The Hong Kong Polytechnic University
School of Optometry

THE ROLE OF ABERRATIONS IN REFRACTIVE DEVELOPMENT

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Certificate of Originality

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Abstract of thesis entitled 'The role of aberrations in refractive development' submitted by Kwan Chi Kit William for the degree of Doctor of Philosophy at The Hong Kong Polytechnic University in October 2007

Abstract

Background

Axial length elongation induced by poor retinal image quality is thought to be a leading cause of myopia development. The eye's natural optical imperfections induce errors of higher order in the wavefront that cannot be easily corrected with spectacle lenses. This may constitute a form of deprivation myopia. However, previous studies reported conflicting results about the relationship between higher order monochromatic aberrations and refractive error development. The role of monochromatic aberration on refractive error development is still unclear.

Purpose

The objectives of this study are to investigate (1) whether different levels of refractive errors are associated with different levels of monochromatic aberrations; (2) the effect of monochromatic aberrations on the refractive

error development; (3) the change of monochromatic aberrations during the refractive error development.

Methods

Study 1: Monochromatic aberrations of 116 subjects (19 to 29 years old) with different levels of refractive error were compared to determine whether monochromatic aberrations in the more myopic eyes were different from those in the non-myopic eyes. ***Study 2:*** In order to factor out individual variations, we investigated the relationship of monochromatic aberrations and refractive errors in a group of 26 anisometropes. In this study, we wanted to find out if monochromatic aberrations in the more myopic eye were different from those in the less myopic eye of these anisometropes. ***Study 3:*** A one year longitudinal study was carried out to determine the effect of monochromatic aberrations on the development of refractive errors and to investigate the change of monochromatic aberrations during refractive error development. Monochromatic aberrations, refractive errors and axial lengths of 964 children (7 to 9 years old) were measured, under natural accommodation at the beginning and at the end of the one year period. ***Study 4:*** A two year longitudinal study was carried out on a group of 162 children (6 to 12 years old) with closer monitoring of the monochromatic aberrations and refractive development. Monochromatic aberrations, refractive errors, corneal curvatures and axial lengths were measured under cycloplegia in each assessment, at approximately 6-monthly intervals, during the two year period.

Results

Study 1: Our results show that more myopic eyes had significantly smaller root mean square (RMS) value of fourth order aberrations and spherical aberration than non-myopic eyes. Fourth order aberrations and spherical aberration were significantly correlated with myopia and decreased with higher degrees of myopia. *Study 2:* Less myopic eyes of the anisometropes showed significantly larger total higher order aberrations, third order aberrations and spherical aberration than more myopic eyes. *Study 3:* Eyes with low astigmatism showed significantly smaller second order aberrations, third order aberrations, coma and total higher order aberrations than those with high astigmatism. Spherical aberration of the emmetropic eyes significantly increased after the one year period. *Study 4:* Spherical aberration was significantly different among myopic, emmetropic and hyperopic eyes; myopic eyes had the smallest RMS value while hyperopic eyes had the largest RMS value. Myopic eyes with more increase in myopia showed significantly smaller spherical aberration at the beginning of the study than myopic eyes with less increase in myopia. Change of spherical aberration at the end of the study was significantly larger for the hyperopic eyes than the emmetropic and myopic eyes. Both hyperopic eyes with larger spherical equivalent change and with smaller spherical equivalent change showed significant increase in spherical aberration at the end of the study.

Conclusion

Our results suggest that monochromatic aberrations of the eye may be associated with refractive development. There was no evidence to support the notion that high amounts of higher order aberrations drive myopia development. On the contrary, we found that small amounts of spherical aberration may be one of the risk factors for myopia development and higher amounts of spherical aberration in myopic eyes may reduce the risk of myopia. For myopic and emmetropic eyes, spherical aberration was mostly unchanged over the two year study period even though there was significant change in refractive error. For hyperopic eyes, spherical aberration was significantly increased over the two year study period irrespective of refractive error change. More investigations are required to clarify further the role of monochromatic aberrations in myopia development.

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List of Abbreviations

AXL	Axial length
COAS	Complete Ophthalmic Analysis System
cyl	Astigmatism
ec	Emmetropia with refractive change
enc	Emmetropia without refractive change
hc	Hyperopia with refractive change
hnc,	Hyperopia without refractive change
K	Corneal curvature
mc	Myopia with refractive change
mnc,	Myopia without refractive change
RMS	Root mean square
SA	Spherical aberration
SE	Spherical equivalent
ΔAXL	Axial length change
ΔC(4,0)	C(4,0) change
ΔSA	Spherical aberration change
ΔSE	Spherical equivalent change

Chapter 1
Monochromatic Aberrations and Refractive Development

1.1 REFRACTIVE DEVELOPMENT AND VISUAL DEPRIVATION

Prevalence of myopia among Hong Kong schoolchildren is high (Lam et al., 1999). Vitreous depth or axial elongation is the main component contributing to the increase of myopia (Grosvenor and Scott, 1993; Lam et al., 1999). Refractive error development is known being influenced by retinal image quality. Retinal image degradation by eyelid closure or translucent occluders resulting in ocular axial elongation and resultant myopia can be found in animal models (Hodos and Kuenzel, 1984; Napper et al., 1995; Napper et al., 1997; Shaikh et al., 1999; Smith et al., 1999) and in humans (Calossi, 1994; Gee and Tabbara, 1988; Hoyt et al., 1981). Animals can become myopic or hyperopic during growth in response to lenses of different powers placed in front of their eyes (Napper et al., 1997). Such lenses induce first and second order errors in the wavefront entering the eye. These wavefront errors can be easily corrected with spectacle lenses. The eye's natural optical imperfections also induce errors with higher order in the wavefront that cannot be easily corrected with spectacle lenses. These higher order monochromatic aberrations degrade retinal image quality that individuals with significant levels of these aberrations may be prone to form deprivation myopia. However, much less is known about the relationship between higher order monochromatic aberrations and refractive development.

1.2 VISUAL DEPRIVATION INDUCED REFRACTIVE ERROR DEVELOPMENT

Among the animal studies in myopia, visual deprivation resulting in ocular axial elongation and resultant myopia can be found in different spices like chicks (Hodos and Kuenzel, 1984; Napper et al., 1995; Napper et al., 1997), tree shrews (Shaikh et al., 1999) and monkeys (Smith et al., 1999). Minus lens (Shaikh et al., 1999), translucent goggle (Hodos and Kuenzel, 1984; Napper et al., 1995; Napper et al., 1997) and lid fusion (Smith et al., 1999) was used in order to provide different extend of visual deprivation. In human, increase of axial length due to visual deprivation caused by eyelid closure (Hoyt et al., 1981), corneal opacification (Gee and Tabbara, 1988) or cataract (Calossi, 1994) in early infancy has also been reported. In chicks and tree shrews, the induced myopia was reduced significantly under a daily period of exposure to normal visual stimulation (Napper et al., 1995; Napper et al., 1997; Shaikh et al., 1999). Short periods of normal visual stimulation affected the regulation of axial growth strongly in the presence of long periods of abnormal stimulation (Napper et al., 1995; Napper et al., 1997; Shaikh et al., 1999; Smith et al., 1999). If human eyes response similarly, the stimulus of axial growth must be present almost all the time to induce myopia.

Visual deprivation in the presence of long periods can induce axial growth both in humans (Calossi, 1994; Gee and Tabbara, 1988; Hoyt et al., 1981) and spices (Hodos and Kuenzel, 1984; Napper et al., 1995; Napper et al., 1997; Shaikh et al., 1999; Smith et al., 1999). In humans, although the refractive error, i.e. the first and second order error, is corrected, there is still axial growth. This suggested that there is something present in long periods degrading the retinal image, which induce axial elongation. Monochromatic aberrations cannot be fully corrected using ophthalmic lens may be one of the risk factors affecting the refractive development.

1.3 HARTMANN-SHACK ABERROMETER

The Hartmann-Shack aberrometer has become a popular method for measuring ocular monochromatic aberrations in recent years (Liang et al., 1994; Prieto et al., 2000; Thibos and Hong, 1999). With the development and advances of the Hartmann-Shack aberrometer (Atchison 2005; Liang et al., 1994; Liang and Williams., 1997), individual aberration can be measured within a few seconds.

1.3.1 Clinical Hartmann-Shack Aberrometer

The first clinical Hartmann-Shack aberrometer, the complete ophthalmic analysis system (COAS) was commercially available in the United States in 2000. Cheng et al. (2003) measured the monochromatic aberrations of six aspheric reduced eye models to validate the accuracy, tolerance, and repeatability of the COAS. The COAS was reported being accurate and repeated in measuring the aberrations of the model eyes. Salmon et al. (2003) using the COAS measured the monochromatic aberrations of 20 myopic subjects. Refractive errors of the myopic subjects measured by the COAS were compared with the phoropter, the Nidek ARK-2000 autorefractor, with and without cycloplegia. The accuracy, repeatability and instrument myopia in measuring myopes were found similar to those of the autorefractor. These results suggested that the COAS could be used as a reliable, accurate autorefractor.

In order to measure accurate monochromatic aberrations of the eye using a Hartmann-Shack aberrometer, Ginis et al. (2004) suggested that the data used should not be extracted from a single measurement. A single measurement can only represent a static snapshot of a dynamically changing aberration pattern of the eye. Davies et al. (2003) using Hartmann-Shack aberrometer, measured the monochromatic aberrations of nine eyes, and suggested that pupil realignment can be useful in reducing the residual root mean square wavefront values to a minimum. Monochromatic aberration measurement after a blink was stable after the normal interblink interval and started to degrade after about 10 second, leading to gradual increase in aberration (Montés-Micó et al., 2004a; Montés-Micó et al., 2004b).

1.4 MONOCHROMATIC ABERRATIONS AND THE HUMAN EYE

1.4.1 Monochromatic Aberrations and Myopia

Previous studies have shown large individual variations in the monochromatic aberrations of the human eyes (Walsh et al., 1984; Howland and Howland, 1977; Liang and Williams, 1997). Table 1.1 summarizes the studies investigating the relationship of monochromatic aberrations and refractive errors. Applegate (1991), using a subjective single-pass aberroscope, found that myopes have higher amount of aberration. Simonet et al. (1999), using a modified Hartmann-Shack sensor, found a similar result in a population of ametropes aged from 18 to 57 years old, where spherical aberration and coma increased with refractive error. Another similar study by Paquin et al. (2002), using a modified Hartmann-Shack method, also found that aberration increases with the refractive error for pupil diameters of 5 and 9mm. Marcos et al. (2002), using an objective ray-tracing technique, also reported significantly increased aberrations in young myopia subjects. He et al. (2002), using a subjective ray-tracing aberroscope, measured 146 young adults, found that on average myopes have slightly larger combined fourth order and higher aberrations than emmetropes. No significant correlation was found between total aberrations and refractive spherical equivalents. McLellan et al. (2001) using a spatially resolved refractometer, found that total higher order aberrations were not significantly correlated with spherical equivalent refractive error. To the contrary, Collins et al. (1995), using an objective double-pass aberroscope, found that the fourth order aberrations in myopic subjects were lower than that in emmetropic subjects. However, in this study, at least one third of the myopic eyes were too aberrated that no grid image was observed. Llorente et al. (2004), using the laser ray tracing method, found that hyperopic eyes had higher aberrations than myopic eyes.

With the development and advances of the Hartmann-Shack aberrometer (Atchison, 2005; Cheng et al., 2004; Liang et al., 1994; Liang and Williams., 1997), individual aberration can be measured within a few seconds. Several studies have used these technologies to examine large subject populations (Porter et al., 2001; Carkeet et al., 2002; Cheng et al., 2003). Porter et al. (2001) in a population of 109 normal subjects found no link between higher order aberrations and refractive errors. Carkeet et al. (2002) measured the higher order aberrations in 273 cyclopleged Singaporean school children. Although there were some variations with refractive error and race, the authors concluded that there was no evidence for the idea that spherical aberration playing a causative role in myopia development. Cheng et al. (2003) in a population of 100 young adult subjects also found no systematic variations between aberrations and degree of ametropia.

Previous studies in examining the relationship between refractive errors and monochromatic aberrations found large variations. The differences between the results of individual studies may due to different subject groups, techniques and analysis method. Also, individual variation should be a main confounding factor. All previous studies were examining the relationship in a cross-sectional way. Longitudinal studies will help to investigate the role of monochromatic aberrations in refractive development better.

Table 1.1
Summary of studies investigating the relationship between monochromatic aberrations and refractive errors

Studies	No. of eyes	Pupil diameter (mm)	Age range	Dilation	Type of aberrometer	Ocular total higher order aberrations significantly difference	Ocular spherical aberration significantly difference
Collins et al. (1995)	21M, 16E	3.5	17 to 29	No	Objective cross-cylinder aberroscope	Yes	Yes
Paquin et al. (1998)	27M, 7E	5 and 9	18 to 32	Yes	Hartmann-Shack	Yes	Unknown
Simonet et al. (1999)	57M, 12H	5 and 9	18 to 57	Yes	Hartmann-Shack	Yes	Yes
McLellan et al. (2001)	38	6	22.9 to 64.5	Yes	Spatially resolved refractometer	No	Unknown
Porter et al. (2001)	109	5.7	21 to 65	No	Hartmann-Shack	No	No
He et al. (2002)	316	10-29	6	No	Psycho-physical ray tracing	Yes	Yes
Carkeet et al. (2002)	273	5	7.9 to 12.7	Yes	Hartmann-Shack	No	Yes
Cheng et al. (2003)	200	6	26.1 ± 5.6	Yes	Hartmann-Shack	No	No
Llorente et al. (2004)	34M, 22H	6.5	23 to 40	Yes	Laser ray tracing	Yes	Yes

M, myopia; E, emmetropia; H, hyperopia.

1.4.2 Monochromatic aberrations and accommodation

There were a number of studies investigating changes in higher order aberrations with accommodation (Atchison et al., 1995; Buehren and Collins, 2005; Cheng et al., 2004; Collins et al., 1995; Hazel et al., 2003; He et al., 2000; Ninomiya et al., 2002; Ninomiya et al., 2003; Plainis et al., 2005). The similar finding those studies reported was the change of spherical aberration in the negative power direction with accommodation.

Atchison et al. (1995) measuring the monochromatic aberrations of 15 subjects reported that spherical aberration of half of them changed towards the negative power direction. Collins et al. (1995) using the subjective aberroscope technique measured a group of 55 eyes under three different accommodation level. Both emmetropes and myopes showed spherical aberration change towards the negative power direction. He et al. (2000) using a spatially resolved refractometer measured eight subjects with accommodative stimuli varying from 0 to 6D. Although there were substantial individual variations in the aberration change, higher order monochromatic aberrations tended to increase with accommodation. Spherical aberration was found decreasing with accommodation, and most of them changed towards the negative power direction. Ninomiya et al. (2002) using a Hartmann-Shack aberrometer measured the monochromatic aberrations of 33 young adults before and during 3D of accommodation. Spherical aberration changed significantly towards the negative power direction for both the 4mm zone and the 6mm zone without a change of image quality. Hazel et al. (2003) measured the monochromatic aberrations of 20 myopes and 10 emmetropes under accommodation induced by negative lenses. Spherical aberration changed towards the negative power direction for all subjects with increases in accommodative stimulus. Other studies using Hartmann-Shack aberrometer with accommodation demands through a Badal system also reported spherical aberration changed towards the negative power direction and proportional to change in accommodative response (Cheng et al., 2004; Plainis et al., 2005). A case report of two accommodative spasm patients showed that spherical aberration changed from negative to positive after cure the spasm with cycloplegia (Ninomiya et al., 2003). Buehren and Collins (2005) using a modified wavefront sensor investigated the relationship of accommodation stimulus-response function and retinal image quality, and suggested that the combination of higher order aberrations and accommodation errors improved retinal image quality compared with higher order aberrations or accommodation errors alone.

From the above results, it has been suggested that eliminating the physiologic spherical aberration for far vision using customized aberration may not be advantageous.

1.4.3 Monochromatic aberrations and age

Table 1.2 summarizes the studies describing monochromatic aberrations of the eye as a function of age. In general, ocular total higher order aberrations and spherical aberration were found significantly increased with age.

McLellan et al. (2001) using a spatially resolved refractometer, suggested that wave aberrations of the eye increased with age. Spherical aberration, fourth order aberrations and fifth to seventh orders aberrations also increased significantly with age. However, coma and third order aberrations showed no significant correlation with age. In agreement, Fujikado et al. (2004) using Hartmann-Shack aberrometer, also found that ocular total higher order aberrations and spherical aberration were significantly increase with age. However, coma was significantly correlated with age in this study. Shahidi and Yang (2004) using Hartmann-Shack aberrometer reported that ocular higher order aberrations were significantly increased with age. Light scatter was also significantly correlated with age. Brunette et al. (2003) studying the monochromatic aberrations from childhood to advance age suggested that ocular aberrations were best modeled with a quadratic model rather than a linear model with age. Ocular aberrations decreased in young and elderly eyes compared with adult eyes.

Amano et al. (2004) used videokeratography and Hartmann-Shack aberrometer to study the age related changes in corneal and ocular higher order aberrations. Both the corneal and ocular coma showed significant increase with age. The ocular spherical aberration increased significantly with age, whereas the corneal spherical aberration did not change with age. These results suggested that the change in ocular coma with age, mainly due to the increase in the corneal coma, and the change in ocular spherical aberration with age, mainly due to the increase in the internal spherical aberration. Artal et al. (2002) using Hartmann-Shack aberrometer, suggested that the loss of the balance between corneal and internal aberrations was the reason of the degradation of the ocular optics with age. In contrast, Wang et al. (2005) analyzing the distribution of the higher order aberrations from the internal optics and the variations with age, suggested that higher order aberrations did not change with increasing age. Internal spherical aberration was the only significant term correlated with increasing age. In a study of isolated human lenses, spherical aberration was also significantly correlated with increasing age (Glasser and Campbell, 1998).

Previous studies reported conflict results in the relationship between corneal aberrations and increasing age. Guirao et al. (2000) using a videokeratographic system reported total higher order aberrations, spherical aberration and coma of the cornea significantly increased with age. The corneal radius decreased with age and the shape of the cornea changed from ellipsoid to spherical as a function of age. In contrast, Fujikado et al. (2004) reported no significant correlation between corneal aberrations and age. However, the analyzed pupil in this study was different from the study of Guirao et al. (2000), 4mm compared to 6mm. It might be the reason of the different results reported.

Table 1.2
Summary of studies describing monochromatic aberrations of the eye as a function of age

Studies	No. of eyes	Pupil diameter (mm)	Age range	Type of aberrometer	Ocular total higher order aberrations increase with age	Ocular spherical aberration increase with age
Glasser and Campbell (1998)	27	Full diameter	10 to 87	Scanning laser technique	Unknown	Yes
Guirao et al. (2000)	59	4 and 6	20 to 70	Computerized videokerato-graphy	Unknown	Unknown
McLellan et al. (2001)	38	6	22.9 to 64.5	Spatially resolved refractometer	Yes	Yes
Artal et al. (2002)	17	3.85 and 5.9	26 to 69	Hartmann-Shack	Yes	Possibly
Brunette et al. (2003)	114	5	5.7 to 82.3	Hartmann-Shack	Yes (after 40)	Yes (after 20)
Amano et al. (2004)	75	6	18 to 69	Hartmann-Shack	Possibly	Yes
Fujikado et al. (2004)	66	4	4 to 69	Hartmann-Shack	Yes	Yes
Shahidi and Yang (2004)	20	6	21 to 78	Hartmann-Shack	Yes	Unknown
Wang et al. (2005)	144	6	20 to 69	Hartmann-Shack	Unknown	Unknown

1.4.4 Monochromatic aberrations and cataract

Cataract causes image degradation. Monocular triplopia has also been reported (Fujikado et al., 2004). Previous studies have reported that monochromatic aberrations of the cataract patients were increased (Fujikado et al., 2004; Kuroda et al., 2002).

Fujikado et al. (2004), using a Hartmann-Shack aberrometer, examined a patient complaining of monochromatic triplopia to determine whether higher order monochromatic aberrations could account for the triplopia. Spherical aberration and trefoil aberration was increased for a pupil of 4mm in diameter (-0.18µm and –0.16µm, respectively). After cataract surgery, spherical aberration and trefoil aberration was markedly decreased (-0.058µm and –0.017µm, respectively) and the subjective triplopia also disappeared.

Kuroda et al. (2002), using a Hartmann-Shack aberrometer, examined 4 patients with mild nuclear cataract, 14 patients with mild cortical cataract and 9 normal patients. Corneal and ocular monochromatic aberrations were measured for a pupil of 6mm in diameter. Higher order aberrations were calculated up to sixth order. The corneal total higher order aberrations showed no significant difference between cataract patients and normal patients. The ocular total higher order aberrations were significantly larger in cataract patients (0.658µm) than in normal patients (0.430µm). Cataract patients (0.454μm) also showed significantly larger ocular spherical aberration than normal patients (0.273μm). Nuclear cataract patients showed negative ocular spherical aberration while cortical cataract patients showed positive ocular spherical aberration. Contrast sensitivity was reported highly correlated with ocular total higher order aberrations.

