A Randomized Clinical Trial of Progressive Addition Lenses versus Single Vision Lenses on the Progression of Myopia in Children

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PURPOSE. The purpose of the Correction of Myopia Evaluation Trial (COMET) was to evaluate the effect of progressive addition lenses (PALs) compared with single vision lenses (SVLs) on the progression of juvenile-onset myopia.

METHODS. COMET enrolled 469 children (ages 6–11 years) with myopia between −1.25 and −4.50 D spherical equivalent. The children were recruited at four colleges of optometry in the United States and were ethnically diverse. They were randomly assigned to receive either PALs with a +2.00 addition ($n = 235$) or SVLs ($n = 234$), the conventional spectacle treatment for myopia, and were followed for 3 years. The primary outcome measure was progression of myopia, as determined by autorefraction after cycloplegia with 2 drops of 1% tropicamide at each annual visit. The secondary outcome measure was change in axial length of the eyes, as assessed by A-scan ultrasonography. Child-based analyses (i.e., the mean of the two eyes) were used. Results were adjusted for important covariates, by using multiple linear regression.

RESULTS. Of the 469 children (mean age at baseline, 9.3 ± 1.3 years), 462 (98.5%) completed the 3-year visit. Mean (±SE) 3-year increases in myopia (spherical equivalent) were −1.28 ± 0.06 D in the PAL group and −1.48 ± 0.06 D in the SVL group. The 3-year difference in progression of 0.20 ± 0.08 D between the two groups was statistically significant ($P = 0.004$). The treatment effect was observed primarily in the first year. The number of prescription changes differed significantly by treatment group only in the first year. At 6 months, 17% of the PAL group versus 30% of the SVL group needed a prescription change ($P = 0.0007$), and, at 1 year, 43% of the PAL group versus 59% of the SVL group required a prescription change ($P = 0.002$). Interaction analyses identified a significantly larger treatment effect of PALs in children with lower versus higher baseline accommodative response at near ($P = 0.03$) and with lower versus higher baseline myopia ($P = 0.04$). Mean (± SE) increases in the axial length of eyes of children in the PAL and SVL groups, respectively, were: 0.64 ± 0.02 mm and 0.75 ± 0.02 mm, with a statistically significant 3-year mean difference of 0.11 ± 0.03 mm ($P = 0.0002$). Mean changes in axial length correlated with those in refractive error ($r = 0.86$ for PAL and 0.89 for SVL).

CONCLUSIONS. Use of PALs compared with SVLs slowed the progression of myopia in COMET children by a small, statistically significant amount only during the first year. The size of the treatment effect remained similar and significant for the next 2 years. The results provide some support for the COMET rationale—that is, a role for defocus in progression of myopia. The small magnitude of the effect does not warrant a change in clinical practice. (*Invest Ophthalmol Vis Sci.* 2003;44: 1492–1500) DOI:10.1167/iovs.02-0816

Myopia is a significant public health problem that affects at least 25% of adults in the United States[1] and a much higher percentage of people in Asia.[2] It is a predisposing factor for retinal detachment, myopic retinopathy, and glaucoma, thus contributing to loss of vision and blindness. As might be expected for such a prevalent condition, treatment costs are high, with annual estimates in the United States for eye examinations and correction by spectacles and contact lenses ranging from $2.5 to $4.6 billion.[3] If interventions to retard the progression of myopia are successful, these costs should be reduced.

At present, the mechanisms involved in the etiology of myopia are unclear, and methods for prevention are unproven. Even without a sound scientific rationale, many options for slowing the progression of myopia have been evaluated. Most of the intervention studies have had methodological limitations, such as unmasked examiners and nonrandom assignment to treatment groups. Results of most previous studies in which lenses, mainly bifocals, were used have been equivocal or have applied to restricted populations. Recently, the use of bifocals in children with near-point esophoria was reported to slow progression of myopia by 0.25 D over 30 months, compared with children randomized to SVLs.[4] PALs, sometimes referred to as no-line bifocals or multifocal lenses, have been reported to slow significantly the progression of myopia by approximately 0.50 D after 2 years in one study of 80 Chinese children,[5] but not in two other studies of Chinese children.[6,7] The mean difference in progression after 18 months was 0.21 D in 217 children in Taiwan[6] and was 0.14 D after 2 years of follow-up in 254 children in Hong Kong.[7]

The Correction of Myopia Evaluation Trial (COMET) is a National Eye Institute/National Institutes of Health–supported multicenter clinical trial designed to evaluate whether PALs

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Table 1. Inclusion Criteria

Ages 6 to 11 years inclusive at baseline
Refractive criteria determined by cycloplegic autorefraction
  Spherical equivalent: between -4.5 D and -1.25 D inclusive in
    both eyes
  Astigmatism: ≤ 1.50 D in either eye
  Anisometropia ≤ 1.0 D (spherical equivalent between eyes)
Visual acuity (with distance correction): 0.20 logMAR units or better
    (Snellen equivalent 20/32)
No strabismus by cover test at far (4 m) or near (33 cm) wearing
    distance correction, or at 33 cm wearing $+2.0$ over distance
    correction.
Birth weight ≥ 1250 g
No known ocular, systemic, or neurodevelopmental condition that
    might affect refractive development
No use of medications that might affect refractive development
No prior wear of progressive addition or bifocal lenses
No prior wear of contact lenses

slow the rate of progression of juvenile-onset myopia when compared with conventional correction with SVLs. The rationale for COMET was based on reports in animal and human studies suggesting that increased retinal defocus is a factor in the pathogenesis of myopia.[8–10] Many studies have documented that the eyes of animals exposed to continuous retinal defocus become myopic.[8,9] In humans, high accommodative lag at near has been associated with myopia.[10,11] Insufficient accommodation when children are engaged in near-work activities may result in retinal defocus, and accurate accommodation may be critical to reduce excessive defocus and thus slow axial elongation.[10] One of the major unknowns is how much defocus must occur and over what period, to stimulate eyes to elongate. Providing children who have myopia with lenses that produce clear vision over a range of viewing distances from near to far, as PALs do, could reduce defocus and slow the progression of myopia.

