Role of Parental Myopia in the Progression of Myopia and Its Interaction with Treatment in COMET Children

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Purpose. The present study investigated the relationship between parental refractive error and myopia progression in their offspring and the interaction between parental ametropia and the effects of wearing progressive-addition (PALs) or single-vision (SVLs) lenses on the progression of myopia in children enrolled in the Correction of Myopia Evaluation Trial (COMET).

Methods. The progression of myopia in a subset of COMET children ($N = 232$; 49% of initial group) was defined as the difference in mean spherical equivalent refraction of both eyes obtained by cycloplegic autorefraction between the baseline and 5-year visit. Parental refractions were obtained by noncycloplegic autorefraction (81%) or from recent eye examination records (19%).

Results. The number of myopic parents (mean spherical equivalent refraction ≤ -0.75 D) was directly related to myopia progression among children wearing SVLs: myopia in children with no (zero) myopic parents progressed (mean ± SE) -1.81 ± 0.18 D and with one myopic parent, -2.04 ± 0.13) D; these amounts were significantly less than the progression of children with two myopic parents (-2.59 ± 0.19 D). In the PAL group, progression was not significantly related to the number of myopic parents and was -2.01 D overall. Among children with two myopic parents, progression was -2.00 D in the PAL group, significantly less than the progression of children wearing SVLs ($P = 0.03$). Among children with zero or one myopic parent, progression did not differ significantly between the lens groups. When the data were adjusted for covariates, the interaction between treatment effect and number of myopic parents was significant ($P = 0.01$). Over the 5-year study period, axial length increased 0.93 ± 0.07 mm in children with two myopic parents wearing PALs and 1.18 ± 0.07 mm in children with two myopic parents wearing SVLs ($P = 0.01$). The axial length increase in children wearing SVLs and with two myopic parents was significantly more than the 0.89 ± 0.07 mm increase in children wearing SVLs and with zero myopic parents ($P = 0.015$).

Conclusions. Parental refraction was related to myopia progression and changes in axial length. Among COMET children with two myopic parents, myopia progression and increases in axial length were slower in the group wearing PALs than in those wearing SVLs, by a statistically significant but clinically minor amount. Because this study was ancillary to COMET and the present analyses are based on a subset of participants, conclusions must be regarded as suggestive. (*Invest Ophthalmol Vis Sci.* 2007;48:562–570) DOI:10.1167/iovs.06-0408

As myopia in school children has achieved the status of a significant public health problem both in urban communities in East Asia[1,2] and the United States,[3,4] a great deal of interest has focused on identifying factors that predict who will and who will not become myopic.[3,5] Several studies have shown that parental myopia is one of the significant risk factors for juvenile onset myopia.[6–9] In particular, the odds of becoming myopic are about six times greater in children with two myopic parents than in children with only one or no myopic parents.[3,10]

To our knowledge, only one published paper (by Saw et al.[11]) has reported an association between parental myopia and the progression of myopia. Saw et al. found a positive relationship between the number of myopic parents and the rate of myopia progression in school children in Singapore. Children with no myopic parents had an average progression rate of 0.42 D per year, whereas those with one or two myopic parents had a significantly higher rate of progression (0.63 D per year), suggesting that parental myopia had a "dose-effect" relationship to myopia progression in their offspring. Furthermore, the myopia of children with two parents reporting high myopia (≥6.0 D) progressed faster than any of the other subgroups in the study. Parental myopia, including the presence of high myopia, was assessed by interview. Autorefraction readings were not performed on the majority of the family members, and no findings from the measurements that were taken were reported.

Like Saw et al.[11] others [8,12] have relied on questionnaires rather than direct measurement to ascertain parental myopia; in particular, these studies considered parents to be myopic if they needed glasses to see far away and if glasses were first prescribed at younger than 16 years of age. Although the validity of these questions has been reported,[13] their specificity and sensitivity were only 0.76 and 0.74, respectively, based on 112 subjects.

Attempts to slow myopia progression with lenses are numerous.[14] Some have been unsuccessful,[15] whereas others have shown limited success.[16–18] No studies to date have evaluated whether the influence of parental myopia on myopia progression in their children might interact with the effect of an intervention. Identifying the variables that interact with treatment is crucial in distinguishing patients for whom the intervention is appropriate from those for whom it is not appropriate.[19] As Wu and Edwards[8] stated, "It will be interesting to see if any myopia retardation effect shown in future studies is greater among children who do not have a family history of myopia."