Aberrometer measurements have shown that in cataract patients, not only light scattering but also ocular higher order aberrations lead to visual deterioration and loss of contrast sensitivity (Fujikado et al., 2004; Kuroda et al., 2002). Measuring ocular monochromatic aberrations in cataract patients is useful to objectively evaluate the deterioration of images. Polarity of spherical aberration also provided additional information about the characteristics of different cataract.

1.4.5 Monochromatic aberrations and orthokeratology

Orthokeratology is a method to achieve temporary reduction in myopia by reshaping the anterior cornea through wearing of a special designed flat fitting rigid contact lens. Previous studies have shown that spherical aberration increased after the therapy, although the refractive error was successfully reduced (Berntsen et al., 2005; Hiraoka et al., 2005; Joslin et al., 2003; Joslin et al., 2004). Berntsen et al. (2005) suggested that increased higher order aberration and spherical aberration lead to low contrast best corrected visual acuity reduced after orthokeratology and reduced even further as pupil size increased. Hiraoka et al. (2008) reported mesopic contrast sensitivity after orthokeratology deteriorated significantly with increased higher order aberrations that depend on the amount of myopic correction.

1.4.6 Monochromatic aberrations and diabetes

Previous study reported that higher order aberrations in diabetes were significantly larger than in normal subjects (Shahidi et al., 2004). This result suggested that the increased higher order aberrations might influence the retinal image resolution in diabetic eyes. The information of the monochromatic aberrations was useful for future designing of high-resolution retinal imaging systems that can be applicable for eyes with retinal disease.

1.4.7 Monochromatic aberrations and retinitis pigmentosa

Rajagopalan et al. (2005) measured monochromatic aberrations of retinitis pigmentosa patients with and without posterior subcapsular cataracts. Increased higher order monochromatic aberrations were present independent of the present of posterior subcapsular cataracts compared to normal subjects. Monochromatic aberrations measurement provided an additional objective and quantitative information for detecting and monitoring the optical changes of the disease eyes.

1.4.8 Monochromatic aberrations and keratoconus

Keratoconus eyes had significantly larger higher order aberrations (Lim et al., 2007). Munson et al. (2001) reported the monochromatic aberrations of a keratonic patient. Before corneal transplantation, the aberrations of the naked keratonic eye were extremely large that could not be measured unless the patient wore a rigid gas permeable contact lens. After surgery, the aberrations reduced with an improvement in uncorrected visual acuity. It was suggested that monochromatic aberrations measurement provided an additional objective and quantitative information for detecting and monitoring the optics of the keratonic eye.

1.5 RESEARCH QUESTIONS

The objectives of this study are to investigate (1) whether difference levels of refractive errors are associated with different levels of monochromatic aberrations; (2) the effect of monochromatic aberrations on the refractive error development; (3) the change of monochromatic aberrations during the refractive error development.

Chapter 2
Monochromatic Aberrations of the Human Eye and Myopia

2.1 INTRODUCTION

The relationship between monochromatic aberrations of the human eye and myopia has been studied for several years (Collins et al., 1995; McLellan et al., 2001; Porter et al., 2001; Carkeet et al., 2002; He et al., 2002; Marcos et al., 2002; Paquin et al., 2002). These studies have produced conflicting results about this relationship. Collins et al. (1995), using an objective double pass aberroscope, measured monochromatic aberrations of a group of 21 young myopes and 16 young emmetropes and found that the fourth order aberrations in myopes were lower than those in emmetropes. However, at least one third of the myopic eyes in this study were so aberrated that no grid image was observed. In contrast, He et al. (2002), using a subjective ray-tracing aberroscope, measured 146 young adults, reported slightly higher fourth order aberrations in myopes than emmetropes. No significant correlation was found between total aberrations and refractive spherical equivalents. Using an objective ray-tracing technique, Marcos et al. (2002) reported that aberrations in highly myopic subjects increased with refractive error. Another similar study by Paquin et al. (2002) found that spherical aberration and coma increased with higher degrees of myopia. Two other studies found no link between higher order aberrations and myopia (McLellan et al., 2001; Porter et al., 2001). However, there was a wide range of ages of the subjects in these studies. It has been claimed that monochromatic aberrations of the human eye increase with increasing age and the majority of the change is due to the internal aberrations (i.e. excluding the corneal aberrations) (McLellan et al., 2001). Hence, wide age ranges of the subjects might confound the reported findings.

This study aimed to establish whether the monochromatic aberrations in the highly myopic eye are different from those in the non-myopic eye in adult subjects from a narrow age band.

2.2 METHODS

2.2.1 Subjects

One hundred and sixteen Chinese subjects (age range, 19-29 years; mean age, 21.8 years; male, 54; female, 62) were enrolled in this study. They had a spherical equivalent refractive error between +1.38D and -10.38D and a refractive astigmatism of less than -3.00D. The mean of the absolute spherical equivalent differences between left and right eyes was 0.12 ± 0.94D. Subjects having any pathology (i.e., keratoconus, cataract, etc.) or ocular surgery were excluded. The monochromatic aberrations of the eyes were measured in a dark room with natural pupils larger than 5mm. The refractions and axial lengths of the eyes were measured under natural accommodation (Chat and Edwards, 2001; Heatlley et al., 2002; Mallen et al., 2001). Written informed consent was obtained from every subject before participation.

All the subjects were categorized into three groups according to their mean refractive spherical equivalent from autorefraction (Table 2.1).

2.2.2 Apparatus

The Complete Ophthalmic Analysis System (COAS) Wavefront Analyzer, a clinical Shack-Hartmann aberrometer, was used to measure the monochromatic aberrations of the eyes, based on the Zernike polynomial. The Shin-Nippon SRW5000 autorefractor was used to measure the refractive errors of the subjects. Axial lengths of the subjects were measured with A-scan ultrasonography.

2.2.3 Procedures

The monochromatic aberrations of the right eyes of the 116 subjects were measured under natural accommodation in a dark room. Natural pupils were used. All pupils were larger than 5 mm after adaptation to the dark. The subject was placed in the chin rest with the right eye looking into the examination window. The subject was instructed to focus on the fixation target of the COAS in order to align the optical axis of the eye and to link it to the optical axis of the COAS. The eye that was not being examined had a free view past the COAS. The monochromatic aberrations were automatically calculated up to and including fourth order by using 14 Zernike terms. The pupil diameter used for computation of the aberrations was 5mm. Five measurements were taken after each blink and the averages of coefficients from ocular aberrations were used for analysis.

Refractive errors were measured by Shin-Nippon SRW500 autorefractor with a target at 6m. Axial lengths were measured using A-scan ultrasonagraphy after local anesthesia by 0.4% novesin.

2.2.4 Data Analysis

Subjects with refractive spherical equivalents equal to or greater than -5.00D were classified as highly myopic and those with refractive spherical equivalents equal to or less than -0.50D were classified as non-myopic. Those with refractive spherical equivalent between -5.00D and -0.50D were classified as moderate myopia.

The coefficients of the Zernike polynomials corresponded to the order recommended by the OSA Standardization Committee (Thibos et al., 2000; Thibos et al., 2002). The root mean square (RMS) values of the averaged total higher order aberrations (excluding the first and second order aberrations), third order aberrations, fourth order aberrations, spherical aberration and coma were calculated for analysis. Linear regression and one-way analysis of variance (ANOVA) were used to evaluate the distribution of these aberrations across the three refractive groups.

2.3 RESULTS

All 116 subjects completed the study and results from the right eyes are presented. There were significant differences (ANOVA, $p < 0.0001$) in axial lengths among the three refractive groups (Table 2.1).

Table 2.1
Distribution of refractive errors (SE (D) ± SD)

	SE (D) ± SD	AXL (mm)	No. of Eyes
High myopia (≤ -5.00D)	-6.674 ± 1.443	25.928 ± 0.772	30
Moderate myopia (-5.00D to -0.50D)	-3.029 ± 1.182	24.990 ± 0.768	56
Non-myopia (≥ -0.50D)	0.238 ± 0.413	23.435 ± 0.723	30
ANOVA		p < 0.0001*	

SE, mean refractive spherical equivalence; AXL, mean axial length
*Significant at the 0.05 level

The mean monochromatic aberrations of the three groups are shown in Table 2.2. The distributions of the total higher order aberrations, third order aberrations and coma overlapped. ANOVA showed no statistical difference in the total higher order aberrations ($p = 0.83$), third order aberrations ($p = 0.71$) and coma ($p = 0.98$). The fourth order aberrations ($p = 0.046$) and spherical aberration ($p = 0.019$) differed significantly among the three refractive groups.

Table 2.2
Monochromatic aberrations in three refractive groups (Mean ± SD)

	Total higher order aberrations	Third order aberrations	Fourth order aberrations	Spherical aberration	Coma
High myopia	0.157 ± 0.071	0.137 ± 0.073	0.066 ± 0.031	0.044 ± 0.035	0.097 ± 0.069
Moderate myopia	0.165 ± 0.056	0.138 ± 0.057	0.082 ± 0.038	0.062 ± 0.039	0.095 ± 0.057
Non-myopia	0.161 ± 0.056	0.127 ± 0.056	0.090 ± 0.042	0.073 ± 0.048	0.096 ± 0.046
ANOVA	p = 0.83	p = 0.71	p = 0.046*	p = 0.019*	p = 0.98

*Significant at the 0.05 level

The relationship between the monochromatic aberrations and the refractive spherical equivalents of all the subjects are shown in Figures 2.1 to 2.6. Linear regression analysis showed that the slopes for total higher order aberrations, third order aberrations and coma were not significantly different from zero ($p > 0.05$, $r = 0.025$, -0.072 and -0.058, respectively) while the slopes for fourth order aberrations, spherical aberration and C(4,0) were significantly different from zero ($p < 0.05$, $r = 0.24$, 0.28 and 0.27, respectively). Table 2.3 shows the distribution of refractive errors of the subjects with astigmatism equal to or less than –1.00D. Similar results were found when we analyzed the subjects with low astigmatism only (Table 2.4). Highly myopic subjects tended to have smaller fourth order aberrations and spherical aberration.

Table 2.3
Distribution of refractive errors with cylinder ≤ -1.00D

	SE (D)	No. of Eyes
High myopia	≤ -5.00	18
Moderate myopia	-5.00 to -0.50	48
Non-myopia	≥ -0.50	29

SE, mean spherical equivalence

Table 2.4
Monochromatic aberrations in three refractive groups with cylinder ≤ -1.00D (Mean ± SD)

	Total higher order aberrations	Third order aberrations	Fourth order aberrations	Spherical aberration	Coma
High myopia	0.152 ± 0.077	0.137 ± 0.078	0.060 ± 0.027	0.039 ± 0.027	0.094 ± 0.065
Moderate myopia	0.166 ± 0.056	0.141 ± 0.057	0.080 ± 0.039	0.062 ± 0.039	0.096 ± 0.058
Non-myopia	0.158 ± 0.054	0.124 ± 0.055	0.089 ± 0.042	0.071 ± 0.047	0.093 ± 0.044
ANOVA	p = 0.66	p = 0.51	p = 0.046*	p = 0.033*	p = 0.97

*Significant at the 0.05 level

Figure 2.1
Linear regression of total high order root mean square (RMS) error (Zernike orders 3 to 4) as function of spherical equivalent refractive error (m = 0.0005, p = 0.79, r = 0.025)

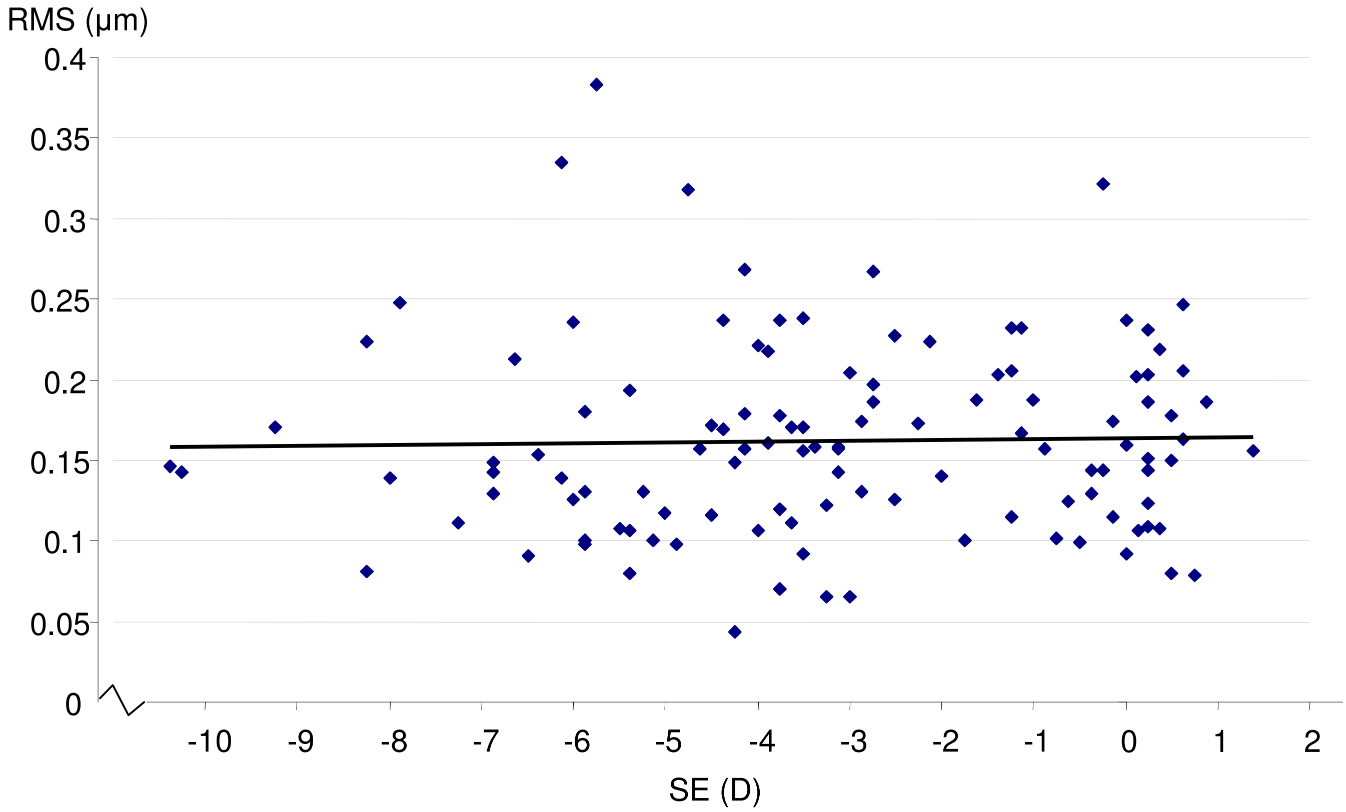


Figure 2.2
Linear regression of third order root mean square (RMS) error as function of spherical equivalent refractive error (m = -0.0016, p = 0.44, r = -0.072)

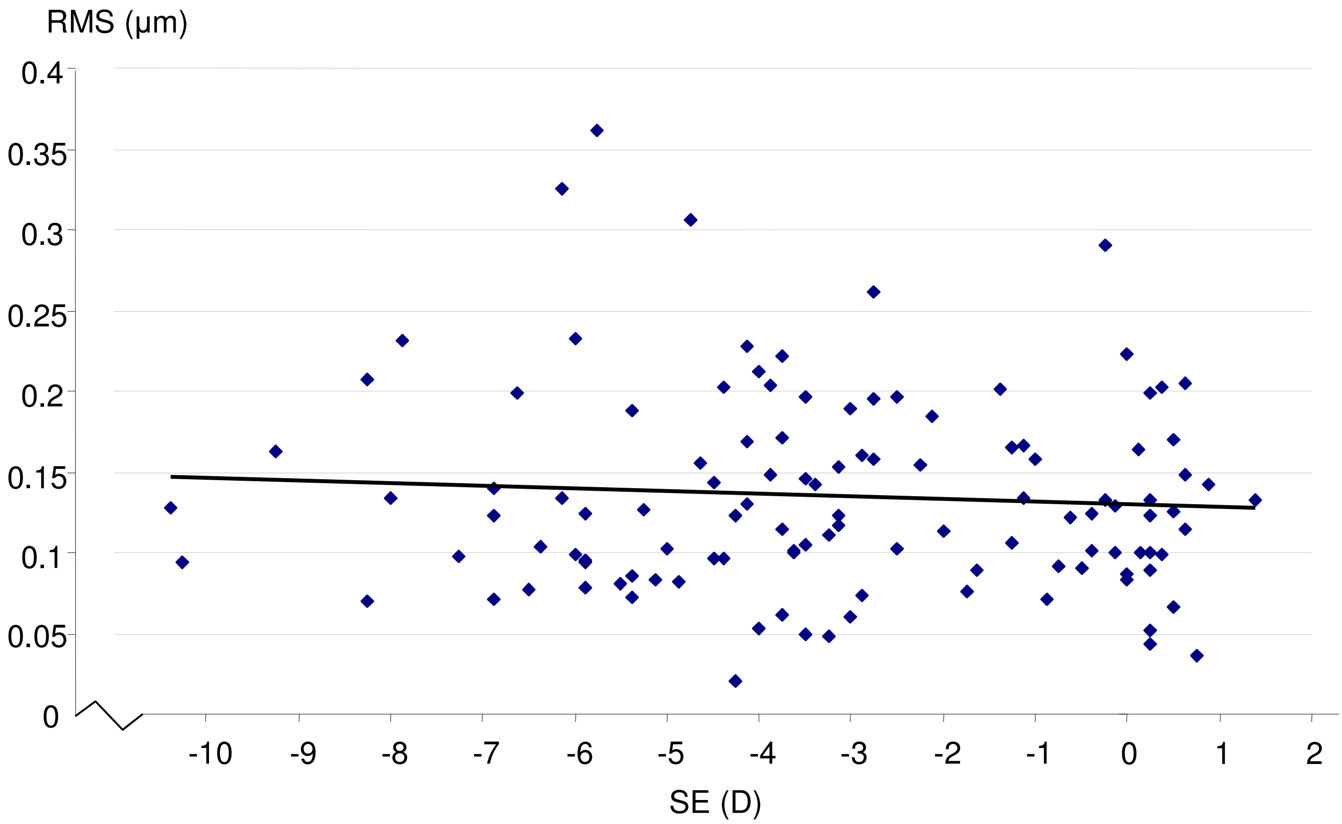


Figure 2.3
Linear regression of fourth order root mean square (RMS) error as function of spherical equivalent refractive error (m = 0.0033, p = 0.011, r = 0.24)

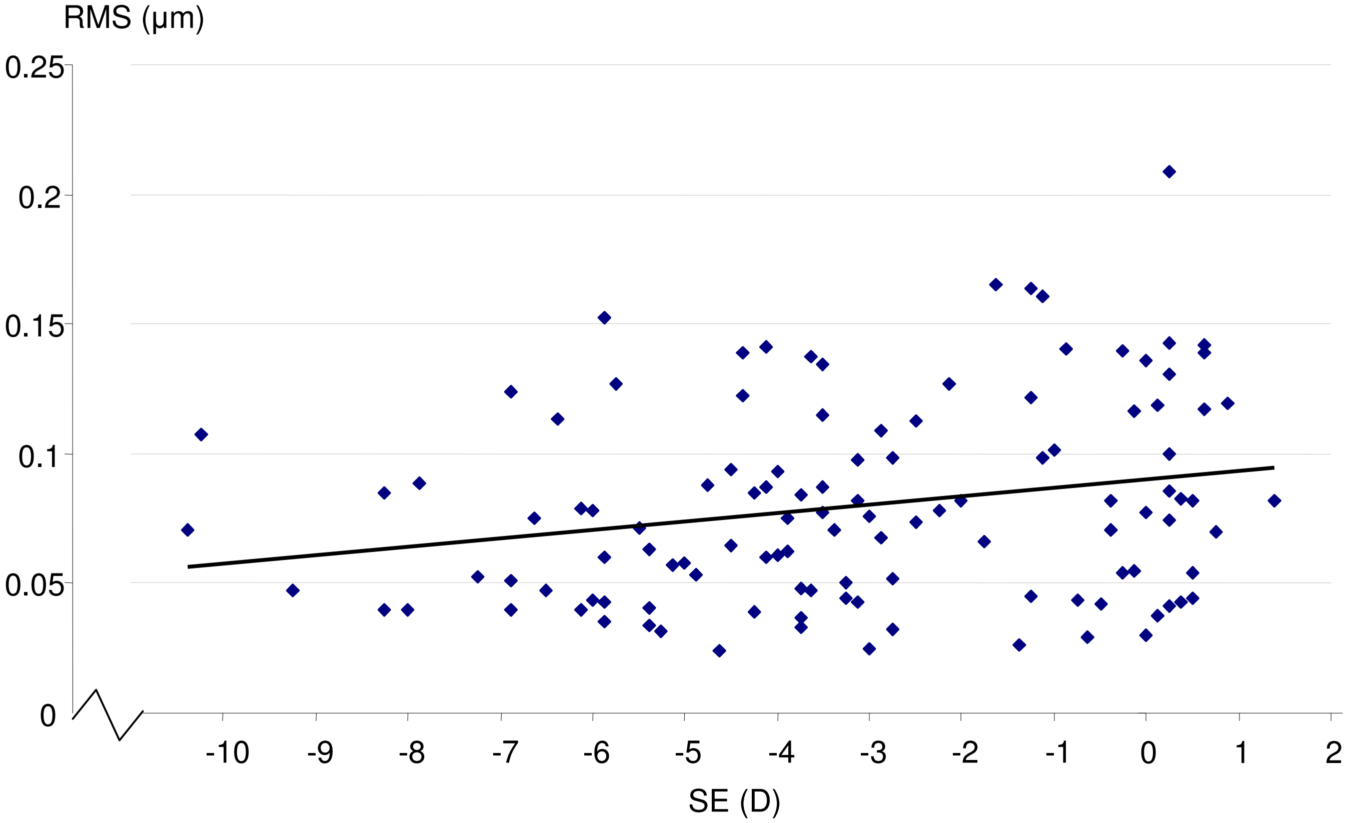


Figure 2.4
Linear regression of spherical aberration root mean square (RMS) error as function of spherical equivalent refractive error (m = 0.0043, p = 0.0022, r = 0.28)