This report presents 3-year outcome measurements of refractive error and ocular components from children enrolled in the COMET and randomized to either PALs or SVLs.

Methods

Details of the study design and demographic characteristics of the study population have been presented previously and are briefly summarized herein.[12,13] Four clinical centers located at schools and colleges of optometry in Birmingham, Alabama; Boston, Massachusetts; Houston, Texas; and Philadelphia, Pennsylvania, enrolled 469 children between September 1997 and September 1998, and took measurements from them for at least 3 years. Children enrolled in COMET met the inclusion criteria listed in Table 1. Before the baseline examination, children and parents agreed to accept either SVLs or PALs as assigned by the randomization scheme, attend follow-up appointments semiannually for at least 3 years, and refrain from wearing contact lenses throughout the study. Children agreed to wear their COMET glasses during all waking hours. The COMET study and protocols conform to the tenets of the Declaration of Helsinki. The institutional review boards of each participating center approved the research protocols. Informed consent (parents) and assent (children) were obtained after verbal and written explanation of the nature and possible consequences of the study.

Study Design

Study Organization. COMET represents a collaborative effort involving a Study Chair, a Coordinating Center, four Clinical Centers, and the National Eye Institute (see Appendix). Three committees (Executive, Steering, and Full Investigator) composed of study investigators provided leadership to the study and reviewed its progress

regularly. Overall study performance and child safety were reviewed by a Data and Safety Monitoring Committee (DSMC).

Intervention. Myopia in children was corrected either with SVLs (the standard treatment) or PALs (Varilux Comfort lenses with a $+2.00$ D addition; Essilor of America, St. Petersburg, FL). This add power was chosen because it was shown to be more effective than $+1.50$ D in slowing progression of myopia in a study by Leung and Brown,[5] and because in pilot testing it brought the focal plane of children with myopia, who often show accommodative insufficiency, to the plane of the test target (0.33 m). All lenses were polycarbonate. PALs were fitted with the top of the channel, 4.0 mm above the pupil, allowing at least 11 mm for distance vision.[14] The fitting protocol was designed to encourage the children to use the near-addition portion of the lenses, because unlike adults with presbyopia, for whom the glasses are typically prescribed, children can accommodate and thus have no need for a near addition for close work.

Randomization. Children were randomized to either PALs or SVLs. The randomization scheme was stratified by clinical center, using a random permuted block design. Randomization assignments were allocated centrally by the coordinating center after eligibility criteria were verified. A child was considered to be enrolled in COMET once the randomization assignment and study number were issued and the child received the assigned lenses.

Masking. Several steps were taken to preserve and monitor masking of study optometrists who collected outcome data. The following highlights the main measures, which have been reported previously.[12,13] Study optometrists did not know the lens assignments; therefore, parents and children were told not to discuss any issues related to the study glasses with the COMET optometrists and not to wear study glasses in their presence. A consulting optometrist, with knowledge of lens assignment and not involved with collection of outcome data, was available to handle any issues regarding visual symptoms or child safety that could lead to unmasking of the study optometrists. An effort was made to mask children and parents by having all lenses fit as though they were PALs and providing uniform wearing instructions based on PALs.

Procedures. Cycloplegic autorefraction was used to assess progression of myopia, the primary outcome measure. As with all data-collection procedures, autorefraction was performed in both eyes by experienced optometrists who were trained and certified on study protocols (Hyman L, Hussein M, Gwiazda J, and the COMET Study Group, ARVO Abstract 4348, 1998). An autorefractor/autokeratometer (ARK 700A; Nidek, Gamagori, Japan) was used to take five consecutive reliable readings, both before and after cycloplegia. The cycloplegic agent was 2 drops of 1% tropicamide, administered 4 to 6 minutes apart, after corneal anesthesia was obtained with either proparacaine or benoxinate. The COMET protocol specified that cycloplegic autorefraction measures be taken 30 minutes after administration of the second drop of 1% tropicamide. Tropicamide (1%) was found to be an effective cycloplegic agent in this group of children with myopia, as documented by residual accommodation measurements taken at baseline by autorefractor (model R-1; Canon USA, Lake Success, NY).[15]

After cycloplegic autorefraction, ocular component dimensions (anterior chamber depth, lens thickness, vitreous chamber depth, and overall axial length [AL]) were measured by ultrasonography (A-2500; Sonomed, Lake Success, NY). Five individual measures were attempted per eye, with at least three measures per eye necessary to qualify for inclusion in the study. Five measures were obtained for 96% of eyes at all visits.

Subjective refraction was completed before cycloplegia according to a standard protocol.[12,13] At baseline, all children received new glasses based on the distance prescription. At follow-up visits they received new glasses if their myopia correction, determined by subjective refraction, had increased by at least 0.50 D spherical equivalent from their current prescription in at least one eye. Smaller prescription changes were made if clinically indicated.

Sample Size and Power. A sample of 450 children was selected, based on detecting a projected 33% reduction in the amount of progression among the PAL versus the SVL group, assuming that the SVL group would progress by a mean of 1.50 D (SD 1.10–1.35 D) after 3 years. This estimate was also based on using a two-sided 1% α level to achieve 84% power, allowing for 20% attrition.