One such attempt to slow myopia progression in children is The Correction of Myopia Evaluation Trial (COMET).[17,20]

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COMET recruited 469 children aged 6 to 11 years at enrollment and 460 (98%) were retained for 5 years. All COMET subjects had between 1.25 and 4.50 D of myopia (spherical equivalent) at the time of enrollment in the study. Half of the children were randomized to progressive addition lenses (+2.00-D add) and the other half to single vision lenses.

COMET followed the progression of subjects' myopia longitudinally and obtained a broad range of biometric, oculomotor, and demographic information. The relationships among many of these factors and myopia progression have been reported.[19,21] Of the 469 children originally enrolled in COMET, 462 (98.5%) completed the 3-year visit. The mean ± SE 3-year increases in myopia (spherical equivalent) were −1.28 ± 0.06 D for the PAL group and −1.48 ± 0.06 D for 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 and remained at the same level over the next 2 years. The COMET Group concluded that the use of PALs versus SVLs slowed the progression of myopia by a small, statistically significant but clinically inconsequential, amount.

We now report relationships between parental myopia and myopia progression as well as interactions between parental myopia and the ability of progressive addition lenses to slow juvenile myopia progression. The present report differs from previously published studies in one or more of the following significant ways:

1. We obtained actual measures of parental ametropia and did not rely on a questionnaire to assess it; thus, we were able to treat parental myopia as both a continuous and a categorical variable, and we could look at the relationship between parental refractive error and myopia progression in their offspring.
2. We were able to investigate relationships among parental ametropia and other variables such as the accommodative response and axial length.
3. We measured the progression of juvenile-onset myopia longitudinally over a five year period.
4. Since COMET was an intervention trial, we were able to investigate the interaction between parental myopia and the effects of treatment with progressive addition lenses versus single vision lenses on myopia progression.

Methods

Data for this ancillary study were collected at all four COMET Clinical Centers: New England College of Optometry, Pennsylvania College of Optometry, University of Alabama at Birmingham School of Optometry, University of Houston College of Optometry. The COMET Coordinating Center at the Department of Preventive Medicine at the State University of New York Stony Brook conducted all data processing and analyses. Children already participating in COMET and their biological parents were the target subject population. Before enrollment in COMET, children and parents were informed of the nature and possible consequences of their participation in the trial, and parental consent and child assent were obtained for the children's participation. Separate consent was obtained from the parents for their participation in the present study. The Institutional Review Boards of each participating institution approved all the research protocols and consent/assent forms. All COMET protocols and procedures conformed to the tenets of the Declaration of Helsinki.

The data on the myopia progression of COMET children were obtained during the normal course of the trial, described in detail elsewhere.[22] In brief, cycloplegic autorefraction readings (ARK700A; Nidek, Gamagori, Japan), the primary outcome measure for COMET, were taken 30 ± 2 minutes after the second of 2 drops of 1.0% tropicamide given 4 to 6 minutes apart. Axial lengths were measured by corneal touch A-scan ultrasonography (model A 2500; Sonomed) using a 10-MHz focused ("hard") transducer 31 to 45 minutes after the application of 2 drops of 1.0% tropicamide.

For parents, the procedure of choice was autorefraction measurements of each eye, performed according to the noncycloplegic COMET protocol. For parents who had undergone any ocular procedure, such as refractive surgery, we used the most recent distance correction before surgery, obtained from lensometry, a written prescription, a clinical record, or a faxed report from another eye care provider. Parents who did not come to one of the clinical centers for autorefraction provided their most recent spectacle prescription by mail or fax.

Subjects

We attempted to acquire refractive data on all parents of participating COMET children. Refractive data were actually obtained on both biological parents for 264 of the COMET children. To avoid counting parental data more than once, we excluded one child at random from the 24 sibling pairs, leaving a set of 240 children. Eight of these 240 were eliminated because they were missing 5-year cycloplegic autorefraction data. Thus, this report is based on 232 COMET children on whom we obtained both 5-year cycloplegic autorefraction data and refractive data on both biological parents.

Eighty-one percent of parental refractive errors were classified on the basis of noncycloplegic autorefraction measurements (mothers, $n = 196$; fathers $n = 180$). The rest of parental refractive errors were classified by distance prescriptions from clinical records less than 5 years old (mothers: $n = 36$; fathers: $n = 52$). No classifications were based on questionnaire. For each eye, the mean of five spherical equivalent autorefraction measurements was calculated. The average refraction of the two eyes was used for these analyses since the eyes were highly correlated (Pearson correlation coefficient for mothers = 0.96, $P < 0.0001$; fathers = 0.90, $P < 0.0001$).