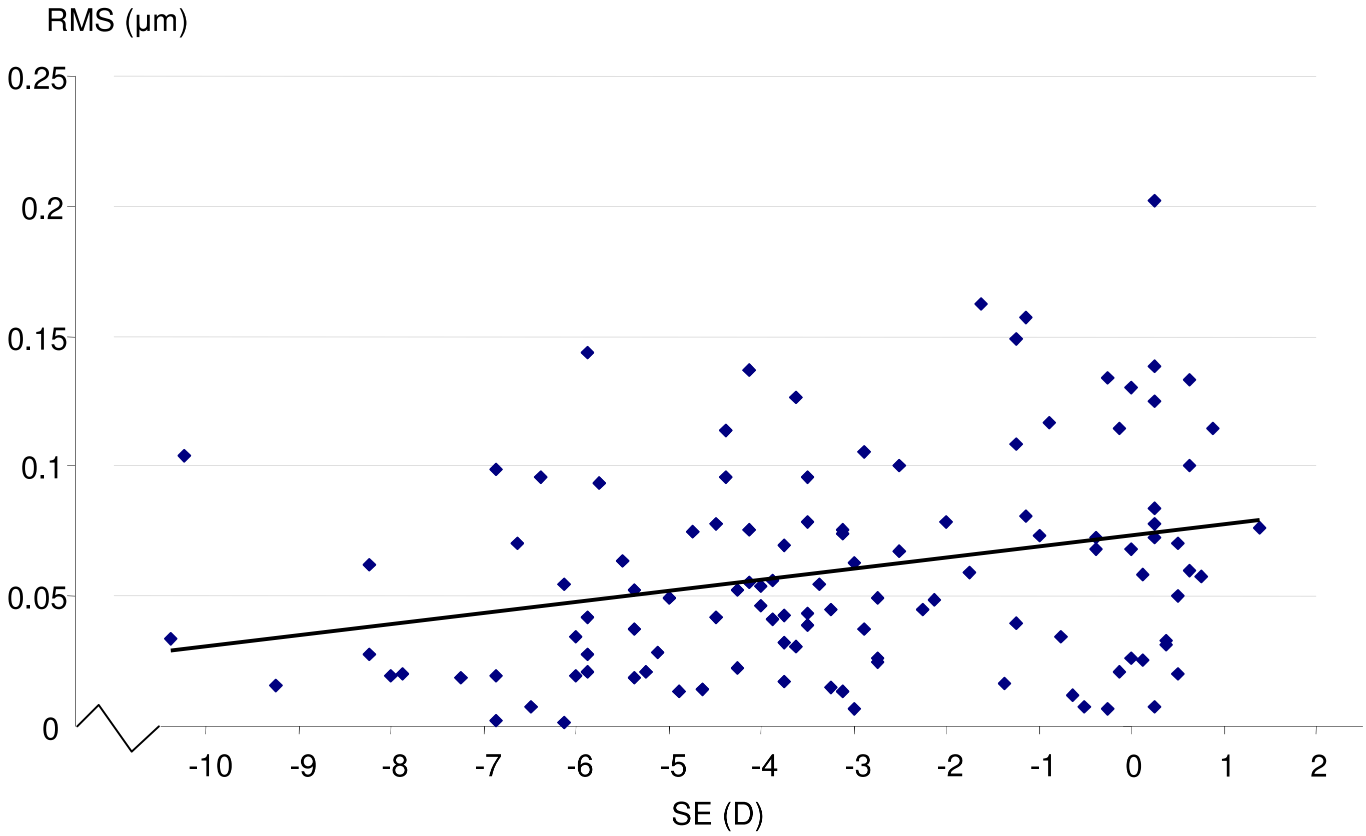


Figure 2.5
Linear regression of coma root mean square (RMS) error as function of spherical equivalent refractive error (m = -0.0012, p = 0.54, r = -0.058)

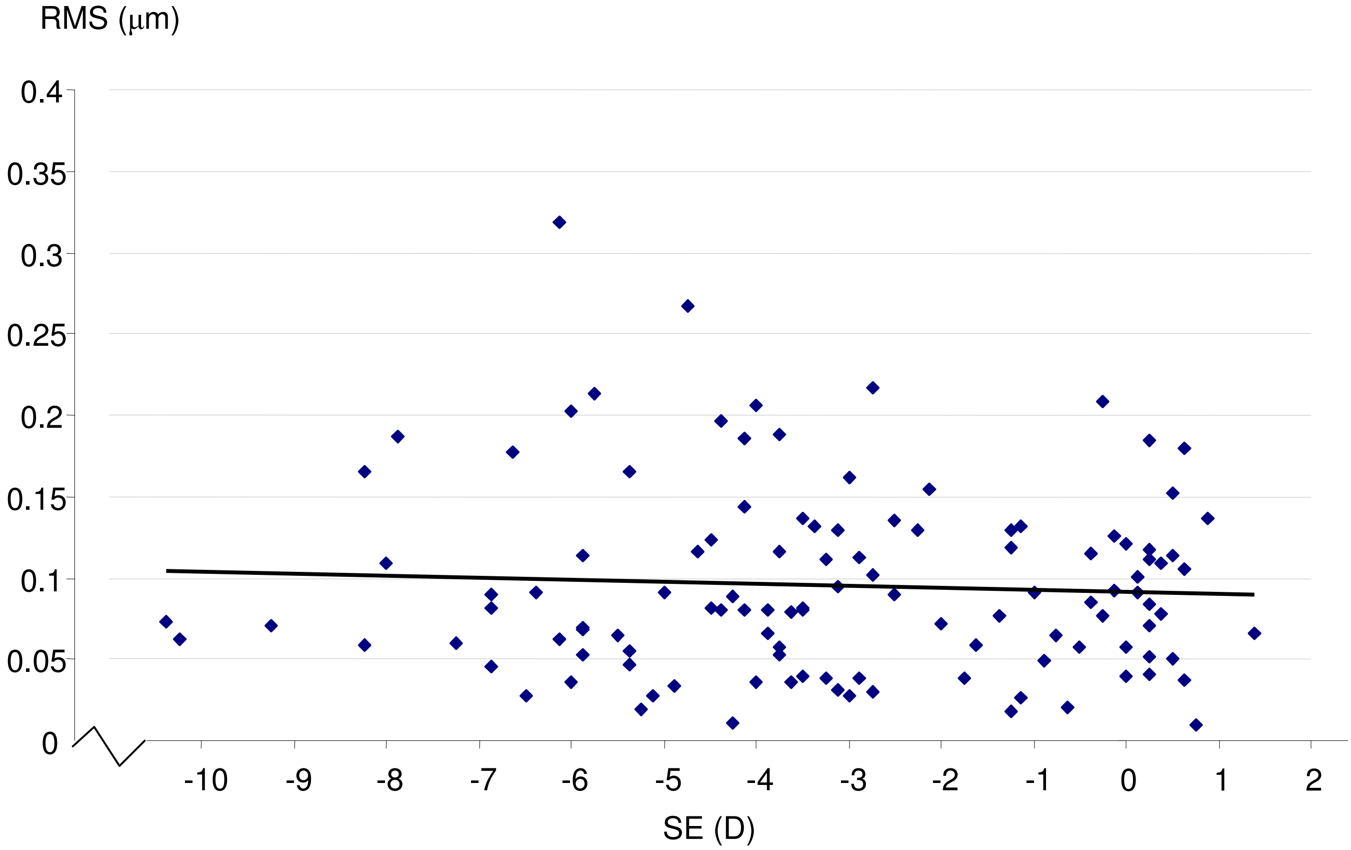
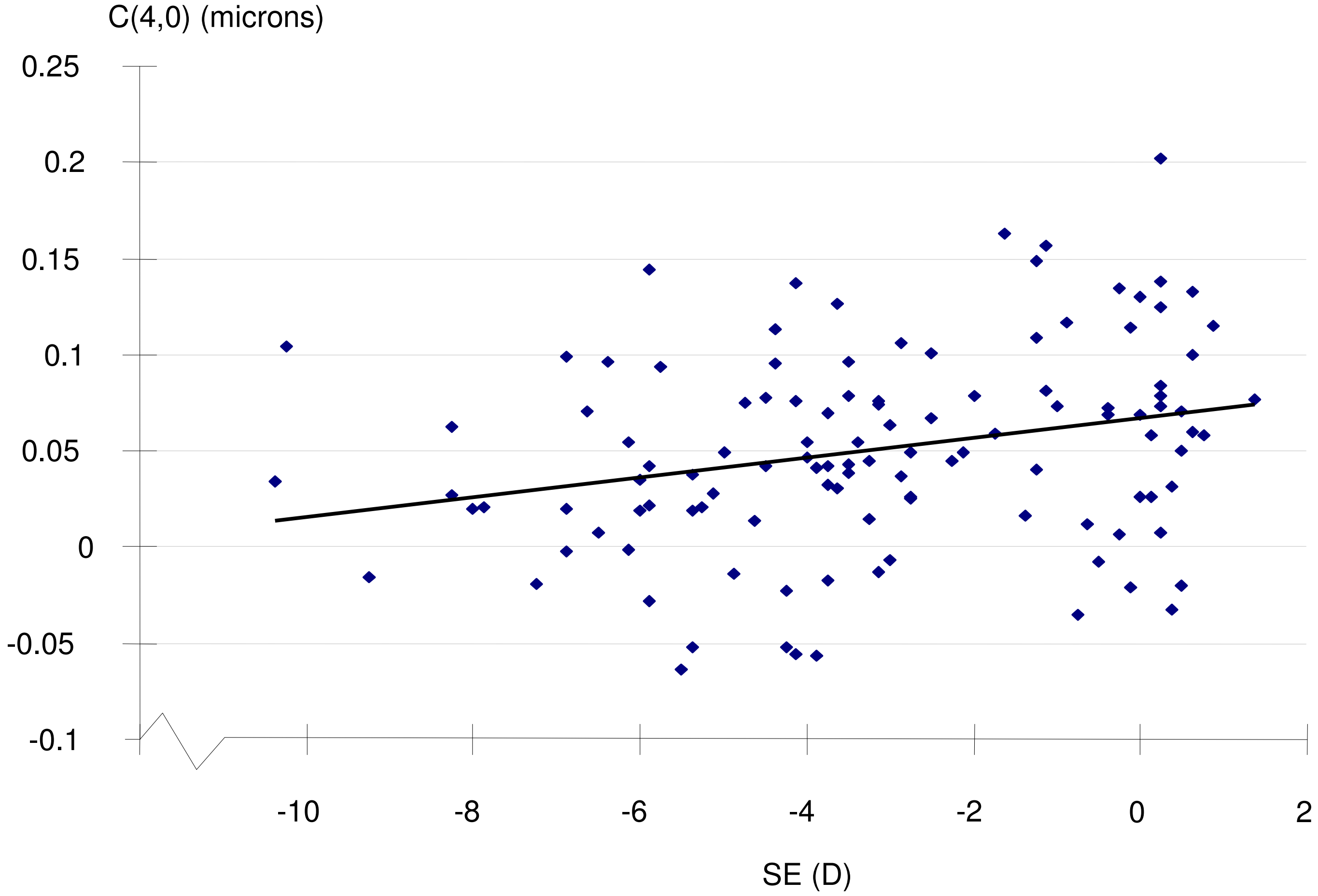


Figure 2.6
Linear regression of C(4,0) as function of spherical equivalent refractive error (m=0.0052, p=0.0033, r=0.27)



2.4 DISCUSSION

Like previous studies (Collins et al., 1995; Carkeet et al., 2002; Castejon-Mochon et al., 2002; Carkeet et al., 2002; He et al., 2002; Cheng et al., 2003), we found that third order aberrations were larger than fourth order aberrations and coma was larger than spherical aberration. In addition, coma and spherical aberration were the largest contributors to the third and fourth order aberrations, respectively (Table 2.2).

In the argument of whether aberration blur plays a role in myopia development. In support of this hypothesis, several articles have found that myopic subjects have larger spherical aberrations than emmetropic subjects (He et al., 2002; Marcos et al., 2002; Paquin et al., 2002). However, others have shown more controversial results (Collins et al., 1995; McLellan et al., 2001; Porter et al., 2001; Carkeet et al., 2002; Cheng et al., 2003). The differences across studies may be due to the different age groups and refractive error ranges. In a group of 38 subjects ranged in age from 22.9 to 64.5 years, McLellan et al. (2001) reported a significant increase in wave aberrations of the eye with age. In this study, we used a narrow age band and a wide refractive error range because a wider age range and low refractive errors may confound the study of the relationship between monochromatic aberrations and refractive development.

The fourth order aberrations ($p = 0.046$) and spherical aberration ($p = 0.019$) differed significantly among the three refractive groups. The spherical aberration of the highly myopic group was significantly smaller than that of the non-myopic group ($p = 0.0085$). This finding is interesting. If we speculate that there is no change in spherical aberration during development of myopia, this result suggests that a lesser amount of spherical aberration may be a risk factor of myopia development. Previous studies have shown that for most subjects, positive spherical aberration decreases and then becomes negative at higher levels of accommodation (Atchison et al., 1995;

Buehren and Collins, 2005; Cheng et al., 2004; Hazel et al., 2003; He et al., 2000; Ninomiya et al., 2002; Plainis et al., 2005). In contrast, if we speculate that there is a change in spherical aberration during myopic development, this result shows that spherical aberration reduces with increasing myopia. To achieve this reduction, the corneal positive spherical aberration may decrease or the crystalline lens negative spherical aberration may increase. Previous studies have shown that there is a slight reduction in corneal peripheral flattering (i.e. the corneal positive spherical aberration increased) when myopia increases (Carney et al., 1997; Horner et al., 2000). This means that a larger increase in the crystalline lens negative spherical aberration would be required to achieve the net reduction of the overall spherical aberration in increasing myopia.

This study found a small correlation between myopia and monochromatic aberrations (fourth order aberrations, spherical aberration and C(4,0)). The root mean square (RMS) of fourth order aberrations, spherical aberration and the relative value of C(4,0) tended to decrease with myopia. Similar to previous studies (Howland and Howland, 1977; Liang and Williams, 1997; Walsh et al., 1984), the total higher order aberrations, third order aberrations and coma showed large variations among the subjects. No significant correlation could be found between the RMS of these aberrations and the refractive spherical equivalents.

Our study is the first to find a relationship that high myopes have smaller fourth order aberrations and spherical aberration. Although this relationship is small, our study shows that the fourth order aberrations and spherical aberration may play a role in refractive development. However, a limitation of this cross-sectional study is that we are still uncertain whether spherical aberration and fourth order aberrations are precursors of or associated with refractive development. Longitudinal studies are required to explore this relationship further.

Chapter 3
Monochromatic Aberrations of the Anisometropic Eyes

3.1 INTRODUCTION

Vitreous depth or axial elongation is the main component contributing to the increase of myopia (Grosvenor and Scott, 1993; Lam et al., 1999). Refractive error development is known to be influenced by retinal image quality, as retinal image degradation by eyelid closure or translucent occluder results in ocular axial elongation and resultant myopia in animal models (Hodos and Kuenzel, 1984; Napper et al., 1995, 1997; Shaikh et al., 1999; Smith et al., 1999) and in humans (Calossi, 1994; Gee and Tabbara, 1988; Hoyt et al., 1981). The eye's natural optical imperfections also induce higher order errors in the wavefront that cannot be easily corrected by spectacle lenses. These higher order monochromatic aberrations degrade retinal image quality such that individuals with significant levels of these aberrations may be prone to deprivation myopia. However, much less is known about the relationship between high order monochromatic aberrations and refractive error development.

Large individual variations are found in the monochromatic aberrations of the eye from person to person (Howland and Howland, 1977; Liang and Williams, 1997; Walsh et al., 1984). The results of studying the relationship between monochromatic aberrations and refractions are controversial (Collins et al., 1995; Simonet et al., 1999; Porter et al., 2001; Carkeet et al., 2002; He et al., 2002; Marcos et al., 2002; Paquin et al., 2002; Cheng et al., 2003; Llorente et al., 2004). Using an objective double pass aberroscope, Collins et al. (1995) measured monochromatic aberrations of a group of 37 subjects and reported that the fourth order aberrations in myopes were lower than those in emmetropes. However, at least one third of the myopic eyes in this study were so aberrated that no grid image was observed. Llorente et al (2004), using the laser ray tracing technique, measured a group of hyperopes and myopes and reported that hyperopic eyes had higher aberrations than myopes. In contrast, He et al. (2002) using a subjective ray-tracing aberroscope, measured 146 young adults and found that 20 percent of myopes have larger RMS from second to seventh order aberrations and on average myopes have slightly larger combined fourth order and higher aberrations than emmetropes. No significant correlation was found between total aberrations and refractive spherical equivalents. Using a modified Hartmann-Shack method, Paquin et al. (2002) found a similar result in a population of 34 optometry students, where aberrations increase with the refractive error for pupil diameters of 5 and 9mm. Marcos et al. (2002), used an objective ray-tracing technique and reported that aberrations in highly myopic subjects increase with refractive error. Another similar study by Simonet et al. (1999) using a modified Hartmann-Shack sensor, also found that spherical aberration and coma increased with refractive error. In contrast, other studies found no link between higher order aberrations and myopia (Porter et al., 2001; Carkeet et al., 2002; Cheng et al., 2003).

Several studies have shown that there are several aberrations that are significantly correlated across the left and right eye (Porter et al., 2001; Castejon-Mochon et al., 2002). To factor out the individual variation, we investigated the relationship between the monochromatic aberrations and refractive error in anisometropes with at least a 2D spherical equivalent difference between left and right eyes. In this study, we aimed to establish whether the monochromatic aberrations in the more myopic eye are different from those in the less myopic eye of the anisometropes.

3.2 METHODS

3.2.1. Subjects

Twenty-six anisometropic Chinese subjects (age range, 19-48; mean age, 29.4), with at least a 2.00D spherical equivalent difference between eyes, were enrolled in this study. Subjects having any pathology (i.e., keratoconus, cataract, etc.) or ocular surgery were not included. The monochromatic aberrations of the eyes were measured in a dark room with the natural pupils larger than 5mm. The refractions, corneal curvatures and axial lengths of the eyes were measured under natural accommodation (Chat and Edwards, 2001; Heatlley et al., 2002; Mallen et al., 2001). Informed consent was given to every subject before participation.

3.2.2. Apparatus

The Complete Ophthalmic Analysis System (COAS) Wavefront Analyzer, a clinical Shack-Hartmann aberrometer, was used to measure the monochromatic aberrations of the eyes, based on the Zernike polynomial. The Shin-Nippon SRW5000 autorefractor, the Canon RK5 Autorefractor & Autokeratometer and the A-scan ultrasonography were used to measure the refractive errors, the corneal curvatures and the axial lengths of the subjects, respectively.

3.2.3. Procedures

The monochromatic aberrations of the right eyes of the 26 subjects were measured under natural accommodation in a dark room. Natural pupils were used. All pupils were larger than 5 mm in diameter after adaptation to the dark. The subject was placed in a chin rest with the right eye looking into the examination window. The subject was instructed to focus on the fixation target of the COAS in order to align the optical axis of the eye and to link it to the optical axis of the COAS. The eye that was not being examined had a free view past the COAS. The monochromatic aberrations were automatically calculated up to and including fourth order using 14 Zernike terms. The pupil used for computation of the aberrations was 5mm. Five measurements were taken after each blink and the averages of coefficients from ocular aberrations were used for analysis. The same procedures were repeated on the left eyes.

Refractive errors were measured with Shin-Nippon SRW500 autorefractor with a target at 6m, corneal curvatures by Canon RK5 autorefractor & autokeratometer, and axial lengths using A-scan ultrasonagraphy after local anesthetic by 0.4% novesin.