Outcome Measures

The primary outcome for COMET was progression of myopia, defined as the change in spherical equivalent refractive error (SER) relative to baseline (a continuous measure). A summary measure of SER was calculated for each of the five autorefraction measurements per eye, and the mean of the five SER measures was then computed. Progression of myopia was analyzed by expressing refractive error as three components: M (spherical equivalent), J_0 (dioptric power of a Jackson cross cylinder at axis 0°), and J_{45} (dioptric power of a Jackson cross cylinder at axis 45°), as determined by Fourier decomposition.[16] Because oblique astigmatism is often mirror symmetric in the two eyes, the average J_{45} values were calculated by transforming the axis values between 91° and 180° to values between 0° and 90° for each eye and then averaging them between the two eyes. The secondary outcome for COMET was change in AL during follow-up relative to baseline measured by A-scan ultrasonography. Before the beginning of data collection, study examiners showed good consistency of both autorefractor and AL measurements with those of a gold standard examiner.[17]

Additional Measures

The study design also included an evaluation of changes in ocular components (i.e., anterior chamber depth, lens thickness, and vitreous chamber depth), by A-scan ultrasonography. Corneal curvature was measured using the keratometry setting of the autorefractor (Nidek). Accommodation at near (33 cm) and far (4.0 m) and concomitant measures of phoria were taken using the autorefractor (Canon R-1), with an attached motorized Risley prism operated by the child. Phoria at near and far also was measured, with the cover test. These procedures have been described in detail.[12,13]

Three measurements of each child's normal reading distance for standardized age-appropriate text were taken by the opticians at each visit. The protocol called for measurement from the child's eye to the page of a book with a tape measure marked in inches. Additional data collected at the annual visits included an assessment of adherence to the use of COMET glasses based on both children's and parents' answers to a questionnaire administered separately and monitoring of child safety.

Statistical Analyses

The balance of baseline clinical and demographic characteristics between the two treatment groups was evaluated by *t*-tests or the Wilcoxon test for continuous variables and the χ^2 test or the Fisher exact test for categorical variables. Follow-up data were analyzed by applying an intent-to-treat principle according to the child's original lens assignment and the last known value of the outcome measures. For the seven children lost to follow-up and thus without data at the third annual visit, progression information from the latest follow-up visit was used.

The primary analysis for progression of myopia in COMET was child based, using the average of both eyes to evaluate the magnitude of change in SER between follow-up and baseline (Pearson correlation coefficient between the eyes at 3 years = 0.90). The analytic strategy was similar for SER and AL. Univariate analyses were conducted to guide the selection of variables to be included in subsequent multivariate analyses for the overall treatment effect. These analyses used general linear modeling of the multiple linear regression approach,[18] to allow adjustment of the potentially most prognostic covariates: age, gender, ethnicity, baseline refractive error, axial length, accommodative response, and phoria, all chosen because of their known relationship to progression of myopia. In addition, interaction analyses adjusting for multiple comparisons were conducted, using specific macros

(developed in SAS software; SAS, Inc., Cary, NC) to obtain preliminary estimates of a possible differential effect of PALs among categories of these selected covariates. The unadjusted and adjusted annual rates of change were calculated for each year of follow-up. Linear modeling techniques were used to evaluate the association between changes in SER and AL.

RESULTS

Four hundred sixty-nine children were enrolled in COMET, with 235 randomized to PALs and 234 to SVLs, as shown in Figure 1. Each of the four clinical centers enrolled between 108 and 133 children. Three-year retention was excellent, with only seven children, six in the PAL group and one in the SVL group, who did not return for the 3-year visit. Two children changed lens assignments, both from SVLs to PALs, due to binocular vision problems. Of 2939 possible study visits of the children with 3-year visits, only 10 (4 in the PAL group and 6 in the SVL group) were missed. Baseline characteristics were balanced, with no statistically significant differences between treatment groups, as shown in Table 2.

Primary Outcome

At baseline the SER was the same in the two treatment groups. Mean change in SER and astigmatism (J_0 and J_{45}) at each annual visit is plotted in Figure 2. The difference in progression of myopia between the PAL and SVL groups occurred in the first year, as illustrated by the dashed lines in Figure 2a. The treatment effect based on the adjusted (for age, gender, ethnicity, baseline SER, accommodative response, and near point phoria) annual rate of change between baseline and 1 year was 0.18 D ($P < 0.0001$). This difference persisted but did not increase over the next 2 years, with the mean difference in the change between treatment groups from year 1 to year 2 equal to 0.04 D and from year 2 to year 3 equal to −0.02 D. The addition of these three annual differences resulted in an adjusted 3-year treatment effect of 0.20 ± 0.08 D, which is statistically significant (95% confidence interval [CI]: 0.06–0.33; $P = 0.004$).

J_0, which was close to zero in both groups at baseline, increased at each annual visit. Figure 2b shows that the change in the first year was slight, but significantly greater in the SVL than the PAL group (mean difference = 0.04 D, $P = 0.002$). This difference was maintained in the second year (mean difference = 0.04, $P = 0.05$), but not at 3 years (difference = 0.01, $P = 0.74$). As shown in Figure 2c, the change in J_{45} in children in both the PAL and SVL groups was close to zero at all annual visits. Overall, the mean amount of astigmatism increased by slightly more than 0.25 D over 3 years, with no significant difference between treatment groups.

Table 3 presents the adjusted 3-year mean progression rates for both treatment groups and the corresponding adjusted mean differences for each baseline characteristic in the table. Significant differences between treatment groups were observed in children with lower baseline myopia (0.30 ± 0.11 D; 95% CI: 0.04–0.55; $P = 0.0097$) and lower baseline accommodative response (0.33 ± 0.11 D; 95% CI: 0.07–0.58; $P = 0.005$). Table 3 also shows that the 3-year adjusted SER increased from baseline by 1.28 ± 0.06 D in the PAL group and 1.48 ± 0.06 D in the SVL group, resulting in the overall adjusted 3-year treatment effect of 0.20 D.