Data Analyses

Progression of myopia in the COMET children was defined as the change in spherical equivalent refraction relative to baseline based on cycloplegic autorefraction. For each eye, the mean of the five spherical equivalent autorefraction measurements was computed for each visit. The average of the two eyes was used to evaluate the change in spherical equivalent refractive error between 5-year follow-up and baseline.

Myopia progression and axial length measurements of COMET children were analyzed in relation to the refraction error of their parents both as a continuous and as a categorical variable (i.e., zero, one, or two myopic parents), where parents were considered to have myopia if their spherical equivalent refraction was −0.75 D or more minus (mean of both principal meridians of both eyes). For the analyses using parental refraction as a continuous independent variable, linear regression analysis was conducted to evaluate the relationship between parental (maternal, paternal, and midparental) refractive error and myopia progression and changes in axial length of their children.

In the analyses based on parental refraction as a categorical variable, two-way ANOVA was used to investigate the effects of lens treatment and number of myopic parents on myopia progression and changes in axial length of their children. These analyses were conducted without and with adjustment for factors previously shown by COMET to influence myopia progression and changes in axial length, including lens assignment, baseline age, baseline myopia, baseline accommodative response, gender, ethnicity, baseline axial length, and baseline corneal curvature. In the analyses with adjustment for baseline factors, the F-test was used to investigate interactions between the number of myopic parents and lens treatment or between the number of myopic parents and any of the baseline variables. Only interactions with $P < 0.05$ were included in the final models for progression and for changes in axial length.

Baseline characteristics and 5-year myopia progression for COMET children included in these analyses were summarized using descriptive

TABLE 1. Baseline Characteristics and Three-Year and Five-Year Progression in COMET Children Included and Excluded from Analyses

Characteristic	Children Included (n = 232)		Children Excluded (n = 237)		P
	n	%	n	%	
Baseline age (y)					
6	4	2	6	3	
7	15	6	17	7	
8	37	16	46	19	
9	60	26	51	22	
10	70	30	64	27	
11	46	20	53	22	
Mean ± SD	9.36 ± 1.24		9.30 ± 1.34		0.65*
Sex					
Male	109	47	114	48	0.85†
Female	123	53	123	52	
Ethnicity					
White	119	51	99	42	
African American	44	19	79	33	
Hispanic	32	14	36	15	**0.002**†
Asian	24	10	12	5	
Mixed/Other	13	6	11	5	
Baseline cycloplegic autorefraction (D)‡	−2.43 ± 0.84		−2.35 ± 0.75		0.30*
Baseline axial length (mm)‡	24.16 ± 0.71		24.09 ± 0.72		0.27*
Baseline accommodative response at 33 cm (D)‡	2.44 ± 0.59		2.50 ± 0.63		0.33*
3-Year myopia progression‡	−1.43 ± 0.82		−1.25 ± 0.80 (n = 230)		**0.02***
5-Year myopia progression‡	−2.10 ± 1.12		−1.82 ± 1.14 (n = 201)		**0.01***

P values significant at less than 0.05 are bold faced.
* Based on two-sample t-test.
† Based on χ^2 test.
‡ Data are mean ± SD.

statistics and compared with the COMET children not included in these analyses. Comparisons of continuous or categorical variables between two groups were conducted using two-sample t-tests or the χ^2 test. Statistical tests suggested that assumptions of constant variance and normality were valid.

RESULTS

Overview

Participation in the analyses presented in this article ranged from 40% to 63% among the four clinical centers. At baseline, the children included in this report did not differ significantly from the remainder of COMET children with respect to the distributions of sex, age, refractive error, axial length, and accommodative response at near (Table 1). However, children included in this analysis had a different ethnic distribution (i.e., higher proportion of white and Asian children and lower proportion of African-American children) and faster myopia progression at the three and the 5-year examinations than children not included in the present analysis (Table 1). Among the 232 children included in this study, 36 (15.5%) had no myopic parents, 109 (47.0%) had one myopic parent, and 87 (37.5%) had two myopic parents.

At baseline the levels of myopia and axial length were similar across treatment groups for each myopic parent category (Table 2). The differences in baseline myopia among the three groups with differing number of myopic parents were not statistically significant (P = 0.23). A similar pattern was observed for baseline axial length.