3.2.4. Data Analysis

Among the 26 anisometropic subjects, eyes with more negative spherical equivalents were classified as more myopic eyes and eyes with less negative spherical equivalents were classified as less myopic eyes.

The analysis of the monochromatic aberration of the eye was based on a 5mm pupil diameter. The coefficients of the Zernike polynomials are correspond to the order recommended by the OSA Standardization Committee (Thibos et al., 2000; Thibos et al., 2002). The root mean square (RMS) values of the total higher order aberrations (third to fourth order aberrations), third order aberrations, fourth order aberrations, spherical aberration and coma were calculated for analysis. Paired t-tests were used to evaluate the differences of the spherical equivalents, axial lengths, corneal curvatures and aberrations between the more myopic and less myopic eyes of the anisometropic subjects.

3.3 RESULTS

All 26 anisometropic subjects completed the study. The spherical equivalents and axial lengths of the more myopic eyes were significantly ($p < 0.0001$ and $p < 0.0001$, respectively) larger than the less myopic eyes (Table 3.1). The corneal curvatures and astigmatism were not significantly ($p = 0.66$ and $p = 0.91$, respectively) different between the more myopic and less myopic eyes (Table 3.1). The difference in spherical equivalent between the eyes of the anisometropic subjects is associated with the difference in the axial lengths of the eyes.

Table 3.1
Distribution of ocular data

	SE (D) ± SD	AXL (mm) ± SD	Mean K (D) ± SD	CYL (D) ± SD
More myopic eye	-5.20 ± 3.66	25.62 ± 1.69	43.65 ± 1.63	-1.15 ± 1.01
Less myopic eye	-1.80 ± 3.74	24.36 ± 1.73	43.62 ± 1.61	-1.17 ± 0.95
Paired t-test	p<0.0001*	p<0.0001*	p=0.66	p=0.91

SE, mean refractive spherical equivalence; AXL, mean axial length; K, mean corneal curvature; CYL, mean astigmatism; SD, standard deviation
*Significant at the 0.05 level

Table 3.2 shows the total higher order (third to fourth order) aberrations, third order aberrations, fourth order aberrations, spherical aberration and coma of the anisometropic eyes. The more myopic eyes showed statistically significantly lower total higher order aberrations, third order aberrations and spherical aberration than the less myopic eyes ($p < 0.05$, $p < 0.05$ and $p < 0.01$, respectively). The more myopic eyes also showed lower fourth order aberration and coma than the less myopic eyes but these were not significant ($p = 0.060$ and $p = 0.084$, respectively).

Table 3.2
Monochromatic aberration in the anisometropic eyes (Mean (RMS) ± SD)

	Total higher order aberration	Third order aberration	Fourth order aberration	Spherical aberration	Coma
More myopic eye	0.200 ± 0.079	0.157 ± 0.084	0.110 ± 0.050	0.088 ± 0.055	0.117 ± 0.077
Less myopic eye	0.245 ± 0.106	0.201 ± 0.097	0.127 ± 0.073	0.108 ± 0.062	0.147 ± 0.089
Paired t-test	p<0.05*	p<0.05*	p=0.060	p<0.01*	p=0.084

RMS, root mean square; SD, standard deviation
*Significant at the 0.05 level

3.4 DISCUSSION

As shown in Table 3.1, the axial lengths of the more myopic eye were significantly larger than the less myopic eyes and no significant different was found in the corneal curvatures. The amount of myopia was highly dependent on axial length, which is in agreement with previous studies (Carroll, 1982).

In our study, among 26 anisometropic subjects, we found that the aberrations of the more myopic eyes were smaller than the aberrations of the less myopic eyes (Table 3.2). The total higher order aberrations, third order aberrations and spherical aberration showed statistically significant differences ($p < 0.05$, $p < 0.05$ and $p < 0.01$, respectively), and the fourth order aberrations and coma did not reach statistically significant levels. As shown in Table 3.3, there was a high degree of correlation between Zernike coefficients in both eyes of the anisometropic subjects, with negative correlation values found in coefficients that exhibited odd symmetry about the y-axis (C(2,-2), C(3,1), C(3,3), C(4,-2) and C(4,-4)). All but the last two were significant, indicating that the anisometropic subjects had considerable mirror symmetry between the two eyes, which is in agreement with previous studies (Porter et al., 2001; Castejon-Mochon et al., 2002). The mean absolute correlation coefficient for the anisometropic subjects was 0.56 ± 0.30.

Table 3.3
Correlation coefficients between Zernike terms of the left and right eyes of the anisometropes

Zernike terms	Correlation coefficient	P value
C(2,-2)	-0.5266	0.0057*
C(2,0)	0.9514	<0.0001*
C(2,2)	0.7996	<0.0001*
C(3,-3)	0.4646	0.0168*
C(3,-1)	0.7446	<0.0001*
C(3,1)	-0.6817	0.0001*
C(3,3)	-0.7471	<0.0001*
C(4,-4)	-0.0745	0.7175
C(4,-2)	-0.0889	0.6660
C(4,0)	0.9008	<0.0001*
C(4,2)	0.3912	0.0481*
C(4,4)	0.3317	0.0978

*Significant at the 0.05 level

In a large population study, Porter et al. (2001) reported evidence of mirror symmetry between left and right eyes. Using a near-infrared Shack-Hartmann wave-front sensor, in a population of 59 young subjects, Castejon-Mochon et al. (2002) also reported a good correlation between most of the second and third order terms for the left and right eyes. In our study, anisometropic eyes, with different degrees of myopia between left and right eyes, showed significant different aberrations between the more myopic and the less myopic eyes. The correlations between monochromatic aberrations and spherical equivalent of the anisometropic eyes and the subjects of Chapter 2 are shown in Figures 3.1 to 3.6. The slopes for fourth order aberrations and spherical aberration were significantly different from zero in both the anisometropic eyes and the subjects of Chapter 2 (Figure 3.3 and Figure 3.4). The slope for C(4,0) was significantly different from zero in the subjects of Chapter 2 but not in the anisometropic eyes (Figure 3.6). The slopes in Figure 3.4 and Figure 3.6 were not significantly different ($p = 0.27$ and $p = 0.36$, respectively) while the slopes in Figure 3.3 were significant different ($p = 0.036$). These suggest that anisometropic eyes might be having an effect beyond that expected from the levels of ametropia. We suggest that our findings could be attributed to the relationship between monochromatic aberrations and refraction. In anisometropic eyes, the axial lengths were significantly different between the more myopic and less myopic eyes. More myopic eyes with longer axial lengths showed significantly smaller total higher order aberrations, third order aberrations and spherical aberration than less myopic eyes. Monochromatic aberrations may have an association with myopic development.

Figure 3.1
Comparison of total high order root mean square (RMS) error (Zernike orders 3 to 4) for the subjects of Chapter 2 (rhombus symbols) with those for anisometropic eyes (triangle symbols). Solid line is linear regression of the subjects of Chapter 2 (m=0.0005, p=0.79, r=0.025). Dotted line is linear regression of anisometropic eyes (m=0.0061, p=0.065, r=0.26)

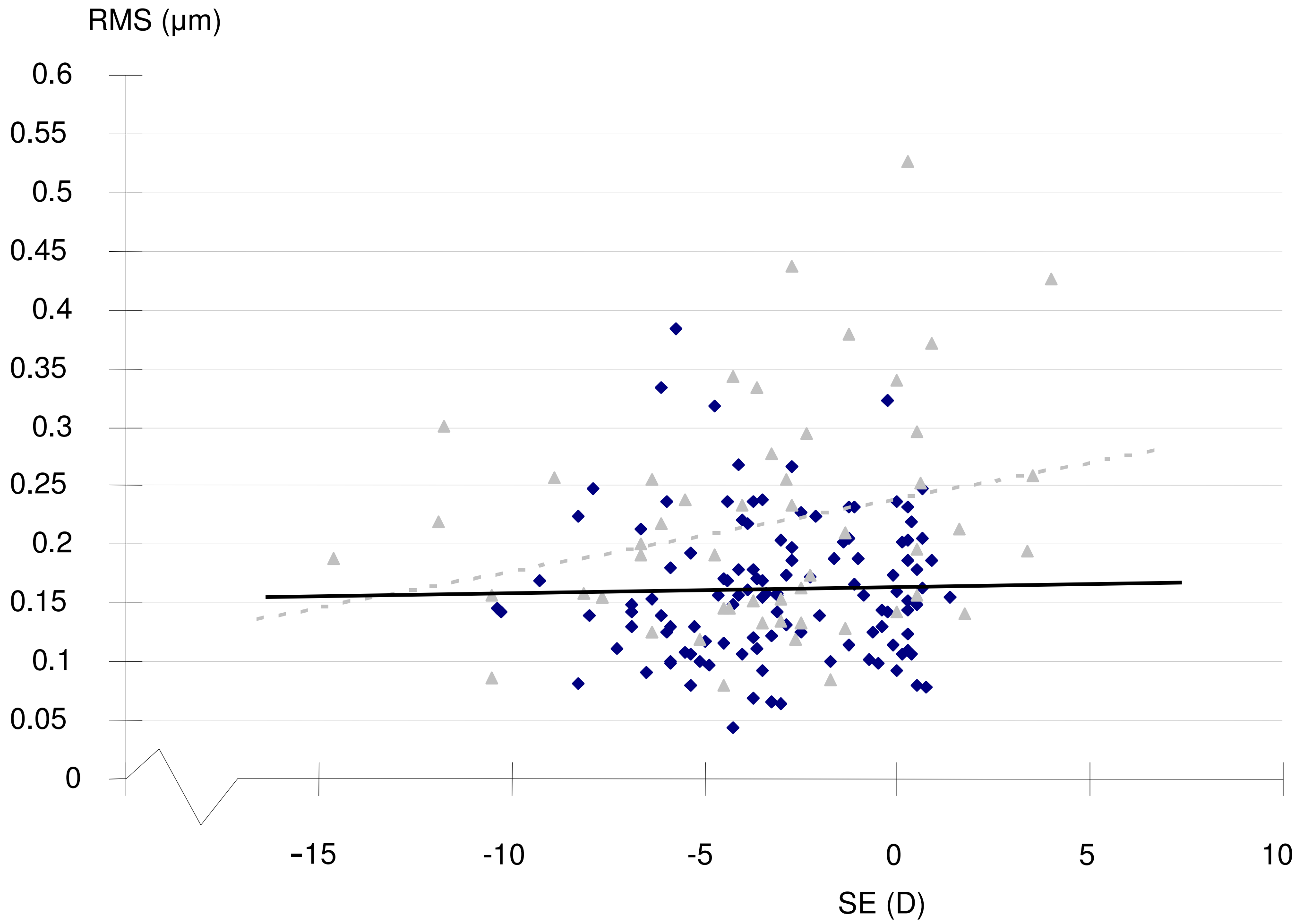


Figure 3.2
Comparison of third order root mean square (RMS) error for the subjects of Chapter 2 (rhombus symbols) with those for anisometropic eyes (triangle symbols). Solid line is linear regression of the subjects of Chapter 2 (m=-0.0016, p=0.44, r=-0.072). Dotted line is linear regression of anisometropic eyes (m=0.0043, p=0.18, r=0.19)

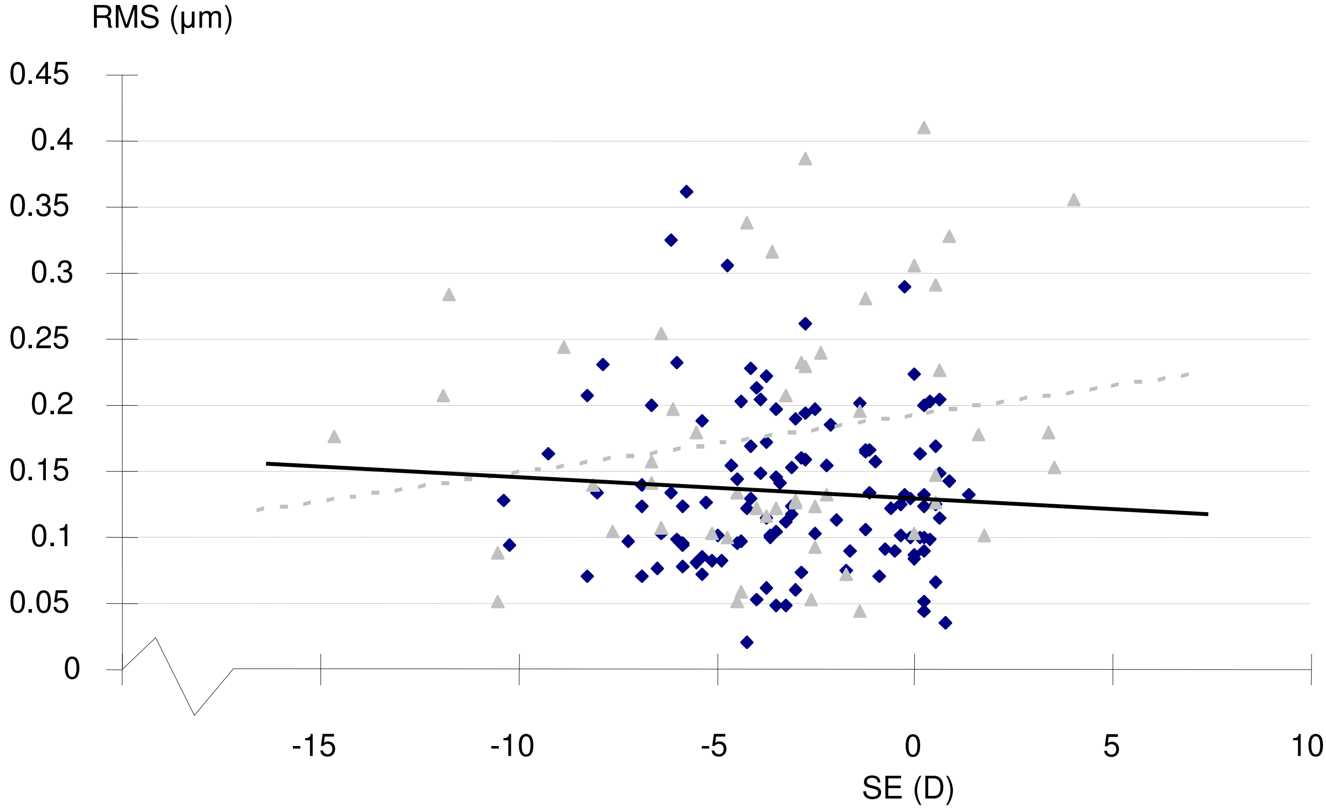


Figure 3.3
Comparison of fourth order root mean square (RMS) error for the subjects of Chapter 2 (rhombus symbols) with those for anisometropic eyes (triangle symbols). Solid line is linear regression of the subjects of Chapter 2 (m=0.0033, p=0.011, r=0.24). Dotted line is linear regression of anisometropic eyes (m=0.0048, p=0.023, r=0.32)

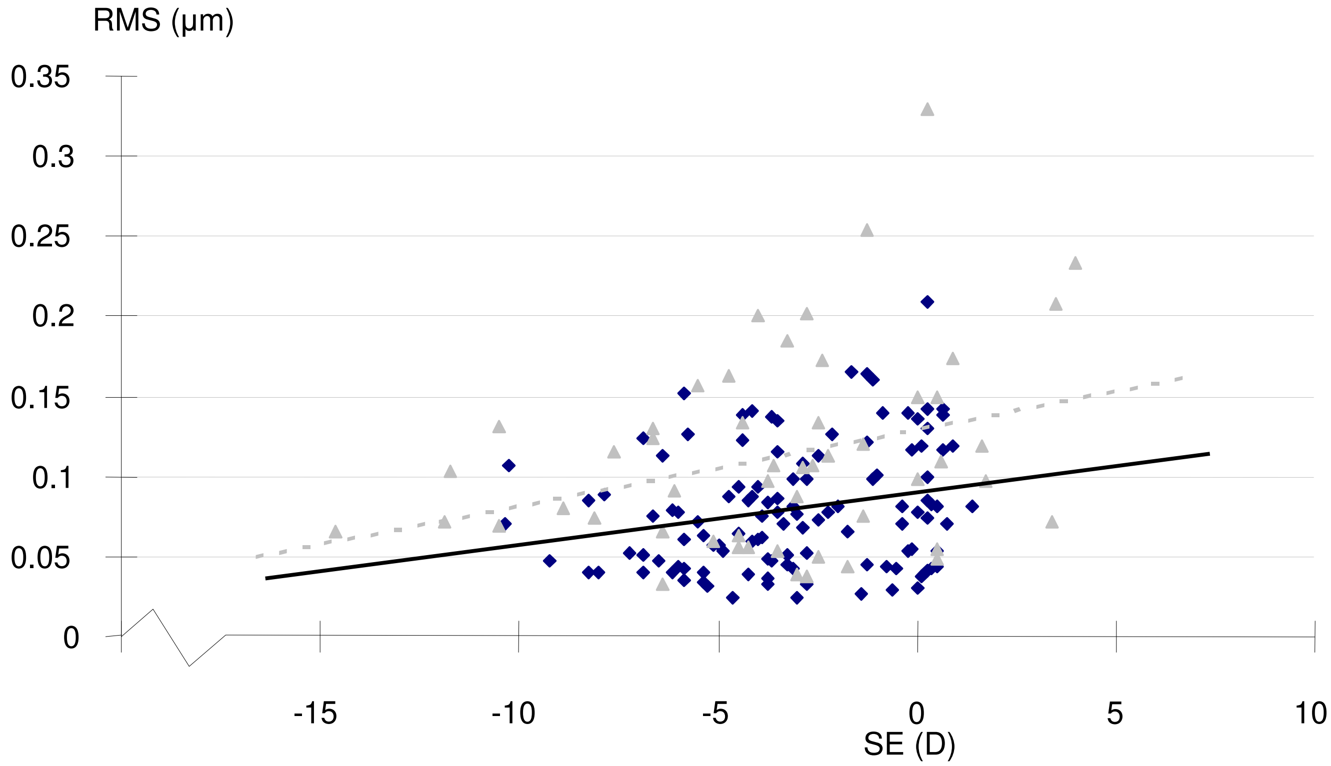


Figure 3.4
Comparison of spherical aberration root mean square (RMS) error for the subjects of Chapter 2 (rhombus symbols) with those for anisometropic eyes (triangle symbols). Solid line is linear regression of the subjects of Chapter 2 (m=0.0043, p=0.0022, r=0.28). Dotted line is linear regression of anisometropic eyes (m=0.0041, p=0.038, r=0.29)

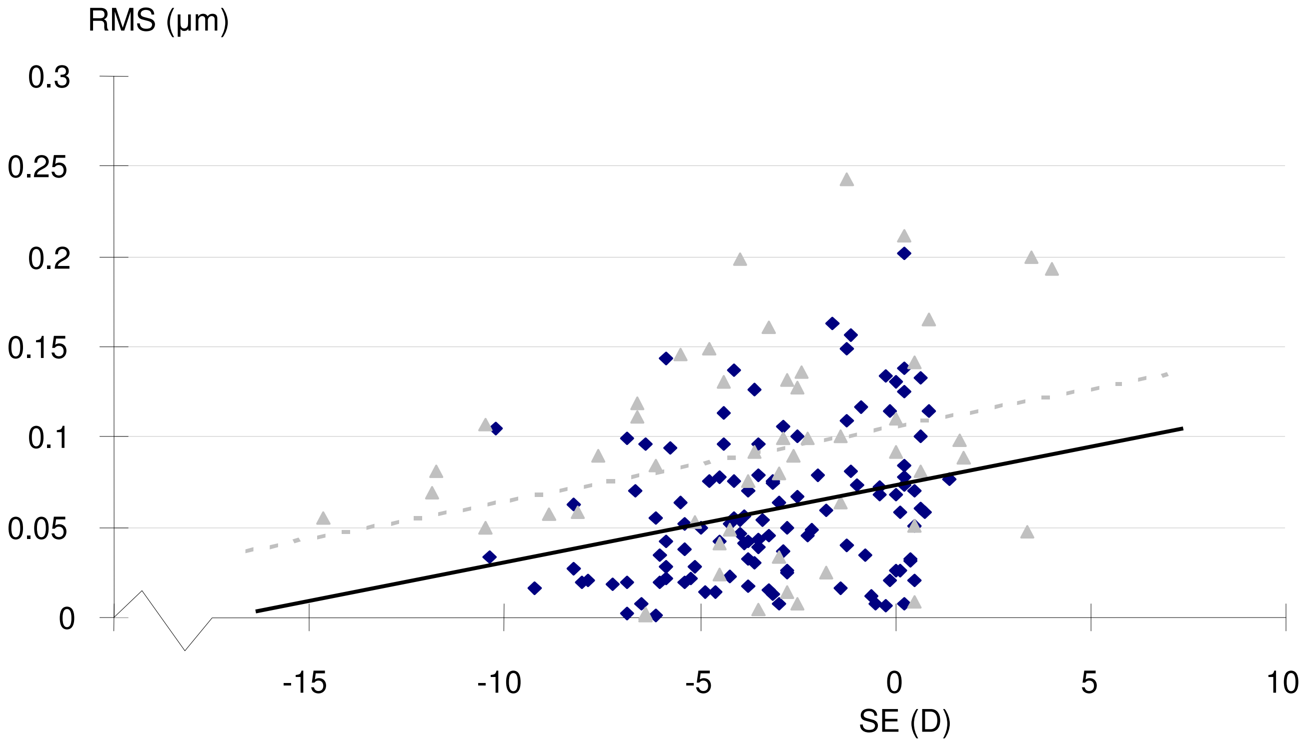


Figure 3.5
Comparison of coma root mean square (RMS) error for the subjects of Chapter 2 (rhombus symbols) with those for anisometropic eyes (triangle symbols). Solid line is linear regression of the subjects of Chapter 2 (m=-0.0012, p=0.54, r=-0.058). Dotted line is linear regression of anisometropic eyes (m=0.0010, p=0.73, r=0.049)