Interaction analyses were conducted to identify whether the treatment effect differed within any of the baseline characteristics included in Table 3 (e.g., was there a greater treatment effect in children with lower versus higher baseline accommodative response?). A significant interaction was found between treatment and baseline accommodative response, with the treatment found to be more effective by 0.26 D ($P =$
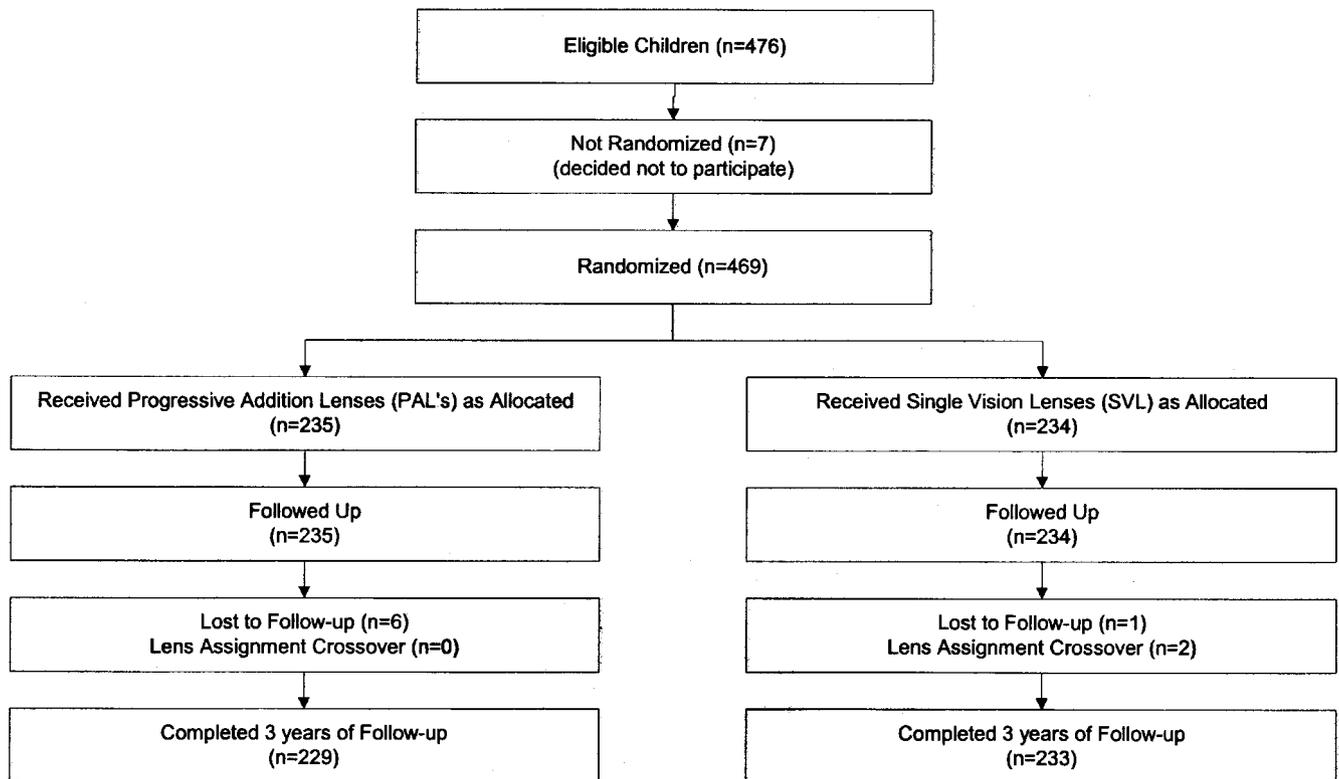
FIGURE 1. Participant flow and randomization assignment of COMET children.

0.03) in children with lower versus higher accommodative response. There was also a significant interaction between treatment and baseline myopia, with the treatment more effective by 0.20 D ($P = 0.04$) in children with lower versus higher myopia.

Progression is presented in Figure 3 for baseline myopia and accommodative response, the only factors that showed statistically significant interactions with treatment. The unadjusted mean progression of myopia in the PAL and SVL groups is plotted for lower (Fig. 3a) and higher (Fig. 3b) baseline myo-

pia, and lower (Fig. 3c) and higher (Fig. 3d) baseline near accommodative response. At each annual visit, the difference between treatment groups was larger in children with lower than in those with higher baseline myopia, with a 3-year difference of 0.32 ± 0.11 D in children with lower baseline myopia and 0.07 ± 0.10 D in those with higher myopia. Similarly, at each annual visit the difference between treatment groups was larger for children with lower compared with higher accommodative response, with a 3-year difference of 0.34 ± 0.11 D in the lower accommodative response group and 0.02 ± 0.10 D in the higher accommodative response group.