Parental Data

The mean ± SD age of the mothers and the fathers was 44.1 ± 5.1 and 46.3 ± 5.9 years, respectively, at the time refractive data were collected. Among the 464 parents who made up our

TABLE 2. Baseline Refraction and Baseline Axial Length by Number of Myopic[1] Parents and Treatment Group

Number of Myopic Parents	PAL		SVL		All	
	n	Mean ± SE	n	Mean ± SE	n	Mean ± SE
Baseline refraction (spherical equivalent diopters)						
0	16	−2.21 ± 0.11	20	−2.24 ± 0.17	36	−2.22 ± 0.10
1	52	−2.43 ± 0.11	57	−2.42 ± 0.11	109	−2.43 ± 0.08
2	46	−2.49 ± 0.12	41	−2.53 ± 0.16	87	2.51 ± 0.10
Baseline axial length (mm)						
0	16	24.12 ± 0.20	20	24.10 ± 0.16	36	24.11 ± 0.12
1	52	24.12 ± 0.12	57	24.20 ± 0.09	109	24.16 ± 0.07
2	46	24.19 ± 0.10	41	24.16 ± 0.10	87	24.18 ± 0.07

Myopia was based on the average spherical equivalent refractive error of two eyes; defined as noncycloplegic autorefraction ≤ −0.75 D.

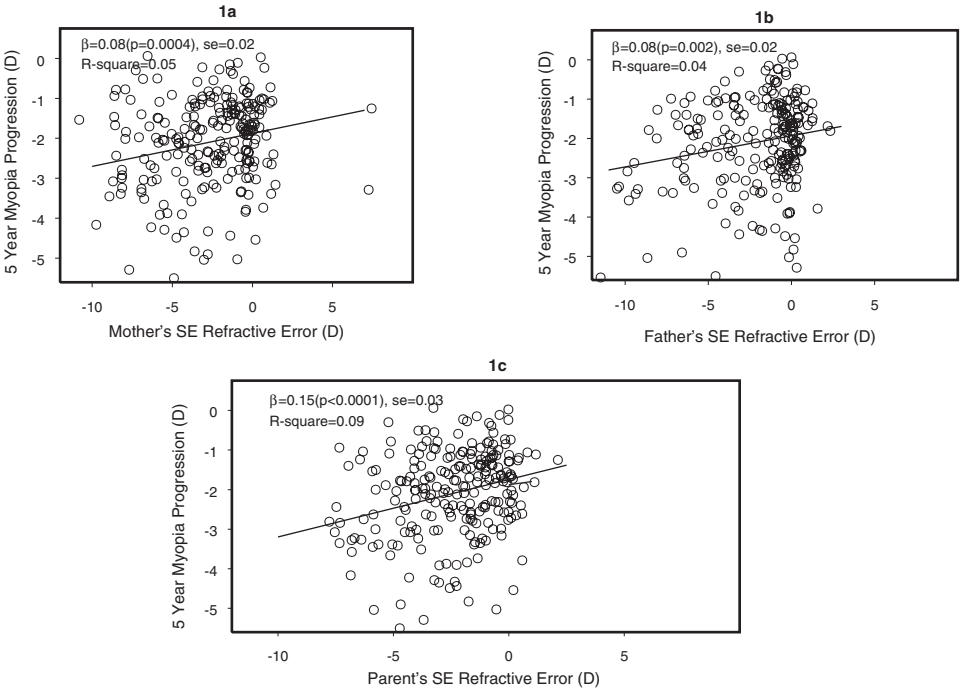

FIGURE 1. Scatterplots of parental spherical equivalent refractive error versus 5-year myopia progression ($n = 232$).

sample, 283 (61.0%) were myopic. Mothers had a higher frequency of myopia than did fathers (67.6% versus 54.3%; $P = 0.003$). The mean refractive error was -2.74 ± 3.14D in mothers and -2.16 ± 2.94 in fathers, a significant difference ($P = 0.04$). The frequency of "high" myopia (spherical equivalent refraction of -6.0 D or more minus) was similar in mothers and fathers with 15.5% of mothers and 13.4% of fathers having at least this amount. The Pearson correlation coefficient between mothers' and fathers' refractions was 0.12 ($P = 0.08$).

Relationship between Parental Refraction and 5-Year Myopia Progression in Their Offspring

Maternal, paternal, and midparent refractive errors were evaluated first as continuous variables. Scatterplots of parental refractive error and 5-year myopia progression in their offspring are shown in Figure 1 (not shown in Fig. 1a: one value < -12 (-20.975); not shown in Figure 1b: two values < -12 (-12.1875, -12.15); and not shown in Figure 1c: one value < -12 (-16.225). Both maternal and paternal refractive error showed a statistically significant association with myopia progression in their children, such that each additional diopter of refractive error toward myopia was associated with an increase in progression of 0.08 D ($P = 0.0004$ for mothers, $P = 0.002$ for fathers; Figs. 1a and 1b, respectively). This suggests a weak, equal influence of maternal and paternal refractive error on myopia progression in their children. Therefore, all four parental eyes were averaged to obtain the midparent refraction. The association between parental refraction and progression in their offspring was 0.15 D per 1.0 D of parental ametropia over the 5-year study period ($P < 0.0001$, Fig. 1c). Interactions between treatment effect and maternal refractive error, paternal refractive error, or midparent refractive error were not statistically significant in the linear regression analyses when parental refraction was treated as a continuous variable.