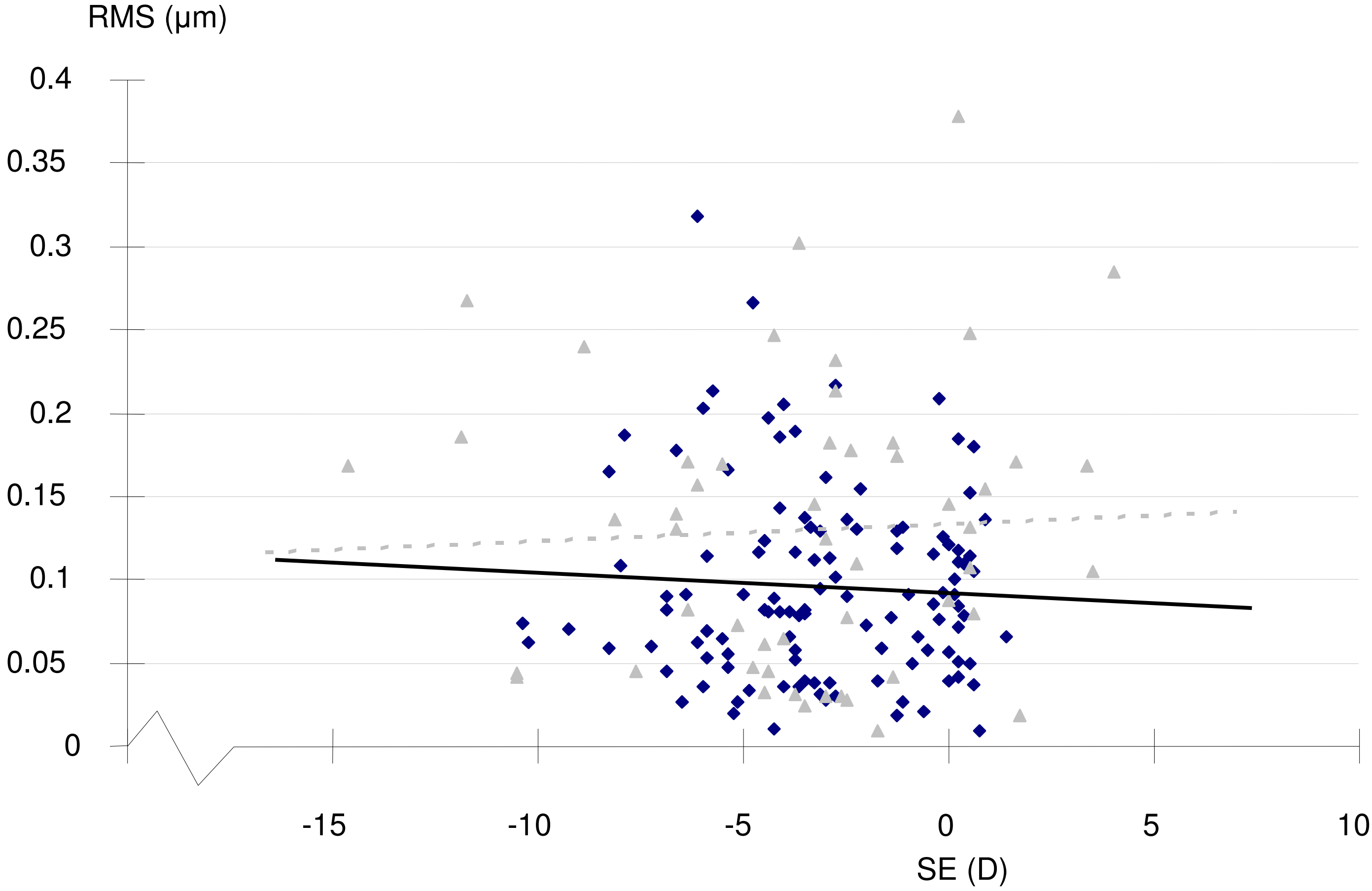
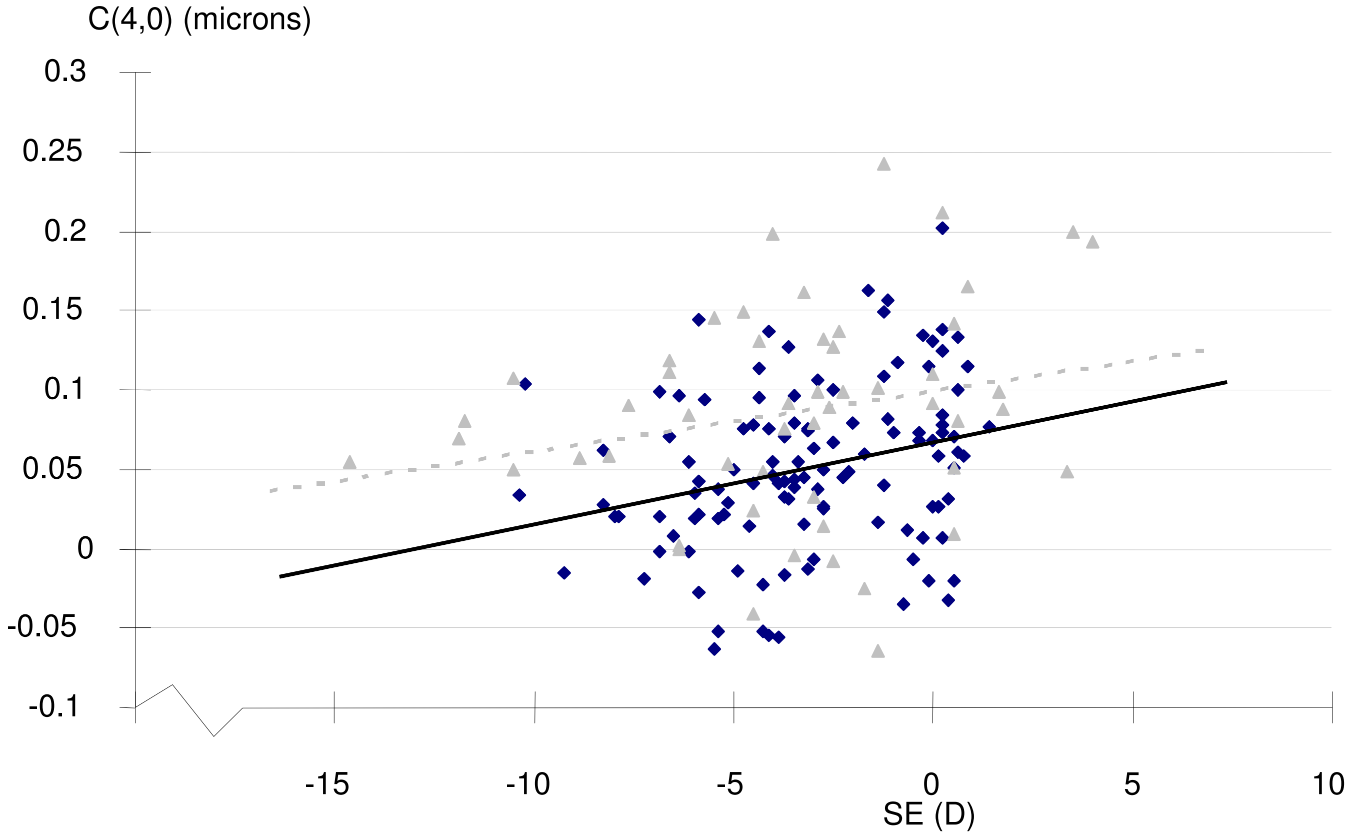


Figure 3.6
Comparison of C(4,0) for the subjects of Chapter 2 (rhombus symbols) with those for anisometropic eyes (triangle symbols). Solid line is linear regression of the subjects of Chapter 2 (m=0.0052, p=0.0033, r=0.27). Dotted line is linear regression of anisometropic eyes (m=0.0038, p=0.097, r=0.23)



In agreement with the hypothesis that increased aberrations play a role in the development of myopia, several previous studies have reported higher amounts of aberration in high myopes (He et al., 2002; Paquin et al., 2002). In contrast, Llorente et al (2004) reported that hyperopic eyes tend to have greater total higher order aberrations than myopic eyes. Our findings do not support the hypothesis that increased aberrations play a role in the development of myopia. Monochromatic aberrations may be an accompaniment to myopia, related to the axial elongation, rather than a precursor. Using a reduced-eye model, Cheng et al. (2003) predicted spherical aberration should increase systematically with axial elongation. Our results show a larger spherical aberration in the less myopic eyes of the anisometropic subjects, which does not agree with that prediction. The reason for this lack of agreement may be the difference in the optical components of the anisometropic eyes. In order to achieve a smaller spherical aberration in the more myopic eye (longer axial length), the corneal positive spherical aberration may be smaller or the crystalline lens negative spherical aberration may be larger in the more myopic eye.

Our study is the first to investigate the relationship between the monochromatic aberrations and refractive errors among anisometropic eyes. In order to factor out the individual variations, anisometropes with significant refractive error differences between left and right eyes, made a good population to investigate this relationship. Our results provide no evidence to support the suggestion that high monochromatic aberrations are a precursor to myopia. It is more likely that the extent of monochromatic aberrations plays a role as an accompaniment to myopia. Longitudinal studies are needed to further investigate the relationship between monochromatic aberrations and refractive development.

Chapter 4

A Longitudinal Study of Refractive Error Changes and Monochromatic Aberrations Changes in Hong Kong Primary School Children - in school measurement and under natural accommodation

4.1 INTRODUCTION

It is well established that refractive error development is influenced by retinal image quality. Animal studies have shown that retinal image degradation can lead to ocular elongation and resultant myopia (Hodos and Kuenzel, 1984; Napper et al., 1995, 1997; Shaikh et al., 1999; Smith et al., 1999). Similar outcomes have been suggested humans (Calossi, 1994; Gee and Tabbara, 1988; Hoyt et al., 1981). The eye's natural optical imperfections also induce higher order errors in the wavefront that cannot be easily corrected with spectacle lenses. These higher order monochromatic aberrations degrade retinal image quality. Individuals with significant levels of these aberrations may be prone to form deprivation myopia. However, conflicting findings have been reported regarding the relationship between higher order aberration and refractive development.

Studies have shown large individual variations in the monochromatic aberrations of human eyes (Howland and Howland, 1977; Liang and Williams, 1997; Walsh et al., 1984). Applegate (1991), using a subjective single-pass aberroscope, found that myopic eyes have higher amount of aberrations. Simonet et al. (1999), using a modified Hartmann-Shack sensor, found a similar result in a population of ametropes aged from 18 to 57 years old; spherical aberration and coma increased with refractive error. A similar study by Paquin et al. (2002), using a modified Hartmann-Shack method, also found that aberration increases with the refractive error for pupil diameters of 5 and 9mm. Marcos et al. (2002), using an objective ray-tracing technique, reported significantly increased aberrations in young myopia subjects. He et al. (2002), using a subjective ray-tracing aberroscope, in a sample of 146 young adults, found that on average, myopes have slightly larger combined fourth order and higher aberrations than emmetropes. No significant correlation was found between total aberrations and refractive spherical equivalents. On the other hand, Collins et al. (1995), using an objective double-pass aberroscope, found that the fourth order aberrations in myopic subjects were lower than that in emmetropic subjects. However, in this study, at least one third of the myopic eyes were too aberrated and no grid image was observed. Llorente et al. (2004), using the laser ray tracing method, found that hyperopic eyes had higher aberrations than myopic eyes.

With the further development and commercialization of the Hartmann-Shack aberrometer (Atchison 2005; Liang et al., 1994; Liang and Williams., 1997), individual aberration can now be measured within a few seconds. Several studies have used of these new instruments to examine large subject populations (Porter et al., 2001; Carkeet et al., 2002; Cheng et al., 2003). Porter et al. (2001), in a population of 109 normal subjects, found no link between higher order aberrations and refractive errors. Carkeet et al. (2002) measured the higher order aberrations in 273 cyclopleged Singaporean school children. Although there were some variations with refractive error and race, the authors concluded that there was no evidence to support the hypothesis that spherical aberration played a causative role in myopia development. Cheng et al. (2003), in a population of 100 young adult subjects, also found no systematic variations between aberrations and degree of ametropia.

Differences in the findings from previous studies may due to different subject groups, techniques and methods of analysis. Also, differences between individuals may also be a main confounding factor. All previous studies were examining were cross-sectional in nature. To minimize these confounding factors, we conducted a 1-year longitudinal study in a relatively large group of children.

4.2 METHODS

4.2.1. Subjects

Nine hundred and ninety-four Primary 2 and Primary 3 Chinese schoolchildren from 3 schools participated in this study. Subjects with any pathology (e.g. cataract, strabismus), history of ocular surgery, wearing orthokeratology lenses, wearing kids progressive lenses or wearing contact lenses were excluded. Among the 994 subjects, 964 of them (492 Females and 472 males) completed all two assessments, at the beginning and at the end of the 1-year period. Mean subject age for females was 8.15 years old (range 7 to 9 years) and for males was 8.18 years old (range 7 to 9 years). All measurements were performed at the subjects' schools. The monochromatic aberrations of the eyes were measured in a dark room with natural pupils larger than 5mm in diameter. The refractions and axial lengths were measured under natural accommodation (Chat and Edwards, 2001; Heatlley et al., 2002; Mallen et al., 2001). Informed consent was obtained from every subject's parent before participation.

4.2.2. Apparatus

The Complete Ophthalmic Analysis System (COAS) Wavefront Analyzer, a clinical Shack-Hartmann aberrometer, was used to measure the monochromatic aberrations of the eyes. The Shin-Nippon SRW5000 autorefractor and the Zeiss IOL Master were used to measure the refractive errors and the axial lengths of the subjects respectively.

4.2.3. Procedures

All measurements were taken at the respective primary school during the school hours over a period of approximately 3 to 5 days. The refractive errors of the right eyes and left eyes of the subjects were measured 3 times under natural accommodation using the Shin-Nippon SRW500 autorefractor with a fixation target set at 6m. Axial lengths were then measured 3 times using Zeiss IOL Master. Lastly, the monochromatic aberrations were measured in a dark room. Natural pupils were used. All pupils were larger than 5 mm in diameter after adaptation to the dark. The right eyes of the subjects were measured 5 times after each blink. The monochromatic aberrations were automatically calculated up to and including fourth order using 14 Zernike terms. The pupil diameter used for computation of the monochromatic aberrations was 5mm. Results reported were based on the average value in each eye. The left eyes of the subjects were then measured under the same conditions. The procedures were repeated after one year.

4.2.4. Data Analysis

Previous studies have reported strong correlation of the components of refractive error (McKendrick & Brennan, 1996) and higher order monochromatic aberrations (Porter et al., 2001) between left and right eye. Therefore, data for the right eyes only are reported in this chapter. Data for left eyes are reported in the appendix.

All subjects were categorized into twelve groups according to their astigmatism and mean refractive spherical equivalent (SE) at the beginning of the 1-year period and their mean refractive spherical equivalent change at the end of the 1-year period (Table 4.1).

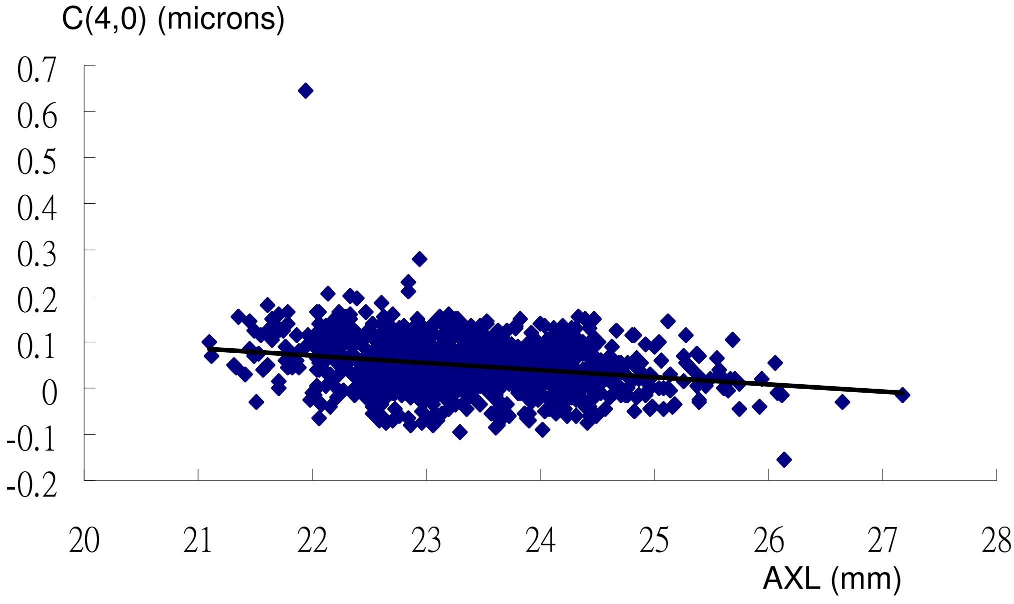
The analysis of the monochromatic aberration of the eye was based on a 5mm-pupil diameter. The coefficients of the Zernike polynomials correspond to the order recommended by the OSA Standardization Committee (Thibos et al., 2000; Thibos et al., 2002). The root mean square (RMS) values of the total higher order aberrations (third to fourth order aberrations), second order aberrations (exclude defocus), third order aberrations, fourth order aberrations, spherical aberration and coma were calculated for analysis.

The variance of aberrations among groups at the beginning of the 1-year period was analyzed to investigate whether different aberration level was a risk factor of refractive development. One-way analysis of variance was conducted with the second order, third order, fourth order, spherical aberration, coma and total higher order aberrations as the dependent variables, followed by Turkey post hoc testing. The statistical approach in assessing whether different refractive change had an effect on aberration change was to use paired t-test, evaluate the differences of the monochromatic aberrations between beginning of the 1-year period and end of the 1-year period.

4.3 RESULTS

Nine hundred and sixty four children completed the study and the relationship between C(4,0) and axial length at the beginning of the 1-year period was shown in Figure 4.1. Linear regression analysis showed that the slope was significantly different from zero ($p < 0.0001$, $r = -0.25$).

Figure 4.1
Linear regression of C(4,0) as function of axial length (m=-0.016, p<0.0001, r=-0.25) at the beginning of the 1-year period



Spherical equivalent change (ΔSE, SE of older eye minus SE of younger eye) was significantly correlated with initial C(2,0) ($p < 0.0001$, $r = -0.31$) and initial axial length ($p < 0.0001$, $r = -0.29$) (Figure 4.2 and Figure 4.3, respectively). Figure 4.4 and Figure 4.5 have shown that spherical equivalent change was not significantly correlated with initial C(4,0) ($p = 0.40$, $r = 0.027$) and initial total higher order aberration ($p = 0.20$, $r = 0.41$) respectively.