TABLE 2. General Baseline Characteristics of COMET Children by Study Group

| Characteristic/Variable	PAL Children (*n* = 235)		SVL Children (*n* = 234)		*P*
	%	Mean ± SD	%	Mean ± SD	
Gender					
Female	52		53		0.85
Ethnicity					
White	46		47		0.75
African American	26		26		
Hispanic	14		15		
Asian	9		6		
Mixed/Other	5		6		
Age (y)		9.3 ± 1.30		9.4 ± 1.30	0.63
Cycloplegic autorefraction (D)					
Spherical equivalent		−2.40 ± 0.75		−2.37 ± 0.84	0.38
J_0		0.03 ± 0.25		0.05 ± 0.24	0.51
J_{45}		−0.02 ± 0.07		0.00 ± 0.08	0.15
Axial length (mm)		24.10 ± 0.72		24.14 ± 0.72	0.56
Accommodative response at near (D)		2.47 ± 0.67		2.48 ± 0.60	0.91
Phoria at near (PD)		1.86 ± 6.49		2.57 ± 6.88	0.25
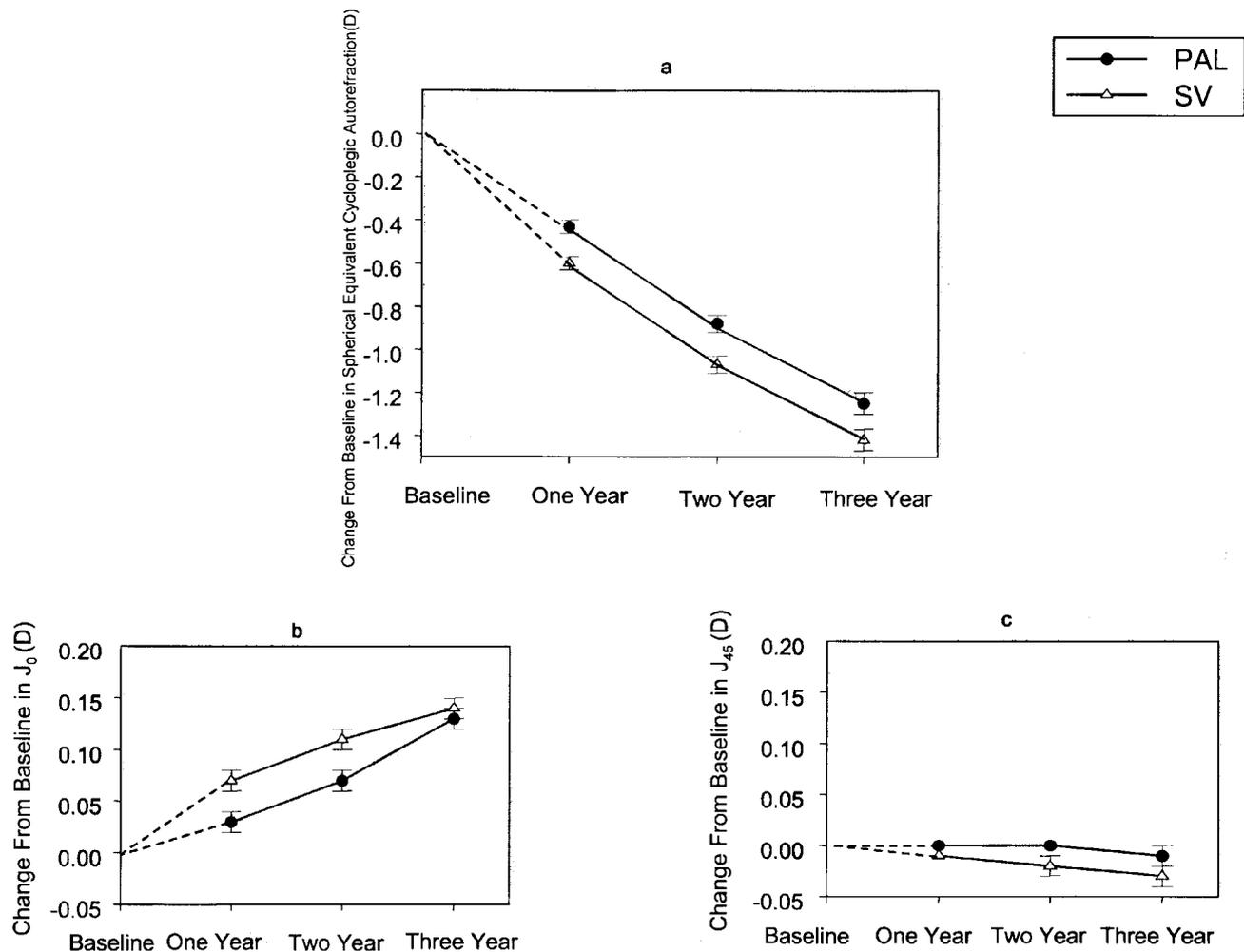
FIGURE 2. Mean change in (a) spherical equivalent refractive error (M), (b) J_0, and (c) J_{45} at each annual visit in the PAL and SVL groups. *Dashed lines* are included for illustrative purposes to demonstrate the similarity of the two treatment groups at baseline. Error bars, SE.

In a separate analysis, the treatment effect was found to be larger in children with a reading distance closer than the median of 12 in. In this group, the mean difference in progression of myopia between the PAL and the SVL groups was 0.22 D at 1 year ($P < 0.0001$), 0.26 D at 2 years ($P = 0.002$), and 0.23 D at 3 years ($P = 0.03$). In the group with reading distances greater than 12 in., the treatment effect was 0.11 D ($P < 0.01$), 0.15 D ($P = 0.03$), and 0.13 D (NS) for each year, respectively. As with the other measurements, the main effect was observed in the first year.

Consistent with the overall treatment effect occurring in the first year, the number of prescription changes also differed significantly by treatment group at both the 6-month and 1-year visits. At 6 months 17% of the PAL group versus 30% of the SVL group required one change in prescription, a statistically significant difference ($P = 0.0007$). At 1 year, the pattern was similar and also statistically significant ($P = 0.002$), with 43% of the PAL group versus 59% of the SVL group requiring a prescription change. At 3 years, however, there was no statistically significant difference in the number of prescription changes between treatment groups. Overall, 86% of the PAL group versus 91% of the SVL group had at least one prescription change.

Secondary Outcome

The adjusted mean AL increased from baseline to 3 years by 0.64 ± 0.02 mm in the PAL group and 0.75 ± 0.02 mm in the SVL group, resulting in an overall adjusted 3-year treatment effect of -0.11 ± 0.03 mm ($P = 0.0002$; 95% CI: -0.16 to -0.05). Figure 4 shows mean increases in the AL of eyes of children in the PAL and SVL groups at each annual visit. The mean change in AL was greater in the SVL group at the first annual visit, and the magnitude of the difference between groups increased through the second year. The adjusted annual rate of change showed a statistically significant benefit of PALs versus SVLs from baseline to the first year (difference = -0.07 ± 0.02 mm; $P < 0.001$) and a reduced but still significant effect between the first and second years (difference = -0.03 ± 0.01 mm; $P = 0.022$). No additional treatment benefit occurred between the second and third years (-0.01 ± 0.01 mm; $P = 0.34$).