Number of Myopic Parents Related to Myopia Progression in Their Offspring

Table 3 presents both adjusted and unadjusted 5-year myopia progression findings for children with 0, 1, or 2 myopic parents for both treatment groups (PAL or SVL). Among children wearing SVLs, progression was higher with increasing numbers of myopic parents. Unadjusted values are shown graphically in Figure 2.

In the SVL group, the unadjusted difference in myopia progression between the zero and the two myopic parents groups of 0.78 D was significant ($P = 0.006$). The difference in myopia progression between the one and the two myopic parents groups of 0.55 D was also significant ($P = 0.01$). The difference of 0.23 D between the zero and one myopic parent groups was not statistically significant, based on a two-sample *t*-test.

In contrast to the findings in the SVL group, among children wearing PALs the number of myopic parents was not related to myopia progression in either the adjusted or the unadjusted data (Table 3). The overall, unadjusted myopia progression in this group was -2.01 D.

The term for interaction between number of myopic parents and treatment group reached statistical significance ($P = 0.01$) in the adjusted analysis. In both the unadjusted and the adjusted analyses there was a *de facto* interaction, in that the effect of treatment with PAL versus SVL varied with the number of myopic parents. In both analyses there was a statistically significant reduction in progression of 0.59 D in the PAL group compared to the SVL for children with two myopic parents ($P = 0.005$ in the adjusted data and $P = 0.03$ in the unadjusted data). In contrast, the treatment effects were not statistically significant for children with zero or one myopic parent in either analysis.

Number of Myopic Parents Related to Changes in Axial Length in Their Offspring

Changes in axial length as a function of number of myopic parents are summarized in Table 4 and shown graphically in Figure 3 (unadjusted means). These findings mirror the findings on myopia progression. Thus, changes in axial length were directly related to the number of myopic parents in the SVL (control) group, but not in the PAL group. The only statistically significant treatment effect was among children with two myopic parents; children wearing PAL had smaller

TABLE 3. Myopia Progression at 5 Years by Treatment Group and Number of Myopic Parents

Number of Myopic* Parents	PAL		SVL		Treatment Effect (PAL − SVL) Diff. (95% CI) P
	n	Mean ± SE	*n*	Mean ± SE	
Unadjusted					
0	16	−2.14 ± 0.23	20	−1.81 ± 0.18	−0.33 (−0.92–0.25) 0.25
1	52	−1.98 ± 0.16	57	−2.04 ± 0.13	0.06 (−0.34–0.47) 0.76
2	46	−2.00 ± 0.19	41	−2.59 ± 0.19	**0.59 (0.06–1.12) 0.03**
Adjusted†					
0	16	−2.38 ± 0.27	20	−1.77 ± 0.23	−0.61 (−1.29–0.08) 0.08
1	52	−1.93 ± 0.15	57	−2.11 ± 0.15	0.18 (−0.19–0.57) 0.33
2	46	−1.91 ± 0.16	41	−2.50 ± 0.16	**0.59 (0.18–1.01) 0.005**

n = 232; PAL = 114, SVL = 118. Data are mean diopters ± SE. *P* values significant at less than 0.05 are bold faced.

* Based on the average spherical equivalent refractive error of two eyes; defined as noncycloplegic autorefraction ≤ −0.75D.

† Based on the model that includes number of myopic parents, treatment, gender, ethnicity, baseline accommodative response at near, age, baseline myopia, baseline phoria, and the **interaction term** for treatment and number of myopic parents, which was statistically significant (***P* = 0.01**).

changes in axial length by 0.25 mm ($P = 0.03$). Interaction was found between the treatment effect and number of myopic parents ($P = 0.04$) when data were adjusted for other covariates.