Figure 4.2

Linear regression of spherical equivalent change as function of initial C(2,0) (m=-0.14, p<0.0001, r=-0.31)

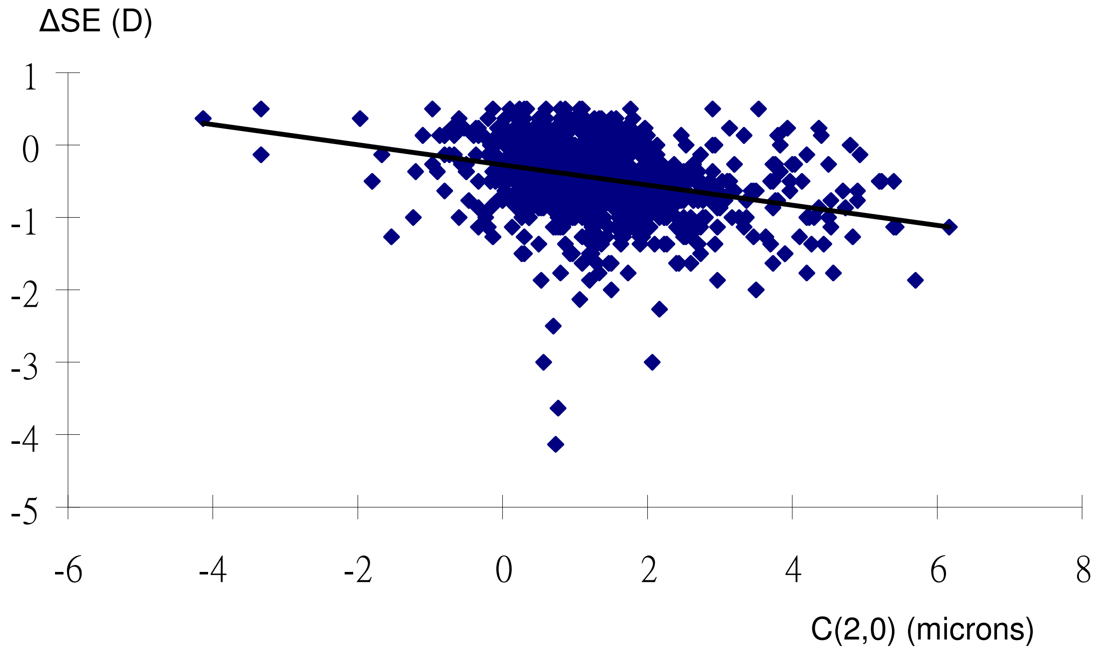


Figure 4.3

Linear regression of spherical equivalent change as function of initial axial length (m=-0.17, p<0.0001, r=-0.29)

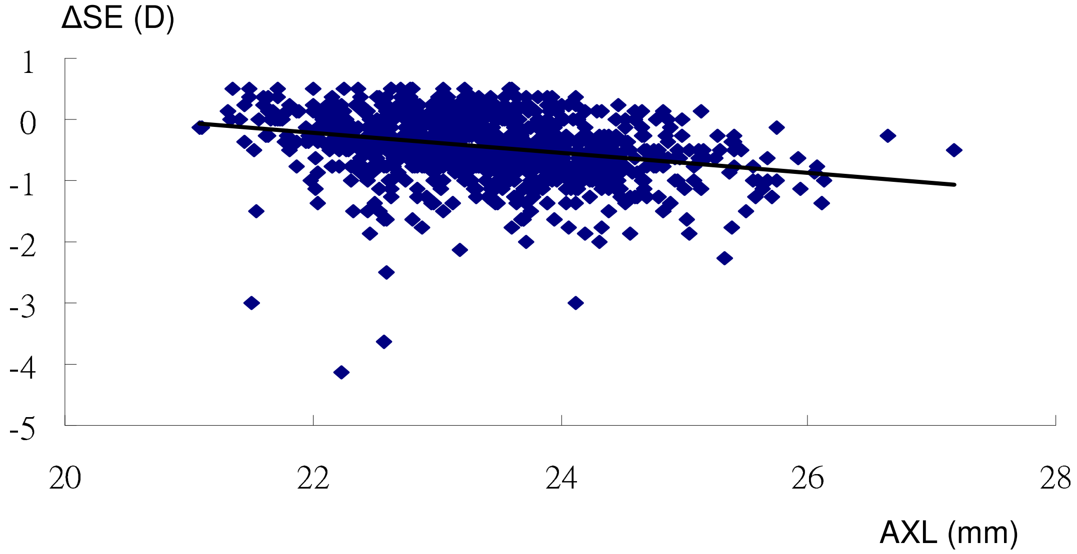


Figure 4.4

Linear regression of spherical equivalent change as function of initial C(4,0) (m=0.24, p=0.40, r=0.027)

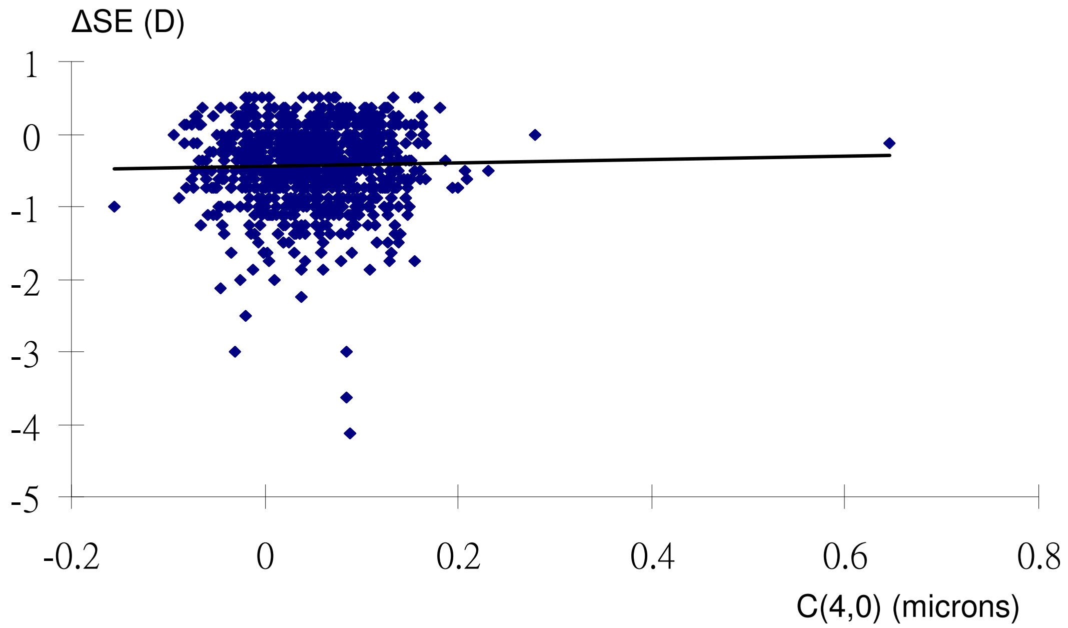
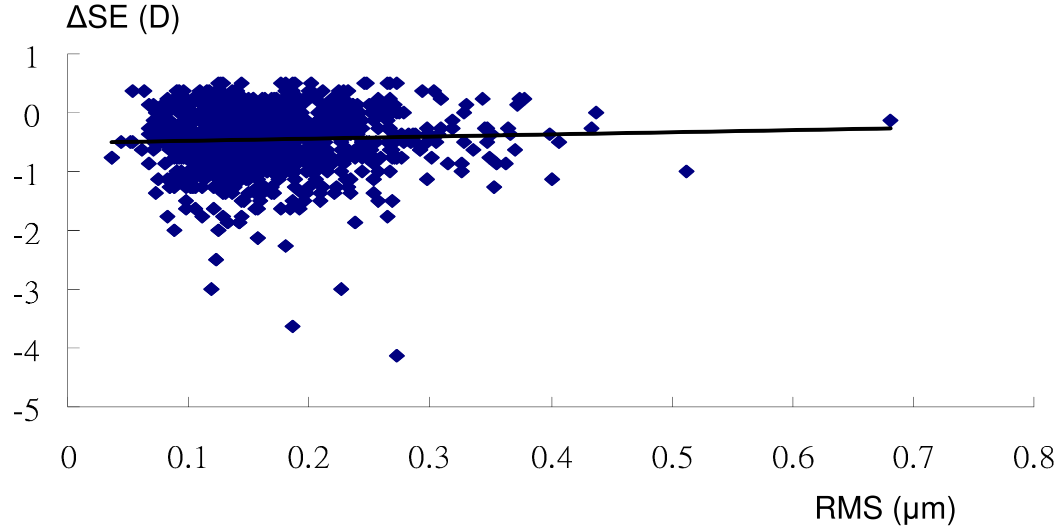


Figure 4.5

Linear regression of spherical equivalent change as function of initial total higher order aberrations (m=0.33, p=0.20, r=0.041)



All 964 children were divided into twelve different refractive groups (Table 4.1). The grouping was based on the astigmatism and spherical equivalent at the beginning of the 1-year period and the refractive error change at the end of the 1-year period. The subjects were first divided into two groups: low astigmatism (≥ -1.00D) and high astigmatism (< -1.00D). In the low astigmatism group, subjects were then divided into six groups: myopia (SE < -0.75D) with refractive change (SE change ≥ 0.50D), 187 subjects; myopia without refractive change (SE change < 0.50D), 63 subjects; emmetropia (+0.75D ≥ SE ≥ -0.75D) with refractive change, 196 subjects; emmetropia without refractive change, 371 subjects; hyperopia (SE > +0.75D) with refractive change, 14 subjects; and hyperopia without refractive change, 27 subjects. Subjects in the high astigmatism group were also divided into six groups: myopia with refractive change, 38 subjects; myopia without refractive change, 11 subjects; emmetropia with refractive change, 19 subjects; emmetropia without refractive change, 29 subjects; hyperopia with refractive change, 2 subjects and hyperopia without refractive change, 7 subjects. Axial length was significant different between the refractive groups (ANOVA, $p < 0.0001$).

Table 4.1
Distribution of refractive errors and axial lengths of the subjects at the beginning of the 1-year period (n=964)

		SE (D) ± SD	AXL (mm) ± SD	No. of Eyes
Low astigmatism (≥-1.00D)	Myopia (<-0.75D), (c)	-2.076 ± 1.052	24.150 ± 0.734	187
	Myopia (<-0.75D), (nc)	-1.877 ± 1.129	24.120 ± 0.773	63
	Emmetropia (-0.75 to +0.75D), (c)	-0.028 ± 0.446	23.317 ± 0.684	196
	Emmetropia (-0.75 to +0.75D), (nc)	+0.111 ± 0.363	23.008 ± 0.698	371
	Hyperopia (>+0.75D), (c)	+1.223 ± 0.351	22.701 ± 0.527	14
	Hyperopia (>+0.75D), (nc)	+1.370 ± 0.689	22.456 ± 0.593	27
High astigmatism (<-1.00D)	Myopia (<-0.75D), (c)	-3.243 ± 1.661	24.406 ± 1.100	38
	Myopia (<-0.75D), (nc)	-1.773 ± 0.762	23.535 ± 0.833	11
	Emmetropia (-0.75 to +0.75D), (c)	+0.125 ± 0.419	23.072 ± 0.881	19
	Emmetropia (-0.75 to +0.75D), (nc)	+0.137 ± 0.508	22.563 ± 0.656	29
	Hyperopia (>+0.75D), (c)	+1.125 ± 0.000	22.915 ± 0.644	2
	Hyperopia (>+0.75D), (nc)	+1.554 ± 1.122	22.117 ± 0.594	7
p			<0.0001*	

Units are microns; SE, mean refractive spherical equivalent; AXL, mean axial length; (c), SE change ≥0.50D at the end of 1-year period; (nc), SE change <0.50D at the end of 1-year period; p, probability value of ANOVA
*Significant at the 0.05 level

Gender showed no significant effect on higher order aberrations (unpaired t-test, p = 0.59). However, higher order aberrations was significantly different for different astigmatism (unpaired t-test, p = 0.0055) and refractive error groups (ANOVA, p = 0.027). As shown in Table 4.2, subjects with low astigmatism showed significant less RMS values of the second order aberrations (unpaired t-test, p < 0.0001), third order aberrations (unpaired t-test, p = 0.0008), coma (unpaired t-test, p = 0.028) and higher order aberrations (unpaired t-test, p = 0.0055) than those with high astigmatism. No significant difference was found for fourth order aberration. Spherical aberration of the low astigmatism subjects shows a larger RMS value than the high astigmatism subjects, 0.062µm compare to 0.053µm, but was not statistically significant (unpaired t-test, p = 0.051).

Table 4.2
Average Zernike coefficients for different astigmatism groups at the beginning of the 1-year period

	2^{nd} order	3^{rd} order	4^{th} order	SA	Coma	3^{rd} to 4^{th} order
Low astigmatism subjects (n=858)	0.300 ± 0.233	0.138 ± 0.065	0.086 ± 0.043	0.062 ± 0.047	0.100 ± 0.065	0.168 ± 0.066
High astigmatism subjects (n=106)	1.147 ± 0.570	0.166 ± 0.081	0.082 ± 0.042	0.053 ± 0.046	0.117 ± 0.074	0.190 ± 0.080
P	<0.0001*	0.0008*	0.43	0.051	0.028*	0.0055*

Units are microns; Errors are SD; p, probability values of unpaired t-test
*Significant at the 0.05 level

Among the six refractive groups of low astigmatism, significant difference was found for the second order aberration (ANOVA, $p = 0.0085$), fourth order aberration (ANOVA, $p = 0.0079$) and spherical aberration (ANOVA, $p = 0.019$). No difference was found for the third order aberration and coma. Turkey post hoc testing showed that the second order aberration for the myopia with refractive change group was significantly more than for the emmetropia with refractive change group ($p < 0.05$) and the emmetropia without refractive change group ($p < 0.05$). The fourth order aberration for the myopia without refractive change group was significantly less than for the emmetropia without refractive change group ($p < 0.05$) and the hyperopia without refractive change group ($p < 0.05$). Spherical aberration for the myopia without refractive change group was significantly less than for the hyperopia without refractive change group ($p < 0.05$). These differences were illustrated in Figure 4.6. When these tests were repeated for the six refractive groups of the high astigmatism subjects, significant difference was found for second order aberrations (ANOVA, $p = 0.034$) and total higher order aberrations (ANOVA, $p = 0.036$). This is illustrated in Figure 4.7. Turkey post hoc testing showed that total higher order aberrations for the myopia with refractive change group was significantly less than for the emmetropia without refractive change group ($p < 0.05$).

Figure 4.6

Average wavefront RMS for second order aberrations, third order aberrations, fourth order aberrations, spherical aberration, coma and total higher order aberrations of the low astigmatism subjects at the beginning of the 1-year period

*Significant at the 0.05 level (ANOVA). (mc, myopia with refractive change; mnc, myopia without refractive change; ec, emmetropia with refractive change; enc, emmetropia without refractive change; hc, hyperopia with refractive change; hnc, hyperopia without refractive change)

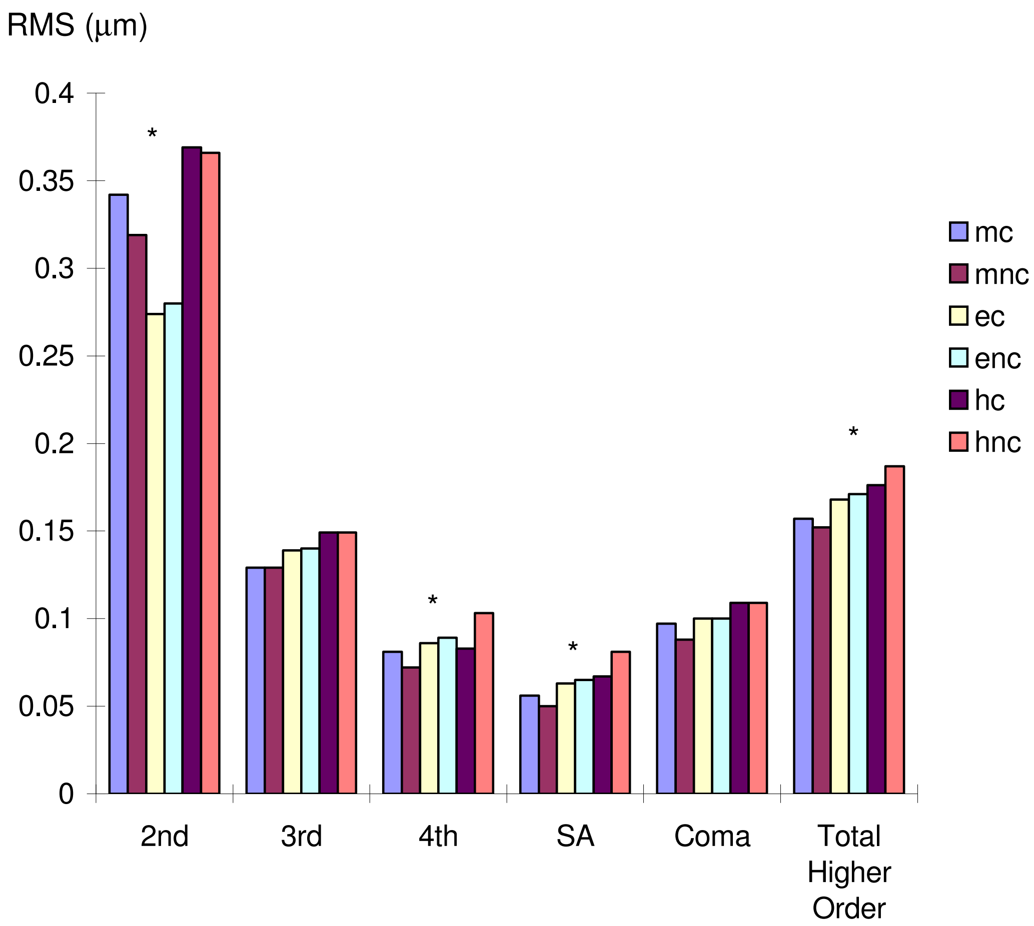


Figure 4.7

Average wavefront RMS for second order aberrations, third order aberrations, fourth order aberrations, spherical aberration, coma and total higher order aberrations of the high astigmatism subjects at the beginning of the 1-year period

*Significant at the 0.05 level (ANOVA). (mc, myopia with refractive change; mnc, myopia without refractive change; ec, emmetropia with refractive change; enc, emmetropia without refractive change; hc, hyperopia with refractive change; hnc, hyperopia without refractive change)

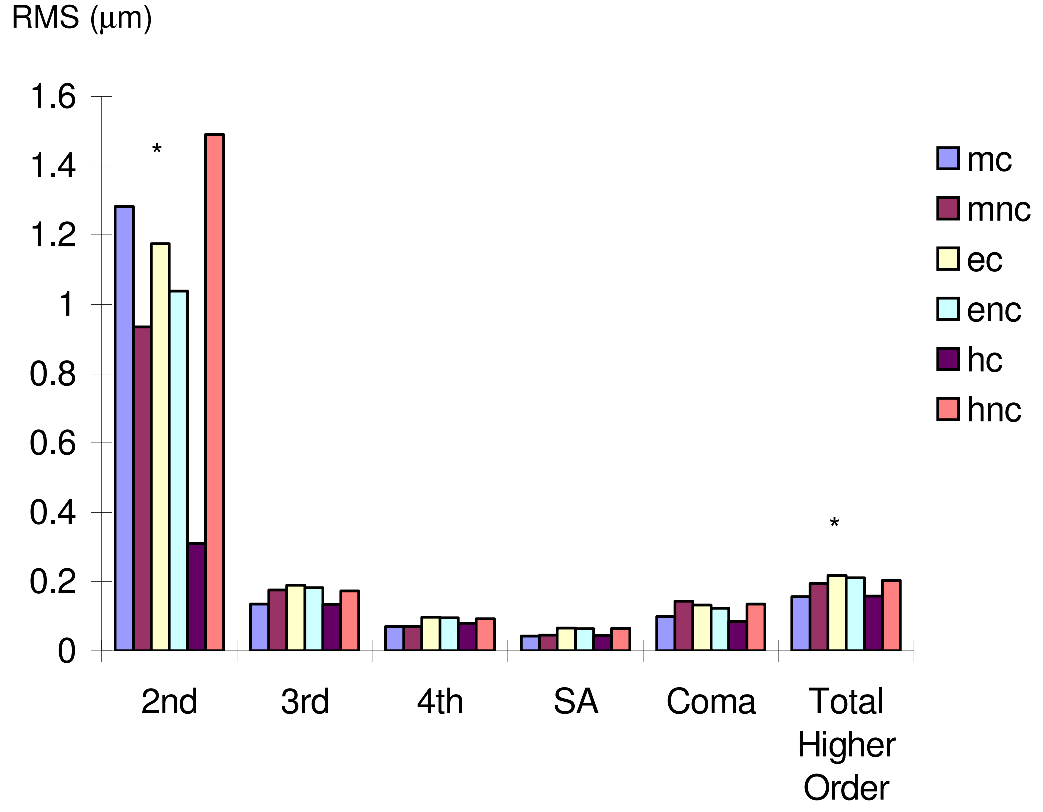


Table 4.3 shows the RMS values of the second order aberrations, third order aberrations, fourth order aberrations, spherical aberration, coma and total higher order aberrations of subjects with low astigmatism at the beginning and at the end of the 1-year period. When the RMS values of the aberrations

of subjects with low astigmatism at the beginning of the 1-year period were compared with those at the end of the 1-year period, significant difference was found in second order aberrations of the subjects with refractive change group (paired t-test, p = 0.010) and spherical aberration of the subjects without refractive change group (paired t-test, p = 0.045). No significant difference was found in third order aberrations, fourth order aberrations, coma and higher order aberrations. When the aberrations at the beginning and at the end of the 1-year period of the individual refractive groups were compared, myopia with refractive change group showed significant larger second order aberrations at the end of the 1-year period than at the beginning (paired t-test, p = 0.0085). Emmetropia without refractive change group showed significantly larger spherical aberration at the end of the 1-year period than at the beginning (paired t-test, p = 0.041). There was no significant difference between the aberrations at the beginning and at the end of the 1-year period in the other refractive groups. When these tests were repeated for subjects with high astigmatism, no significant difference was found. None of the refractive groups showed significant different RMS values of the aberrations between the beginning and the end of the 1-year period. The distribution of the aberrations of the high astigmatism subjects in terms of different refractive groups at the beginning and the end of the 1-year period were shown in table 4.4.