Progression and treatment effects for AL varied within some baseline characteristics, similar to those reported in Table 3 for SER. Significant differences between treatment groups were observed in children with baseline characteristics of low myopia (-0.15 ± 0.05 mm, 95% CI: -0.25 to -0.04), lower accommodative response (-0.18 ± 0.05 mm; 95% CI: -0.28 to -0.07), orthophoria by cover test (-0.16 ± 0.05 mm; 95% CI: -0.28 to -0.03), and in girls (-0.12 ± 0.04 mm; 95% CI: -0.22 to -0.01). Results of phoria measurements by the Maddox rod-Risley prism were similar to those reported for both AL and SER in the cover test. Interaction analyses revealed a statistically significant interaction between treatment and baseline accommodative response, with the treatment more effec-

TABLE 3. Adjusted 3-Year Myopia Progression and Mean Difference between Study Groups by Baseline Characteristics

Baseline Characteristics	PAL		SVL		Difference ± SE†	Simultaneous 95% CI
	n	Adjusted Mean ± SE*	*n*	Adjusted Mean ± SE*		
Age (years)						
6–9	120	−1.59 ± 0.08	112	−1.78 ± 0.08	0.19 ± 0.11	(−0.06 to 0.45)
10–11	115	−0.97 ± 0.08	122	−1.17 ± 0.08	0.20 ± 0.11	(−0.05 to 0.46)
Gender						
Male	113	−1.18 ± 0.08	110	−1.39 ± 0.08	0.21 ± 0.11	(−0.05 to 0.47)
Female	122	−1.38 ± 0.07	124	−1.57 ± 0.08	0.19 ± 0.11	(−0.06 to 0.44)
Ethnicity						
Asian	22	−1.22 ± 0.16	14	−1.61 ± 0.20	0.39 ± 0.26	(−0.41 to 1.19)
African American	62	−0.96 ± 0.10	61	−1.27 ± 0.10	0.31 ± 0.14	(−0.12 to 0.73)
Hispanic	33	−1.51 ± 0.13	35	−1.39 ± 0.13	−0.12 ± 0.18	(−0.69 to 0.44)
White	107	−1.27 ± 0.08	111	−1.49 ± 0.07	0.22 ± 0.11	(−0.10 to 0.53)
Mixed	11	−1.50 ± 0.23	13	−1.64 ± 0.21	0.14 ± 0.31	(−0.83 to 1.10)
Cycloplegic autorefraction (D)§						
Less myopia (≥ −2.25)	109	−1.17 ± 0.08	127	−1.47 ± 0.08	0.30 ± 0.11	(0.04 to 0.55)‖
More myopia (< −2.25)	126	−1.38 ± 0.07	107	−1.48 ± 0.08	0.10 ± 0.11	(−0.15 to 0.36)
Accommodative response to 3 D demand (D)§						
Low (≤2.57)	115	−1.27 ± 0.08	119	−1.60 ± 0.08	0.33 ± 0.11	(0.07 to 0.58)‖
High (≥ 2.57)	120	−1.28 ± 0.08	115	−1.36 ± 0.08	0.07 ± 0.11	(−0.18 to 0.33)
Baseline near point (33 cm) Phoria (Δ) (cover test)						
Exo (≤2)	45	−1.43 ± 0.11	37	−1.38 ± 0.13	−0.05 ± 0.17	(−0.52 to 0.43)
Ortho (−1 to 1)	93	−1.27 ± 0.09	108	−1.57 ± 0.08	0.30 ± 0.12	(0.00 to 0.60)
Eso (≥2)	97	−1.18 ± 0.08	89	−1.39 ± 0.09	0.20 ± 0.12	(−0.11 to 0.52)
Overall	235	−1.28 ± 0.06	234	−1.48 ± 0.06	0.20 ± 0.08	(0.06 to 0.33)

    *Adjusted for all other covariates presented in this table.
    † (PAL − SVL).
    ‡ Adjusted for multiple comparison and interaction.
    § Statistically significant treatment effect ($P < 0.01$).
    ‖ Statistically significant interaction ($P < 0.05$).

tive by 0.14 mm ($P = 0.03$) in children with lower versus higher accommodative response. Overall, the Pearson correlation coefficient between the change in AL and the change in SER was 0.86 in the PAL group and 0.89 in the SVL group.

Mean (±SD) 3-year changes in ocular component measurements in the eyes of children in the PAL and SVL groups, respectively, were 0.06 ± 0.11 and 0.07 ± 0.09 mm (anterior chamber), −0.01 ± 0.10 and −0.01 ± 0.08 mm (lens thickness), and 0.56 ± 0.33 and 0.65 ± 0.34 mm (vitreous chamber). The 3-year difference in vitreous chamber depth was significant between groups (difference = −0.09 ± 0.03 mm, 95% CI: −0.15 to −0.03; $P = 0.002$), but the differences in lens thickness and anterior chamber depth were not significant. Mean (±SD) changes in corneal radii were 0.03 ± 0.03 D in the PAL group and 0.03 ± 0.07 D in the SVL group in the horizontal meridian, and −0.01 ± 0.05 D in the PAL group and −0.01 ± 0.05 D in the SVL group in the vertical meridian. These values did not differ by treatment group.

Adherence and Masking

Self-reported adherence to wearing glasses was excellent, as assessed by answers to questionnaires administered separately to both children and parents at all visits. The number of children and parents responding to the questions varied slightly at each visit. Overall, at any visit, at least 211 (93%) of 229 of the PAL group and 224 (96%) of 234 of the SVL group reported wearing their glasses most or all the time. Parental reports of adherence were similar.

Masking of study optometrists regarding treatment assignment was preserved for most children (464/469; 99%) during the 3 years of follow-up, with unmasking being slightly more frequent in the PAL (4/235; 1.7%) than in the SVL group (1/234; 0.04%).

Data on the success of masking children and parents regarding their lens assignment will be collected when they are informed of the study results.