DISCUSSION

Overview

The present study showed that the number of myopic parents is a statistically significant risk factor for myopia progression in COMET children wearing SVLs, the current standard of care for juvenile onset myopia. Results further showed a direct relationship between the progression rate and the number of myopic parents in the SVL group, as did Saw et al. 2001.[11]

The present study further showed that the number of myopic parents was related to the treatment effect of PALs versus SVLs on the myopia progression of offspring. A statistically significant interaction was found ($P = 0.01$) when the data were adjusted for covariates, such that the treatment effect varied with the number of myopic parents. In particular, for the group of children with two myopic parents, those wearing PALs had less myopia progression than those wearing SVLs, a treatment benefit not seen among the groups with either zero or one myopic parent. In fact, in the PAL group, the direct relationship between progression and number of myopic parents, seen in children wearing SVLs, was not observed, and the progression rate was similar regardless of the number of myopic parents. These findings have not been reported previously. Our interpretation of Wu and Edwards' comment,[8] as quoted in the Introduction to this article, is that they expected treatment effects of PAL versus SVL to be greater among those with no family history of myopia, the opposite of our finding that the benefit of wearing PALs was greater among children with two myopic parents. The effects of parental refractive error were the same on changes in axial length as on the progression of myopia, reinforcing the view that increases in axial length are the anatomic basis of myopia progression in juvenile onset myopia.

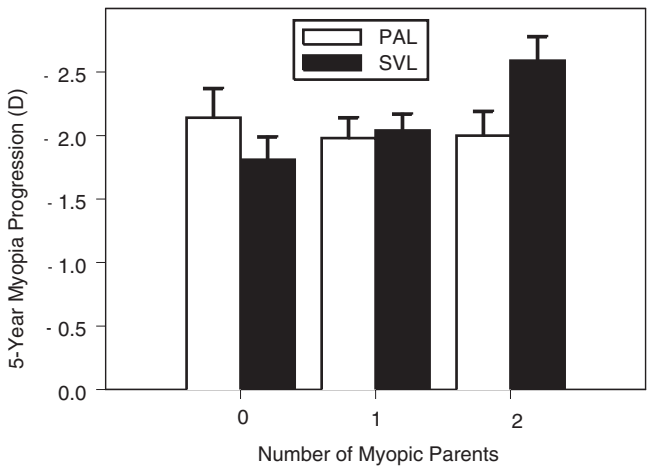

FIGURE 2. Unadjusted 5-year myopia progression by number of myopic parents and treatment ($n = 232$). Myopia is defined as noncycloplegic autorefraction ≤ −0.75 D.

The study by Saw et al., 2001,[11] differed from ours in that their subjects had a different ethnic distribution than our sample, which had a majority who reported themselves as either White or African-American (see Table 1). In addition, since myopia progression in juveniles is non-linear,[23] simply dividing the overall progression by the length of the study to obtain a unit of diopters per year is not appropriate. In light of the fact that Saw et al.[11] observed myopia progression over an average of 28 months while we report data from 60 months, it is difficult to make quantitative comparisons between their findings and ours.

Maternal, paternal, and mid-parent refractive error, when treated as continuous variables, were also statistically associated with myopia progression in their offspring. The effect was quantitatively small (0.08 D per diopter of maternal ametropia; 0.08 D per diopter of paternal ametropia; 0.15 D per diopter of midparent refractive error) and did not interact with the treatment effect. Therefore, as far as the benefits of treatment with PALs are concerned, the number of myopic parents has more predictive power than actual parental refraction. In deciding whether or not to prescribe PALs or SVLs to control juvenile

TABLE 4. Axial Length Increase at 5 Years by Treatment Group and Number of Myopic Parents

	PAL		SVL		Treatment Effect (PAL-SVL) Diff. (95% CI) *P*
Number of Myopic* Parents	***n***	**Mean ± SE**	***n***	**Mean ± SE**	
Unadjusted (n = 230)†					
0	16	0.98 ± 0.11	20	0.89 ± 0.07	0.09 (−0.15–0.34) 0.45
1	51	0.85 ± 0.06	57	0.93 ± 0.06	−0.07 (−0.24–0.10) 0.40
2	45	0.93 ± 0.09	41	1.18 ± 0.08	**−0.25 (−0.49–−0.02) 0.03**
Adjusted‡ (n = 228§)					
0	16	1.06 ± 0.11	20	0.86 ± 0.09	0.20 (−0.09–0.48) 0.17
1	50	0.86 ± 0.06	56	1.00 ± 0.06	−0.14 (−0.30–0.02) 0.08
2	45	0.93 ± 0.07	41	1.16 ± 0.07	**−0.22 (−0.40–−0.05) 0.01**

P values significant at less than 0.05 are bold faced.

* Based on the average spherical equivalent refractive error of two eyes; defined as noncycloplegic autorefraction ≤ −0.75 D.

† Two children had missing axial length findings at year 5.

‡ Based on the linear regression model that includes number of myopic parents, treatment, gender, ethnicity, baseline accommodative response at near, age, baseline axial length, baseline phoria, baseline corneal curvature, and the interaction term for treatment and number of myopic parents, which was statistically significant (***P* = 0.04**).

