophoric /orthophoric	Accommodative lag at 33 cm D)
Our study	0.97 ± 4.98	42%	60%	1.40 ± 0.50
COMET[8,23]	1.86 ± 6.49 (PAL group)	41%	59%	0.53 ± 0.67 (PAL group)
	2.57 ± 6.88 (SVL group)			0.52 ± 0.60 (SVL group)
Yang et al[11]	−1.23 ± 5.38	23%	77%	0.78 ± 0.28
Cheng et al[24]	0.8 ± 5.0	28%	72%	0.96 ± 0.67
COMET 2[15]	5.9 ± 3.4 in the SVL group	100%	none	1.40 ± 0.48 in the SVL group
	5.8 ± 3.2 in the PAL group			1.47 ± 0.53 in the PAL group

PAL = progressive addition lenses, SVL = single vision lenses.

References

[1] Foster PJ, Jiang Y. Epidemiology of myopia. Eye 2014;28:202–8.
[2] You QS, Wu LJ, Duan JL, et al. Prevalence of myopia in school children in greater Beijing: the Beijing Childhood Eye Study. Acta Ophthalmol 2014;92:e398–406.
[3] Cheng SC, Lam CS, Yap MK. Prevalence of myopia-related retinal changes among 12–18 year old Hong Kong Chinese high myopes. Ophthalmic Physiol Opt 2013;33:652–60.
[4] Li X. Beijing Rhegmatogenous Retinal Detachment Study Group. Incidence and epidemiological characteristics of rhegmatogenous retinal detachment in Beijing, China. Ophthalmology 2003;110:2413–7.
[5] Praveen MR, Vasavada AR, Jani UD, et al. Prevalence of cataract type in relation to axial length in subjects with high myopia and emmetropia in an Indian population. Am J Ophthalmol 2008;145:176–81.
[6] Machida S, Hasegawa Y, Kondo M, et al. High prevalence of myopia in Japanese patients with idiopathic focal subretinal neovascularization. Retina 2006;26:170–5.
[7] Gwiazda J. Treatment options for myopia. Optom Vis Sci 2009;86:624–8.
[8] Gwiazda J, Hyman L, Hussein M. the COMET groupA randomized clinical trial of progressive addition lenses versus single vision lenses on the progression of myopia in children. Invest Ophthalmol Vis Sci 2003;44:1492–500.