Safety Outcomes

No serious adverse events were reported during the 3 years of COMET. Protocol deviations occurred relatively infrequently and included children wearing the wrong glasses or contact lenses and the PAL group being given frames that did not meet the fitting protocol.

DISCUSSION

Synopsis

The COMET results demonstrate a statistically significant 3-year treatment effect of PALs ($P = 0.004$), with an adjusted mean difference in 3-year SER between the PAL and the SVL group of 0.20 D, which occurred in the first year. This difference is not clinically significant, suggesting that PALs should not be routinely prescribed for children with myopia as is common in some practices. The projected overall benefit in the PAL versus the SVL group in the design of COMET was 33%, yet the observed overall benefit, although statistically significant, was 14%. Changes in AL between the PAL and SVL groups were similar to those in SER, and the progression of myopia was highly correlated with changes in AL.

Possible Mechanisms

Although the mechanism regulating eye growth is poorly understood at present, the current data provide clues on the possible involvement of active and passive models (i.e., the roles of defocus and lens thinning), two of the prominent
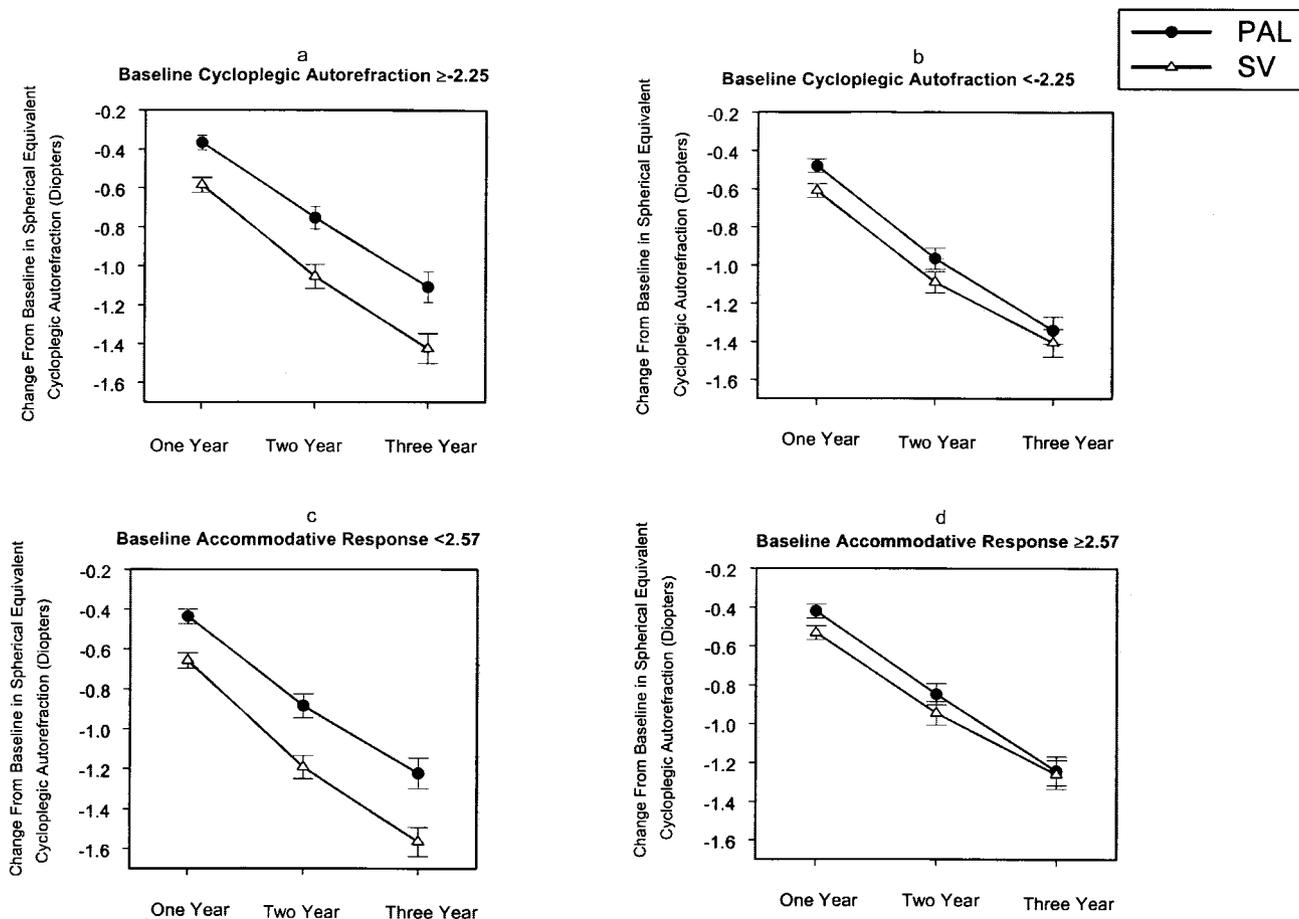
FIGURE 3. Mean progression of myopia in the PAL and SVL groups for two of the covariates, baseline myopia (**a, b**) and baseline accommodative response (**c, d**). Error bars, SE.

hypotheses proposed to account for human myopia. The difference between treatment groups in both SER and AL was larger in children with poorer accommodative response and lower amounts of myopia at baseline. An additional exploratory analysis combining these two significant covariates showed a 3-year treatment effect of PALs of 0.55 D in children

with both poor accommodative response and low baseline myopia. These results suggest a possible role for defocus in human myopia, consistent with the rationale for COMET. Retinal defocus resulting from insufficient accommodation when children with recent onset of myopia are engaged in close work may be a stimulus for increased axial elongation leading