§ Two children missing baseline corneal curvature values were not included in the adjusted analysis since baseline corneal curvature was one of the variables for which the data were adjusted.

myopia progression, the number of parents with myopia is both easier to determine and likely to be more informative than actual parental refractions.

Nature versus Nurture

Previously reported associations between parental myopia and the prevalence or incidence of myopia have been interpreted to demonstrate a genetic contribution to the development of myopia.[3,10,24] Our finding of a direct relationship between progression and number of myopic parents in children wearing SVLs is consistent with a genetic contribution to myopia progression. Both maternal and paternal ametropia were associated with myopia progression in their offspring, and the effects for mothers and fathers were quantitatively the same. When refractions of both parents were combined, the slope of the regression line was nearly equal to the sum of the slopes for each parent separately, suggesting that parental influences are additive.

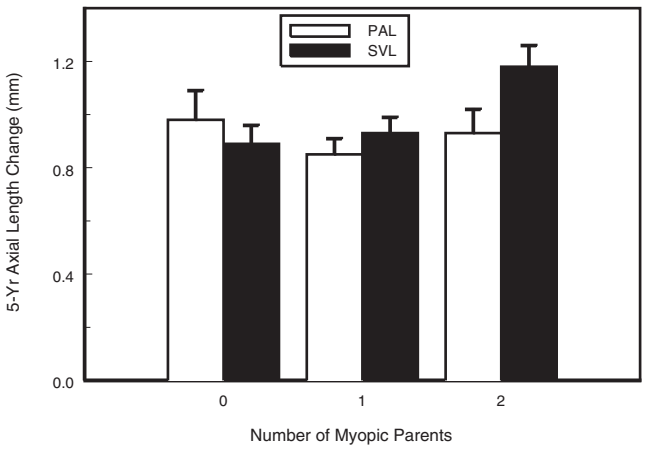

FIGURE 3. Unadjusted 5-year change in axial length by number of myopic parents and treatment (n = 230). *Defined as noncycloplegic autorefraction ≤ −0.75 D.

In light of changes in myopia prevalence in as few as three generations,[25] it is unlikely that genes produce myopia directly. It is, however, plausible that genes affect the susceptibility of eyes to myopigenic environmental factors. For example, one can speculate that genes contribute to the quantity of various higher-order optical aberrations,[26,27] which in turn might influence the amount of retinal blur experienced during near work. Genes could influence the efficiency of the neural pathways that mediate the near triad, resulting in a poorer accommodative response when reading among those with the susceptibility gene.[19,28–30] Genes could also be responsible for the density of neural projections mediating visual acuity, resulting in a larger depth of field and less sensitivity to blur in the susceptible group, which in turn could contribute to less efficient accommodative responses and larger blur during near work.[31] These possibilities are purely speculative, of course. It remains for future studies to investigate such linkages between genes, visual or specific oculomotor functions and myopia progression.

In contrast, parents may influence the incidence and progression of myopia, not through their genetic contributions to their offspring, but by creating visual environments that are conducive to myopia development.[32,33] In the present study, among those wearing PALs, the amount of progression was similar regardless of the number of myopic parents, as if the wearing of PALs, a manipulation of the visual environment not the genetics, counteracted or cancelled out the parental myopia effect. This finding is consistent with the view that the parental myopia effect is mediated by environmental factors. The view that parents affect progression via the environment is further supported by data showing that parental ametropia was directly and monotonically related to their educational level. When parental educational levels were divided into five groups (did not complete high school, completed high school, completed some college, graduated from a 4-year college, completed graduate or professional school), we found that mean

parental refractions ranged from −0.33 D for parents without a high school diploma to −3.41 D for those who completed graduate education. The odds of having myopia were 11 times higher in the latter than in the former group (95% CI = 5.12–23.46).[34]

However, the present study investigated neither the visual environment at home in sufficient detail nor the genes of its subjects to distinguish the nature and the nurture interpretations. Those studies remain to be undertaken.