Table 4.3
Average Zernike coefficients for different refractive error groups, all subjects (low astigmatism) at the beginning and at the end of the 1-year period

		2nd order	3rd order	4th order	SA	Coma	Total higher order
Myopes (c) (n=187)	1st visit	0.342 ±0.273	0.129 ±0.062	0.081 ±0.034	0.056 ±0.040	0.097 ±0.060	0.157 ±0.060
	2nd visit	0.394 ±0.292	0.127 ±0.059	0.081 ±0.035	0.059 ±0.040	0.097 ±0.060	0.155 ±0.057
P		0.0085*	0.68	0.91	0.31	0.97	0.71
Myopes (nc) (n=63)	1st visit	0.319 ±0.234	0.129 ±0.055	0.072 ±0.033	0.050 ±0.037	0.088 ±0.048	0.152 ±0.054
	2nd visit	0.324 ±0.237	0.128 ±0.052	0.079 ±0.040	0.058 ±0.042	0.086 ±0.052	0.155 ±0.053
P		0.89	0.83	0.16	0.12	0.69	0.58
Emmetropes (c) (n=196)	1st visit	0.274 ±0.216	0.139 ±0.061	0.086 ±0.041	0.063 ±0.046	0.100 ±0.061	0.168 ±0.062
	2nd visit	0.296 ±0.253	0.141 ±0.061	0.092 ±0.058	0.068 ±0.063	0.101 ±0.061	0.174 ±0.072
P		0.22	0.65	0.18	0.29	0.79	0.27
Emmetropes (nc) (n=371)	1st visit	0.280 ±0.212	0.140 ±0.065	0.089 ±0.048	0.065 ±0.052	0.100 ±0.066	0.171 ±0.069
	2nd visit	0.313 ±0.287	0.144 ±0.069	0.091 ±0.045	0.069 ±0.050	0.106 ±0.067	0.176 ±0.070
P		0.34	0.30	0.13	0.041*	0.10	0.12
Hyperopes (c) (n=14)	1st visit	0.369 ±0.212	0.149 ±0.066	0.083 ±0.029	0.067 ±0.029	0.109 ±0.061	0.176 ±0.057
	2nd visit	0.312 ±0.221	0.161 ±0.063	0.085 ±0.035	0.062 ±0.043	0.112 ±0.061	0.187 ±0.057
P		0.31	0.35	0.83	0.66	0.83	0.41
Hyperopes (nc) (n=27)	1st visit	0.366 ±0.230	0.149 ±0.049	0.103 ±0.047	0.081 ±0.055	0.109 ±0.061	0.187 ±0.050
	2nd visit	0.335 ±0.258	0.156 ±0.065	0.099 ±0.043	0.070 ±0.054	0.123 ±0.070	0.191 ±0.061
P		0.32	0.59	0.50	0.10	0.28	0.71
All subjects (c) (n=397)	1st visit	0.309 ±0.246	0.134 ±0.062	0.083 ±0.038	0.060 ±0.043	0.099 ±0.060	0.163 ±0.061
	2nd visit	0.342 ±0.275	0.135 ±0.061	0.087 ±0.048	0.064 ±0.053	0.099 ±0.060	0.166 ±0.065
P		0.010*	0.85	0.21	0.18	0.84	0.44
All subjects (nc) (n=461)	1st visit	0.291 ±0.217	0.139 ±0.063	0.088 ±0.047	0.064 ±0.051	0.099 ±0.064	0.169 ±0.066
	2nd visit	0.316 ±0.279	0.142 ±0.067	0.090 ±0.044	0.068 ±0.049	0.104 ±0.066	0.174 ±0.068

P		0.40	0.34	0.086	0.045*	0.10	0.14

Units are microns. Errors are SD. (c), SE change ≥0.50D at the end of the 1-year period. (nc), SE change <0.50D at the end of the 1-year period; p, probability value of paired t-test
*Significant at the 0.05 level

Table 4.4
Average Zernike coefficients for different refractive error groups, all subjects (high astigmatism) at the beginning and at the end of the 1-year period

		2nd order	3rd order	4th order	SA	Coma	Total higher order
Myopes (c) (n=38)	1st visit	1.282 ±0.538	0.136 ±0.065	0.071 ±0.044	0.043 ±0.045	0.099 ±0.067	0.157 ±0.070
	2nd visit	1.090 ±0.681	0.126 ±0.058	0.071 ±0.029	0.044 ±0.037	0.086 ±0.058	0.149 ±0.054
P		0.11	0.43	0.53	0.32	0.39	0.76
Myopes (nc) (n=11)	1st visit	0.935 ±0.585	0.176 ±0.076	0.071 ±0.029	0.046 ±0.037	0.144 ±0.057	0.194 ±0.069
	2nd visit	1.004 ±0.614	0.202 ±0.099	0.076 ±0.032	0.055 ±0.036	0.159 ±0.104	0.220 ±0.096
P		0.77	0.42	0.61	0.44	0.64	0.42
Emmetropes (c) (n=19)	1st visit	1.175 ±0.643	0.189 ±0.094	0.097 ±0.046	0.066 ±0.051	0.133 ±0.093	0.218 ±0.091
	2nd visit	1.205 ±0.610	0.187 ±0.077	0.095 ±0.042	0.064 ±0.052	0.125 ±0.058	0.214 ±0.075
P		0.65	0.90	0.80	0.80	0.73	0.84
Emmetropes (nc) (n=29)	1st visit	1.038 ±0.497	0.182 ±0.084	0.095 ±0.036	0.064 ±0.045	0.123 ±0.078	0.211 ±0.076
	2nd visit	0.855 ±0.501	0.187 ±0.092	0.095 ±0.040	0.065 ±0.044	0.132 ±0.075	0.215 ±0.087
P		0.072	0.77	0.94	0.87	0.58	0.79
Hyperopes (c) (n=2)	1st visit	0.310 ±0.095	0.135 ±0.015	0.080 ±0.023	0.045 ±0.007	0.085 ±0.000	0.158 ±0.001
	2nd visit	0.886 ±0.313	0.182 ±0.146	0.071 ±0.030	0.045 ±0.041	0.160 ±0.176	0.205 ±0.119
P		0.30	0.75	0.85	0.99	0.65	0.68
Hyperopes (nc) (n=7)	1st visit	1.490 ±0.630	0.173 ±0.089	0.093 ±0.050	0.065 ±0.058	0.136 ±0.076	0.203 ±0.085
	2nd visit	1.306 ±0.838	0.180 ±0.087	0.103 ±0.045	0.088 ±0.050	0.155 ±0.083	0.216 ±0.074
P		0.32	0.74	0.54	0.32	0.46	0.58

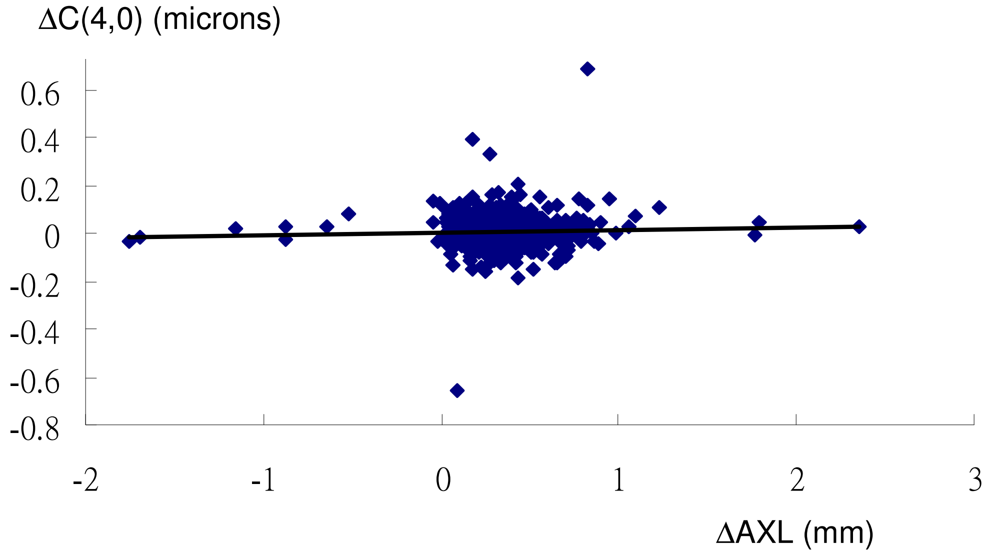
All subjects (c) (n=59)	1st visit	1.214 ±0.587	0.153 ±0.078	0.080 ±0.045	0.051 ±0.047	0.110 ±0.077	0.177 ±0.081
	2nd visit	1.120 ±0.646	0.147 ±0.072	0.079 ±0.035	0.050 ±0.043	0.101 ±0.064	0.172 ±0.069
P		0.14	0.59	0.92	0.95	0.45	0.61
All subjects (nc) (n=53)	1st visit	1.072 ±0.547	0.180 ±0.083	0.086 ±0.038	0.056 ±0.045	0.125 ±0.071	0.205 ±0.077
	2nd visit	0.923 ±0.583	0.188 ±0.091	0.090 ±0.038	0.064 ±0.042	0.135 ±0.082	0.214 ±0.085
P		0.068	0.49	0.40	0.21	0.37	0.40

Units are microns. Errors are SD. (c), SE change ≥0.50D at the end of the 1-year period. (nc), SE change <0.50D at the end of the 1-year period; p, probability value of paired t-test
*Significant at the 0.05 level

As shown in Figure 4.8, C(4,0) change was not significantly correlated with axial length change over the 1-year study period.

Figure 4.8

Linear regression of C(4,0) change as function of axial length change (m=0.0103, p=0.188, r=0.0424)



Spherical equivalent, axial length and C(4,0) in each visit was shown in Figure 4.9, Figure 4.10, Figure 4.11 respectively. Spherical equivalent became significantly more negative ($p < 0.0001$) after the 1-year period (Table 4.5). Axial length increased significantly ($p < 0.0001$) after the 1-year period (Table 4.6). C(4,0) became significantly more positive ($p = 0.0002$) after the 1-year period. But when we divided the subjects into myopic, emmetropic and hyperopic groups, only emmetropic group showed a significantly more positive C(4,0) ($p = 0.0015$), not myopic group ($p = 0.069$) and hyperopic group ($p = 0.53$) (Table 4.7).

Figure 4.9
Spherical equivalent of the subjects in each visit

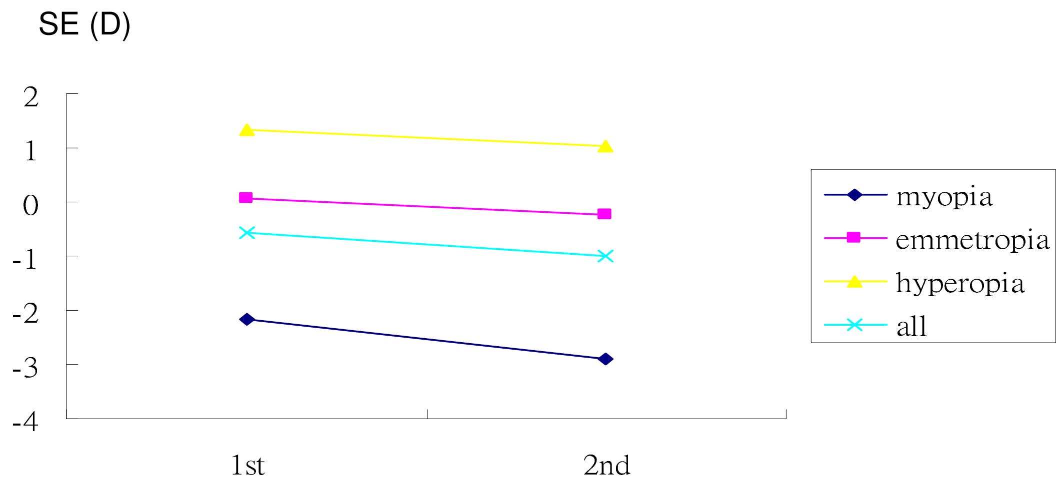


Figure 4.10

Axial length of the subjects in each visit

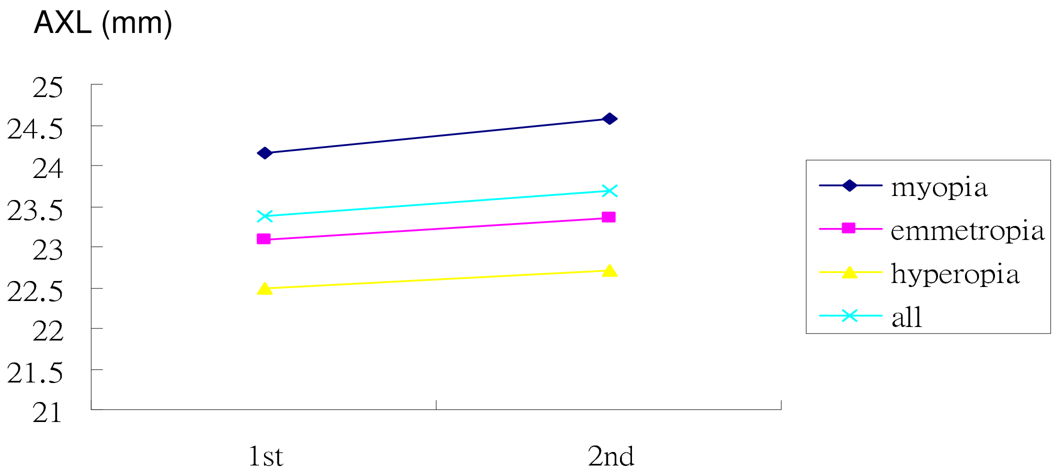


Figure 4.11

C(4,0) of the subjects in each visit

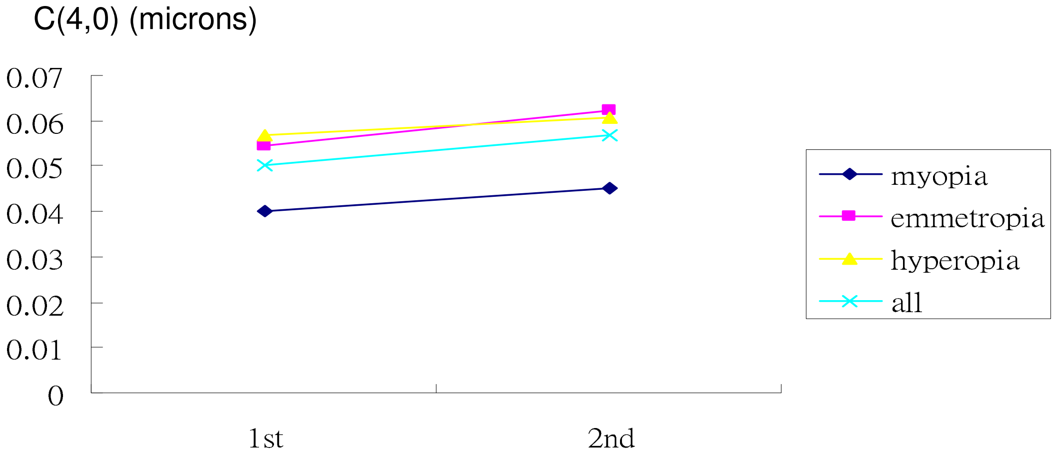


Table 4.5

Spherical equivalent of the subjects in each visit

	SE (1) (D)	SE (2) (D)	P
Myopia	-2.171	-2.897	< 0.0001*
Emmetropia	0.0682	-0.245	< 0.0001*
Hyperopia	1.345	1.023	0.0003*
All subjects	-0.560	-1.001	< 0.0001*

SE, spherical equivalent; (1), first visit; (2), second visit; p, probability value of paired t-test

*Significant at the 0.05 level

Table 4.6
Axial length of the subjects in each visit

	AXL (1) (mm)	AXL (2) (mm)	P
Myopia	24.153	24.575	< 0.0001*
Emmetropia	23.087	23.352	< 0.0001*
Hyperopia	22.496	22.717	< 0.0001*
All subjects	23.387	23.698	< 0.0001*

AXL, axial length; (1), first visit; (2), second visit; p, probability value of paired t-test
*Significant at the 0.05 level

Table 4.7
C(4,0) of the subjects in each visit

	C(4,0) (1) (microns)	C(4,0) (2) (microns)	P
Myopia	0.0400	0.0452	0.069
Emmetropia	0.0543	0.0622	0.0015*
Hyperopia	0.0568	0.0607	0.53
All subjects	0.0500	0.0568	0.0002*

(1), first visit; (2), second visit; p, probability value of paired t-test
*Significant at the 0.05 level

4.4 DISCUSSION

Similar to the results of Chapter 2 and Chapter 3, we found that eyes with longer axial length showed less positive spherical aberration. In common with a previous study (Cheng et al., 2003), we found that astigmatic eyes tended to have larger RMS value of higher order aberrations. Cheng et al. (2003) studied a population of 200 normal adult eyes of 100 subjects with refractive errors from +5.00D to -10.00D. They found that the total higher order aberrations were significantly larger for subjects with high astigmatism than subjects with low astigmatism. Similarly, among our population of 964 children, subjects with high astigmatism also showed significantly larger total higher order aberrations than subjects with low astigmatism (unpaired t-test, $p = 0.0055$). In addition, second order aberrations, third order aberrations and coma also showed significantly larger RMS value for subjects with high astigmatism than subjects with low astigmatism (unpaired t-test, $p < 0.0001$, $p = 0.0008$ and $p = 0.028$, respectively). These variations of aberrations in subjects with different astigmatism may help to explain the conflicting conclusions reached by other studies, where astigmatism was usually not considered in the data analysis.

In general, after the 1-year period, spherical equivalent of our subjects became more negative, axial length increased and spherical aberration became more positive. Previous study has also shown that spherical aberration increased with age (Fujikado et al., 2004). When we divided our subjects into myopic, emmetropic and hyperopic groups, only emmetropic eyes showed significant more positive spherical aberration. This suggests that eyes with different refractive error might be having an effect beyond that expected from the years of age.

In this study, we divided our subjects into "low astigmatism" ($n = 858$) and "high astigmatism" ($n = 106$) groups. Each astigmatism group was then subdivided into 6 refractive groups. Among the six low astigmatism refractive groups, significant differences were found in second order aberrations, fourth order aberrations, spherical aberration and total higher order aberrations. However, in the six high astigmatism refractive groups, only second order aberrations and total higher order aberrations showed significant difference. This difference found may due to the effect of high astigmatism on monochromatic aberrations and the small number of subjects in the high astigmatism groups, especially in the hyperopia with refractive change group (n = 2). As shown in our results, monochromatic aberrations varied significantly with the astigmatism. High astigmatism may be one of the confounding factors that affect the study of the relationship between myopic development and higher order aberrations.

In the low astigmatism groups, the spherical aberration and the fourth order aberrations of the myopic subjects were in general smaller than that of the emmetropic and hyperopic subjects. Statistically significant value was found in the comparison of the myopia without refractive change group and the hyperopia without refractive change group for the spherical aberration. For the fourth order aberration, the myopia without refractive change group showed a significantly smaller RMS value than the emmetropia without refractive change group and the hyperopia without refractive change group. Collins et al. (1995) also reported that spherical aberration of adult myopic subjects was less positive than that of emmetropic subjects and Llorente et al. (2004) found that hyperopic eyes tend to have larger higher order aberrations than myopic eyes. Carkeet et al. (2002) studied a population of

Singapore children and reported that the low myopia group tended to show less spherical aberration than other refractive groups. Rearrangement of the grouping of our subjects was done in order to make a better comparison of our results with those of Carkeet et al. (2002). Average Zernike coefficients for different refractive error groups from our study and Carkeet et al. (2002) are shown in Table 4.8. Both studies found significant differences in the coefficient of Z(2,0) and Z(2,2), the lower order aberration which denotes defocus and horizontal/vertical astigmatism, respectively. However, we also found a significant difference in the coefficient of Z(2,-2), the lower order aberration which denotes oblique astigmatism. It should be not surprising that significant difference was found in the coefficient of defocus because the grouping of the subjects was based on refractive error. The coefficient of Z(4,0), primary spherical aberration and the RMS value of the spherical aberration of our high myopia group were smaller than that of low myopia, emmetropia and hyperopia group. These findings are different from the findings of Carkeet et al. (2002). Carkeet et al. (2002) found that the low myopia group showed the smallest value compare to other groups. Inter-study differences such as different age groups, different measuring procedure and different refractive error of the subjects may account to the different findings. The age of our subjects was on average 1 year younger and the age range was also narrower. The age range of our study group was 7 to 9 years old compared to 7.9 to 12.7 years old in Carkeet et al. (2002). The measurements on our subjects were under natural accommodation, while Carkeet et al. (2002) measured their subjects under cycloplegia. The astigmatism of our subjects was restricted to below or equal to –1.00D while the astigmatism of the subjects of Carkeet et al. (2002) was not restricted. This refractive error difference might also be a reason of the inter-study difference.