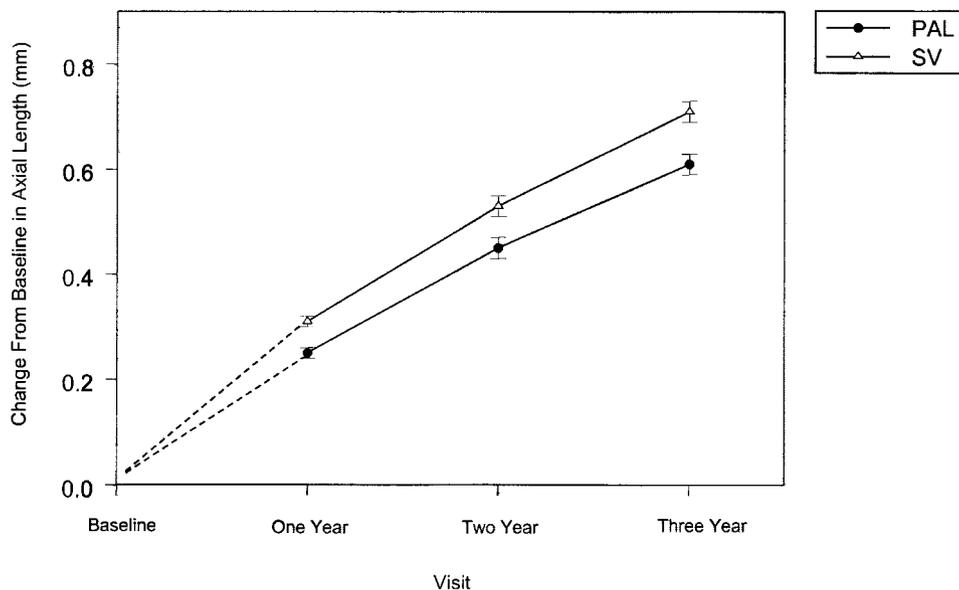**FIGURE 4.** Mean increases in the axial length of eyes of children in the PAL and SVL groups at each annual visit. *Dashed lines* are included for illustrative purposes, to show the similarity of the two treatment groups at baseline. Error bars, SE.

to myopia, similar to animal models. The larger treatment effect found in children with a closer reading distance and a preliminary analysis suggesting that the treatment effect was larger in children with more hours of weekly near work are also consistent with this hypothesis. A recent model suggests that the interaction of accommodative response, the target's closeness, and time spent in near viewing could be important factors in determining whether eyes become myopic or whether extant myopia progresses.[19]

Lens thinning cannot account for the differential progression of myopia in the two treatment groups; we found no evidence of lens thinning in COMET children during the 3 years of follow-up. This finding was unexpected, given the reports of crystalline lens-thinning between 6 and 10 years of age in a sample of children most of whom did not have myopia.[20] This does not support a role for crystalline-lens–based interactions with eye growth in children with myopia.

One factor that has not been investigated in COMET but could be related to the size of the treatment effect is familial myopia. There is good evidence suggesting that myopia, especially high myopia, may be inherited.[21-23] Most persons with myopia, including COMET children, have a moderate refractive error that is probably the result of a combination of genetic and environmental influences. Whether the effectiveness of an intervention that manipulates the visual environment is associated with familial myopia remains to be determined.

For both of COMET's outcome measures, the treatment effect occurred in the first year. There are several possible reasons that PALs slowed progression of myopia more than SVLs during the first year. One is that there may be limitations on the ability of an environmental intervention to restrain progression, and these limitations may be exceeded after 1 year. To the extent that genetic and environmental factors are involved in development of myopia, PALs or other potential treatments may be able to affect progression by only a certain amount. If PALs reduce defocus, the mechanism may not be straightforward. It is known that ocular aberrations are larger in eyes with more myopia and that higher-order aberrations cannot be corrected with conventional spectacles.[24,25] Also, aberrations inherent in spectacles increase with minus lens power. After 1 year, some children in the PAL group may have reached a level of myopia such that the reduction in defocus during near work produced by the PALs was counteracted by increased defocus from other sources.

Comparison with Other Studies

Several recent studies also have evaluated whether spectacle interventions (bifocals or PALs versus SVLs) can slow the progression of myopia. The size of the treatment effect in COMET is similar to that reported in other studies, ranging from slightly less than 0.25 D in COMET (and in Refs. 4,6,7) to slightly more than 0.50 D.[5] The other studies had some methodological limitations, including unmasked examiners and a relatively small sample size,[5] high losses to follow-up unevenly distributed across treatment groups,[6] and inadequate statistical analysis of the data.[7] Even with limitations and with differences in study design, the similar magnitude of the treatment effect across studies suggests that a spectacle lens intervention may have a limited effect. The early effect of an intervention to slow myopia is not restricted to COMET, although to our knowledge it has not been addressed previously. Other reports of an effect occurring in the first 6 to 12 months include recent investigations of PALs,[7] atropine plus PALs,[6] and RGP contact lenses.[26] This result is important for guiding future myopia interventions and has implications for mechanisms of myopia pathogenesis, as has been discussed.

Strengths and Weaknesses

An evaluation of COMET results should consider methodologic strengths of the trial. COMET recruited an ethnically diverse group of children with moderate myopia from four different geographic locations, suggesting generalizability of the results. COMET had outstanding retention of children, with only 7 of 469 children lost to follow-up by the 3-year visit, resulting in complete ascertainment of the study outcomes on 98% of enrolled children. Balance by lens assignment was found at baseline in all critical study measures. The protocol provided standardization of key outcome measures across clinical centers and was designed to maintain masking of treating clinicians and family members. Very few examiners became aware of a child's lens assignment. Study personnel were certified according to a standard protocol before collecting data. Reliability of the outcome measurements, monitored throughout the trial, was high. There were no serious adverse events and very few protocol deviations.

A weakness is that COMET was not powered to look for differences in progression of myopia between the PAL and the SVL groups by ethnicity. In addition, aside from white children who were represented at all four centers, most of the children in the other ethnic groups were clustered at one or two clinical centers, making it difficult to separate ethnic from possible center differences. Future multiethnic investigations should ensure adequate representation of each ethnic group at each center.

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Appendix

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