[9] Gwiazda J, Hyman L, Norton TT. the COMET groupAccommodation and related risk factors associated with myopia progression and their interaction with treatment in COMET children. Invest Ophthalmol Vis Sci 2004;45:2143–51.
[10] Hasebe S, Ohtsuki H, Nonaka T, et al. Effect of progressive addition lenses on myopia progression in Japanese children: a prospective, randomized, double-masked, crossover trial. Invest Ophthalmol Vis Sci 2008;49:2781–9.
[11] Yang Z, Lan W, Ge J, et al. The effectiveness of progressive addition lenses on the progression of myopia in Chinese children. Ophthal Physiol Opt 2009;29:41–8.
[12] Goss D. Effect of bifocal lenses on the rate of childhood myopia progression. Am J OptomPhysiol Opt 1986;63:135–41.
[13] Brown B, Edwards MH, Leung JTM. Is esophoria a factor in slowing of myopia by progressive lenses? Optom Vis Sci 2002;79:638–42.
[14] Berntsen DA, Sinnott LT, Mutti DO, et al. A randomized trial using progressive addition lenses to evaluate theories of myopia progression in children with a high lag of accommodation. Invest Ophthalmol Vis Sci 2012;53:640–9.
[15] Correction of Myopia Evaluation Trial 2, Study Group for the Pediatric Eye Disease Investigator GroupProgressive-addition lenses versus single-vision lenses for slowing progression of myopia in children with high accommodative lag and near esophoria. Invest Ophthalmol Vis Sci 2011;52:2749–57.
[16] Smith ELIII, Hung LF, Arumugam B. Visual regulation of refractive development: insights from animal studies. Eye 2014;28:180–8.
[17] Charman WN, Radhakrishnan H. Peripheral refraction and the development of refractive error: a review. Ophthal Physiol Opt 2010;30:321–38.
[18] Berntsen DA, Barr CD, Mutti DO, et al. Peripheral defocus and myopia progression in myopic children randomly assigned to wear single vision and progressive addition lenses. Invest Ophthalmol Vis Sci 2013;54: 5761–70.
[19] Smith ELIII. Optical treatment strategies to slow myopia progression: effects of the visual extent of the optical treatment zone. Exp Eye Res 2013;114:77–88.
[20] Sankaridurg P, Holden B, Smith EIII, et al. Decrease in rate of myopia progression with a contact lens designed to reduce relative peripheral hyperopia: one-year results. Invest Ophthalmol Vis Sci 2011;52:9362–7.
[21] Jiang BC, Tea YC, O'Donnell D. Changes in accommodative and vergence responses when viewing through near addition lenses. Optometry 2007;78:129–34.
[22] Cheng D, Schmid KL, Woo GC. The effect of positive-lens addition and base-inprism on accommodation accuracy and near horizontal phoria in Chinese myopicchildren. OphthalmicPhysiol Opt 2008;28:225–37.
[23] Bao J, Wang Y, Zhuo Z, et al. Influence of progressive addition lenses on reading posture in myopic children. Br J Ophthalmol 2016;100: 1114–47.
[24] Cheng D, Schmid KL, Woo GC, et al. Randomized trial of effect of bifocal and prismatic bifocal spectacles on myopic progression: two-year results. Arch Ophthalmol 2010;128:12–9.
[25] Cheng D, Woo GC, Drobe B, et al. Effect of bifocal and prismatic bifocal spectacles on myopia progression in children: three-year results of a randomized clinical trial. JAMA Ophthalmol 2014;132:258–64.
[26] Cheng D, Schmid KL, Woo GC. The effect of positive-lens addition and base-in prism on accommodation accuracy and near horizontal phoria in Chinese myopic children. Ophthalmic Physiol Opt 2008;28: 225–37.
[27] Lan W, Yang Z, Li W, et al. A longitudinal study on the relationship between myopia development and near accommodation lag in myopic children. Ophthalmic Physiol Opt 2008;28:57–61.
[28] Berntsen DA, Sinnott LT, Mutti DO, et al. Accommodative lag and juvenile-onset myopia progression in children wearing refractive correction. Vision Res 2011;51:1039–46.
[29] Yu X, Bao J, Drobe B, et al. Comparison of near addition value prescription methods for myopic children. Optom Vis Sci 2016; 93:27–35.
[30] Curtin BJ. The Myopias: Basic Science and Clinical Management. 1985; Harper and Row, Philadelphia:36–38.
[31] Lee D. Kaiser, Dynamic randomization and a randomization model for clinical trials data. Statist Med 2012;31:3858–73.
[32] Raj PS, Villada JR, Lewis AE, et al. Comparative evaluation of the Allergan Humphrey 570 andCanon RK-1 autorefractors: I. Objective autorefraction innormal subjects. Eye 1992;6:284–6.
[33] Davies LN, Mallen EA, Wolffsohn JS, et al. Clinical evaluation of the Shin-Nippon NVision-K 5001/GrandSeiko WR-5100K autorefractor. Optom Vis Sci 2003;80:320–4.
[34] Jiang BC, Bussa S, Tea YC, et al. Optimal dioptric value of near addition lenses intended to slow myopic progression. Optom Vis Sci 2008;85: 1100–5.
[35] Gwiazda J, Thorn F, Bauer J, et al. Myopic children show insufficient accommodative response to blur. Invest Ophthalmol Vis Sci 1993; 34:690–4.
[36] Gwiazda J, Marsh-Tootle WL, Hyman L, et al. COMET Study GroupBaseline refractive and ocular component measures of children enrolled in the correction of myopia evaluation trial (COMET). Invest Ophthalmol Vis Sci 2002;43:314–21.
[37] Chen W, McAlinden C, Pesudovs K, et al. Scheimp flug-Placido topographer and optical low-coherence reflectometry biometer: repeatability and agreement. J Cataract Refract Surg 2012;38:1626–32.
[38] Thibos LN, Wheeler W, Horner D. Power vectors: an application of Fourier analysis to the description and statistical analysis of refractive error. Optom Vis Sci 1997;74:367–75.
[39] Li SM, Liu LR, Li SY, et al. the Anyang Childhood Eye Study GroupDesign, methodology and baseline data of a school based cohort study in central China: The Anyang childhood eye study. Ophthalm Epidemiol 2013;20:348–59.
[40] Hasebe S, Nonaka F, Nakatsuka C, et al. Myopia control trial with progressive addition lenses in Japanese schoolchildren: baseline measures of refraction, accommodation, and heterophoria. Jpn J Ophthalmol 2005;49:23–30.
[41] Rosenfield M, Abraham-Cohen JA. Blur sensitivity in myopes. Optom Vis Sci 1999;76:303–7.
[42] Hashemi H, Khabazkhoob M, Asharlous A, et al. Cycloplegic autorefraction versus subjective refraction: the Tehran Eye Study. Br J Ophthalmol 2016;100:1122–7.
[43] Choong YF, Chen AH, Goh PP. A comparison of autorefraction and subjective refraction with and without cycloplegia in primary school children. Am J Ophthalmol 2006;142:68–74.
[44] Zadnik K, Manny RE, Yu JA, et al. Collaborative Longitudinal Evaluation of Ethnicity and Refractive Error (CLEERE) Study Group-Ocular component data in school children as a function of age and gender. Optom Vis Sci 2003;80:226–36.
[45] Garner LF, Meng CK, Grosvenor TP, et al. Ocular dimensions and refractive power in Malay and Melanesian children. Ophthalmic Physiol Opt 1990;10:234–8.
[46] Zadnik K, Mutti DO, Fusaro RE, et al. Longitudinal evidence of crystalline lens thinning in children. Invest Ophthalmol Vis Sci 1995;36:1581–7.
[47] Li SM, Li SY, Kang MT, et al. Distribution of ocular biometry in 7- and 14-year-old Chinese children. Optom Vis Sci 2015;92:566–72.
[48] Goss DA, Jackson TW. Clinical findings before the onset of myopia in youth. I: ocular optical components. Optom Vis Sci 1995;72:870–8.
[49] Grosvenor T, Scott R. Role of the axial length/corneal radius ratio in determining the refractive state of the eye. Optom Vis Sci 1994;71:573–9.
[50] Anderson H, Stuebing KK, Fern KD, et al. Ten-year changes in fusionalvergence, phoria, and near point of convergence in myopic children. Optom Vis Sci 2011;88:1060–5.