Covariance of Parental Ametropia and Other Variables Relevant to Myopia Progression

COMET data have previously shown that children with an accommodative response at the baseline visit (ARb) below the median and with near esophoria at the baseline visit show a significantly slower myopia progression when wearing PALs than when wearing SVLs.[19] In the present data, parental refractive error as a continuous variable (mother, father, or midparent) correlated negatively with the ARb in their children: the more myopic the parental refraction, the lower the ARb (mothers: $\beta = -0.03$, $P = 0.03$; fathers: $\beta = -0.02$, $P = 0.14$; midparent: $\beta = -0.04$, $P = 0.01$, where β is the diopters of ARb per diopter of parental ametropia toward more myopia). These findings show that, although the associations are statistically significant, the levels are so low that ARb in and of itself is not sufficient to account for the influence of parental refraction on their offspring's myopia progression. Comparing ARb to the number of myopic parents also showed a similar trend, such that the mean ARb for children with zero myopic parents was 2.59 ± 0.44, 2.45 ± 0.64 for children with one myopic parent, and 2.36 ± 0.58 for children with two myopic parents ($P = 0.14$, based on the F-test). These data suggest a relationship between ARb and parental refraction similar to but not as strong as that reported by Gwiazda et al. (Gwiazda et al. *IOVS* 2005:46:ARVO E-Abstract 5587). Consequently, it is reasonable to suggest that a poor accommodative response at near in offspring may be one of the ways parental ametropia indirectly influences myopia progression, but it does not act alone. However, we have no data to suggest a possible mechanism for how parental refraction might influence the accommodative responses of their offspring. This must be left to future studies.

How Representative Are Our Data of Children with Juvenile-Onset Myopia and Their Parents?

COMET children are a large, well-characterized, ethnically diverse group with low to moderate, juvenile onset myopia. Because subjects' age at enrollment into the COMET was similar to the age of onset typical of juvenile onset myopia[35–37] and their rate of progression is also typical,[38,39] COMET children appear to be reasonably representative of all children with juvenile onset myopia. However, COMET children are volunteer clinical trial participants, and our data are not population based. Moreover, although the children included in the present analyses were similar to the remainder of the COMET children in many ways, they differed from our other participants in their ethnic distribution and in the amount of their myopia progression both at 3 and at 5 years (Table 1). Thus, children whose data are included in the present analyses are, at best, imperfectly representative of all COMET participants.

In addition, this study on parental ametropia was an ancillary study; the parents who participated did so voluntarily and may not be representative of the mothers and fathers of COMET children, much less of myopic children in general. For example, parents of children who were progressing faster may have been more motivated to participate in the parental study, perhaps because of their personal experiences growing up with myopia or because of their concerns for their children. Thus, our rate of 61.5% myopia among the parents in our sample is higher than one would expect in the general population of similar-aged adults in North America, and it might be higher than one would find in the parents of all juvenile onset myopic children. However, to the best of our knowledge, the prevalence of myopia among parents of myopic offspring has not been reported. Future studies are needed to characterize the parents of myopic children fully.

For all these reasons, we consider our analyses to be exploratory and our findings and conclusions to be suggestive, even when probabilities were below the conventional cutoff level of 0.05.

Parental refractive error was obtained by noncycloplegic autorefraction, which entails some risk of error due to accommodation. However, we have previously shown that these values are in close agreement with cycloplegic measurements in the COMET children.[40] These measures can be expected to agree at least as well in adults with a mean age in their early 40s, whose ability to accommodate is lower than that of children. Thus, parental accommodation can be expected to have little effect on our measurements. We also used a stringent criterion of −0.75D spherical equivalent to classify a parent as having myopia. In addition, our classification of parental refraction was based on actual refractive measurements and is likely to be more accurate than classification based on questionnaire. All these considerations together suggest that parental refractive errors were correctly classified in our study.

Conclusions

The number of myopic parents is a statistically significant risk factor for the progression of myopia in offspring wearing SVLs, but not in children wearing PALs. Furthermore, the number of myopic parents is a useful predictor of the treatment effect of PALs versus SVLs; children with two myopic parents progressed less when wearing PALs than when wearing SVLs. Parental refraction thus joins the constellation of variables, including younger baseline age, ethnicity, and gender,[21] which are predictors of myopia progression, and the number of myopic parents joins baseline phoria and accommodative response at the baseline visit[19] as predictors of the treatment effect of PALs versus SVLs. When viewed in isolation, however, no one of these variables is a quantitatively strong predictor. To ascertain how these and other factors work in combination to predict which myopic individuals are at greatest risk for progression, as well as which individuals are most likely to benefit from various interventions, requires further study. Although this study showed that the number of myopic parents is a statistically significant risk factor for myopia progression, the actual effect is relatively small. Moreover, for children with two myopic parents, a slowed progression in the PAL group relative to the SVL group of 0.59D over a 5-year period may not be considered clinically significant by many clinicians. Finally, because these analyses are ancillary to the original COMET design and are based on a subset of children, they should be considered exploratory, and the findings should be considered suggestive.

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APPENDIX

COMET Study Group

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