Table 4.8
Average Zernike coefficients for different refractive error groups of our study and Carkeet et al. (2002)

	Carkeet et al., 2002				Our study			
	High myopes (n=36)	Low myopes (n=102)	Emme-tropes (n=123)	Hyper-opes (n=12)	High myopes (n=49)	Low myopes (n=282)	Emme-tropes (n=525)	Hyper-opes (n=26)
Z(2,-2)	-0.005	-0.016	-0.053	-0.264	0.026*	0.025*	0.003*	-0.023*
Z(2,0)	3.960*	1.180*	-0.548*	-1.440*	3.379*	1.668*	0.781*	-0.304*
Z(2,2)	-0.600*	-0.261*	-0.176*	-0.443*	-0.420*	-0.213*	-0.201*	-0.337*
Z(3,-3)	-0.254	-0.003	-0.004	0.088	0.024	0.023	0.024	0.040
Z(3,-1)	0.053	0.073	0.076	0.042	0.017	0.036	0.034	0.053
Z(3,1)	0.019	0.023	0.028	-0.008	0.006	0.012	0.007	0.019
Z(3,3)	0.006	0.010	0.006	-0.030	-0.006	-0.008	-0.010	-0.008
Z(4,-4)	0.020	0.015	0.012	-0.008	0.016	0.015	0.015	0.016
Z(4,-2)	-0.011	-0.008	-0.006	0.013	-0.012	-0.008	-0.012	-0.015
Z(4,0)	0.065*	0.047*	0.069*	0.061*	0.037	0.051	0.052	0.061
Z(4,2)	0.006	0.006	0.010	0.039	0.008	0.008	0.004	0.007
Z(4,4)	0.016	0.010	0.012	0.010	0.008	0.008	0.012	0.006
SA	0.066*	0.051*	0.071*	0.061*	0.052	0.059	0.063	0.079
Coma	0.116	0.119	0.128	0.203	0.094	0.096	0.102	0.124
Total higher order	0.187	0.180	0.195	0.255	0.148*	0.161*	0.172*	0.199*

Units are microns
*Significant at the 0.05 level (ANOVA)

Several previous studies found larger aberrations in high myopes (He et al., 2002; Paquin et al., 2002), suggesting higher amount of aberration plays a role in the development of myopia. In our study, both low astigmatic and high astigmatic subjects with refractive change showed in general similar higher order aberrations than those without refractive change (Table 4.3, Table 4.4). No significant larger amount of aberrations was found in subjects with refractive change than those without refractive change. The results of our study showed no evidence to the hypothesis of higher amount of aberration plays a role in the development of myopia.

In common with previous studies (Gwiazda et al., 2007; Saw et al., 2000), we found that subjects who had more myopia progression during the 1-year period, had more initial myopia and longer initial axial length (Figure 4.2 and Figure 4.3, respectively). As shown in Figure 4.4 and 4.5, we found that the initial spherical aberration and initial total higher order aberrations had no significant impact on the degree of myopia progression.

Table 4.9 shows the axial lengths of all subjects at the beginning and at the end of the 1-year period. Subjects with and without refractive change also showed significant increase in axial length after the 1-year period. Subjects with refractive change showed larger increase in axial length than those without refractive change. The axial elongation of the subjects without refractive change might due to the normal growth. Zadnik et al. (2004) reported that axial elongation was one of the hallmarks of normal eye growth from ages 6 to 15 years. A larger increase in axial elongation resulted in the refractive change of the subjects. Cheng et al. (2003), using a reduced-eye model, predicted spherical aberration should have increased systematically with axial elongation. However, among the low astigmatic subjects with refractive change in our study, no significant difference was found in spherical aberration between the beginning and the end of the 1-year period. Spherical aberration was significantly different in subjects without refractive change only. Also spherical aberration change was not significantly correlated with axial length change over the 1-year period (Figure 4.1). The reason why our results did not agree with that prediction might due to the fact that the change in the optical components was different for eye growth with and without refractive change. In agreement with the prediction of Cheng et al. (2003), subjects without refractive change, with axial elongation due to normal eye growth, showed significant increase in spherical aberration. However, subjects with refractive change showed no significant increase in spherical aberration. In order to achieve this result, there would have to be a reduction of spherical aberration from other optical components. The corneal positive spherical aberration may be reduced or the crystalline lens negative spherical aberration may be increased.

Table 4.9
Axial lengths of all subjects at the beginning and at the end of the 1-year period

		Axial length (mm)		p
		1st visit	2nd visit	
With refractive change	Low cyl (n=397)	23.687 ±0.834	24.071 ±0.879	<0.0001*
	High cyl (n=59)	23.926 ±1.202	24.377 ±1.280	<0.0001*
Without refractive change	Low cyl (n=461)	23.128 ±0.816	23.364 ±0.847	<0.0001*
	High cyl (n=53)	22.751 ±0.845	22.969 ±0.870	<0.0001*

Cyl, astigmatism; Errors are SD; p, probability values of paired t-test
*Significant at the 0.05 level

Among the groups with refractive change, we found significant difference in the second order aberration between the beginning and the end of the 1-year period. When results from different refractive groups were analyzed, only myopes showed a significant difference in second order aberration between the beginning and the end of the 1-year period. No significant difference was found in emmetropes and hyperopes. The astigmatism of the myopia with refractive change group was found significantly larger at the end of the 1-year period than that at the beginning (paired t-test, p = 0.0043). The astigmatism was -0.53D at the beginning and -0.62D at the end. This result matched our finding of the second order aberrations.

Previous studies have reported that higher order aberrations increased with age (McLellan et al., 2001; Amano et al., 2004; Fujikado et al., 2004). McLellan et al. (2001) studied 38 subjects aged from 22.9 to 64.5 years and found higher order aberrations shown a positive correlation with age. Amano et al. (2004) studied 75 subjects aged from 18 to 69 years and found that ocular spherical aberration and coma increased with age. Fujikado et al. (2004) studied 66 subjects aged from 4 to 69 years and also found that ocular spherical aberration and coma were significantly correlated with age. Our study also found higher order aberrations increased after 1-year period in subjects both with and without refractive change. Clearly, aberration change due to aging may be a confounding factor when conducting longitudinal studies.

To the best of our knowledge, our study is the first to investigate the relationship of the monochromatic aberrations and refractive errors longitudinally. Our results do not support the hypothesis that higher amounts of high order aberrations may drive myopia development. It is more likely that the amount of higher order aberration changes with refractive change. However, there are several limitations in our study. First, not controlling accommodation during the measurements might confound the results. Previous studies have reported that spherical aberration always shift to a more negative direction during accommodation (Atchison et al., 1995; Buehren and Collins, 2005; Cheng et al., 2004; Collins et al., 1995; Hazel et al., 2003; He et al., 2000; López et al., 1998; Ninomiya et al., 2002; Ninomiya et al., 2003; Plainis et al., 2005). Measurements taken during school time might also confound the results since previous study has reported lid induced changes in corneal aberrations after reading and computer work (Collins et al., 2006). No corneal data was collected from the subjects, so we cannot rule out the possibility of corneal change during the refractive change. A longitudinal study carried out with closer monitoring of spectacle correction, cycloplegic measurements, corneal topography measurements and prevention of measurements after reading may improve our study.

Chapter 5
A Longitudinal Study of Refractive Error Changes and Monochromatic Aberrations Changes in Hong Kong Primary School Children – In Clinic Measurement and Under Cycloplegic Measurement

5.1 INTRODUCTION

To improve the longitudinal study reported in the previous chapter, we investigate the monochromatic aberrations and refractive error development of the children under cycloplegic measurement in this study in order to prevent the confounding effect of accommodation (Atchison et al., 1995; Buehren and Collins, 2005; Cheng et al., 2004; Collins et al., 1995; Hazel et al., 2003; He et al., 2000; He et al., 2003; López et al., 1998; Ninomiya et al., 2002; Ninomiya et al., 2003; Plainis et al., 2005). No reading was allowed before all measurements to prevent the lid induced aberration changes (Collins et al., 2006).

5.2 METHODS

5.2.1. Subjects

Two hundred Chinese primary school children (105 females and 95 males) from 2 schools joined this study. The average age of the subjects was 8.0 ± 1.7 years (range 6 to 12 years). Subjects with any pathology (e.g. cataract, strabismus), a history of ocular surgery, wearing orthokeratology lenses, wearing kids progressive lenses or wearing contact lenses were excluded. Among the 200 subjects, 162 completed all five assessments at approximately 6-month intervals. All measurements were performed at the Optometry Clinic of The Hong Kong Polytechnic University. The monochromatic aberrations of the eyes were measured in a dark room. Accommodation was paralyzed and pupils dilated with the administration of one drop 0.5% cyclopentolate HCL in each eye. All pupils were larger than 5mm in diameter before measurements commenced. The refraction, corneal curvature and axial length of each subject were measured after pupil dilation (Chat and Edwards, 2001; Heatlley et al., 2002; Mallen et al., 2001). Informed consent was obtained from every subject's parent before participation.

5.2.2. Apparatus

A clinical Shack-Hartmann aberrometer, the Complete Ophthalmic Analysis System (COAS) Wavefront Analyzer, was used to measure the monochromatic aberrations of the eyes. The Shin-Nippon SRW5000 autorefractor, the Canon RK5 Autorefractor & Autokeratometer and the Zeiss IOL master were used to measure the refractive errors, the corneal curvatures and the axial lengths of the subjects respectively.

5.2.3. Procedures

All measurements were taken at the Optometry Clinic of The Hong Kong Polytechnic University. One drop of 0.5% cyclopentolate HCL was instilled in each eye of the subjects. All measurements were performed 30 minutes after instillation of the cycloplegic agent. Monochromatic aberrations of the right and left eyes of the subjects were measured using the COAS in a dark room. Five readings were taken after each blink and the averages of coefficients from ocular aberrations were used for analysis. The Zernike coefficients of the monochromatic aberrations were automatically calculated up to and including fourth order using 14 Zernike terms. Refractive errors were then measured using Shin-Nippon SRW500 autorefractor with a fixation target at 6m. Corneal curvatures were measured using the Canon RK5 Autorefractor & Autokeratometer. Axial lengths were finally measured using the Zeiss IOL Master. The procedures were repeated for the following four visits at approximate 6-months interval.

5.2.4. Data Analysis

McKendrick and Brennan (1996) reported a strong correlation of the components of refractive error between left and right eye. Porter et al. (2001)

also reported a strong correlation of the higher order monochromatic aberrations between left and right eye. Therefore, data for the right eyes only are reported here. Data of left eyes are reported in the appendix.

Monochromatic aberrations of the eyes were analyzed based on a 5mm-pupil diameter. The coefficients of the Zernike polynomials correspond to the order recommended by the OSA Standardization Committee (Thibos et al., 2000; Thibos et al., 2002). The average root mean square (RMS) values of the total higher order aberrations (third to fourth order aberrations), second order aberrations (exclude defocus), third order aberrations, fourth order aberrations, spherical aberration and coma were calculated for analysis.

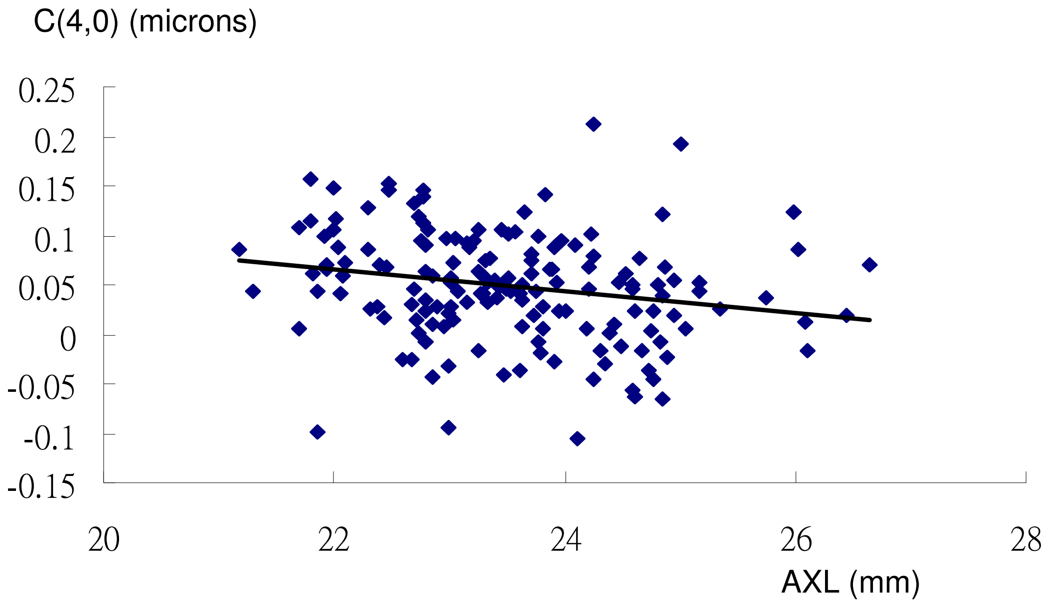
All the subjects were first categorized into three groups according to their spherical equivalent change at the longitudinal study (Table 5.1).

The variance of aberrations among groups at the beginning of the study was analyzed to investigate whether the starting aberration level was a risk factor of refractive development. One-way analysis of variance was conducted with the second order, third order, fourth order, spherical aberration, coma and total higher order aberrations as the dependent variables, followed by Turkey post hoc testing. The statistical approach in assessing whether different refractive change had an effect on aberration change was to use paired t-test, comparing the differences of the monochromatic aberrations between the beginning and the end of the longitudinal study.

5.3 RESULTS

Of the two hundred children who joined the study, 162 (89 females and 73 males) completed all five assessments at approximately 6-monthly intervals. The drop out rate was 19%. Results from the right eyes are presented. The relationship between C(4,0) and axial length of the 162 children at the beginning of the 2-year period was shown in Figure 5.1. Linear regression analysis showed that the slope was significantly different from zero (p = 0.0055, r = -0.22).

Figure 5.1
Linear regression of C(4,0) as function of axial length (m=-0.011, p=0.0055, r=-0.22) at the beginning of the 2-year period



Spherical equivalent change was significantly correlated with initial C(2,0) (p = 0.016, r = -0.19) and initial axial length (p = 0.044, r = -0.16) (Figure 5.2 and Figure 5.3, respectively). Figure 5.4 and Figure 5.5 have shown that spherical equivalent change was not significantly correlated with initial C(4,0) (p = 0.063, r = 0.15) and initial total higher order aberrations (p = 0.050, r = 0.15) respectively. When we divided the children into myopic, emmetropic and hyperopic groups, linear regression analysis showed that the slope for myopic eyes was significantly different from zero (p = 0.037, r = 0.30), not for emmetropic eyes and hyperopic eyes (Figure 5.6, Figure 5.7 and Figure 5.8, respectively).

Figure 5.2
Linear regression of spherical equivalent change as function of initial C(2,0) (m=-0.10, p=0.016, r=-0.19)

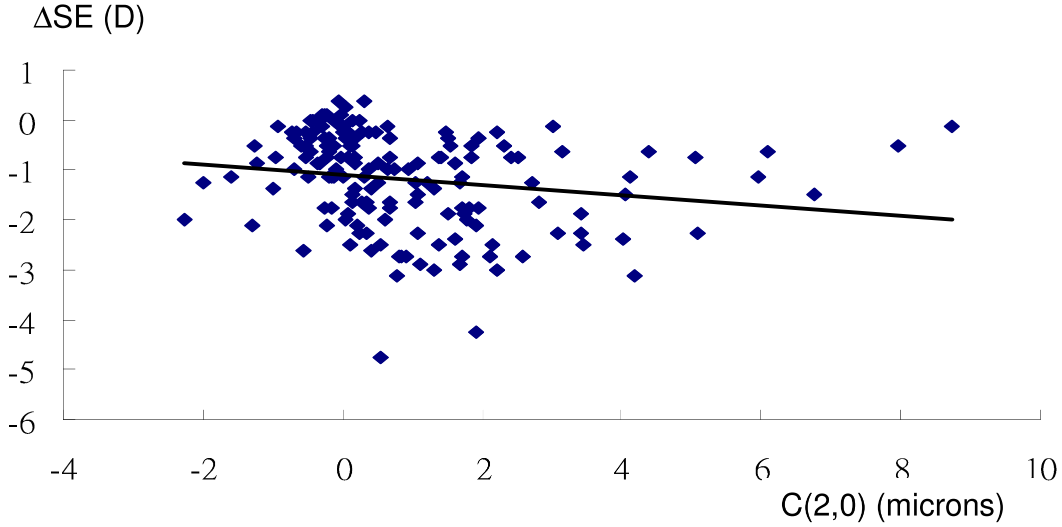


Figure 5.3

Linear regression of spherical equivalent change as function of initial axial length (m=-0.14, p=0.044, r=-0.16)

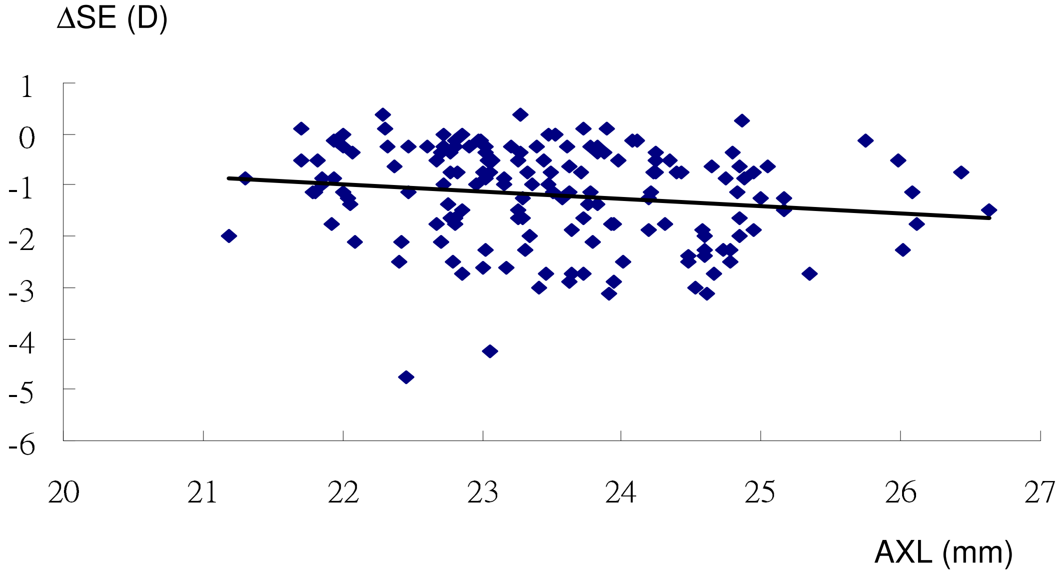


Figure 5.4

Linear regression of spherical equivalent change as function of initial C(4,0) (m=2.55, p=0.063, r=0.15)

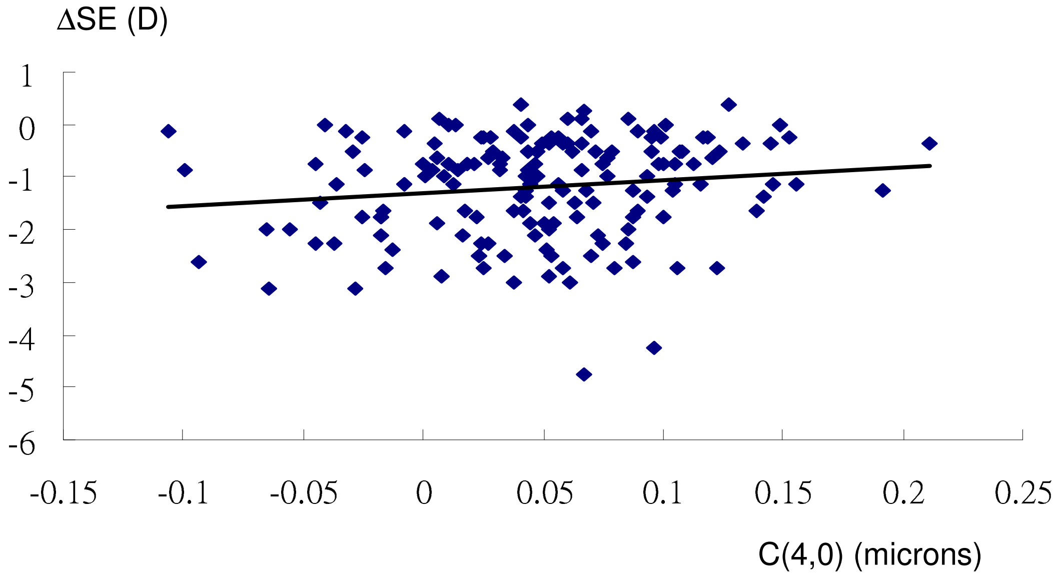


Figure 5.5

Linear regression of spherical equivalent change as function of initial total higher order aberrations (m=2.15, p=0.050, r=0.15)

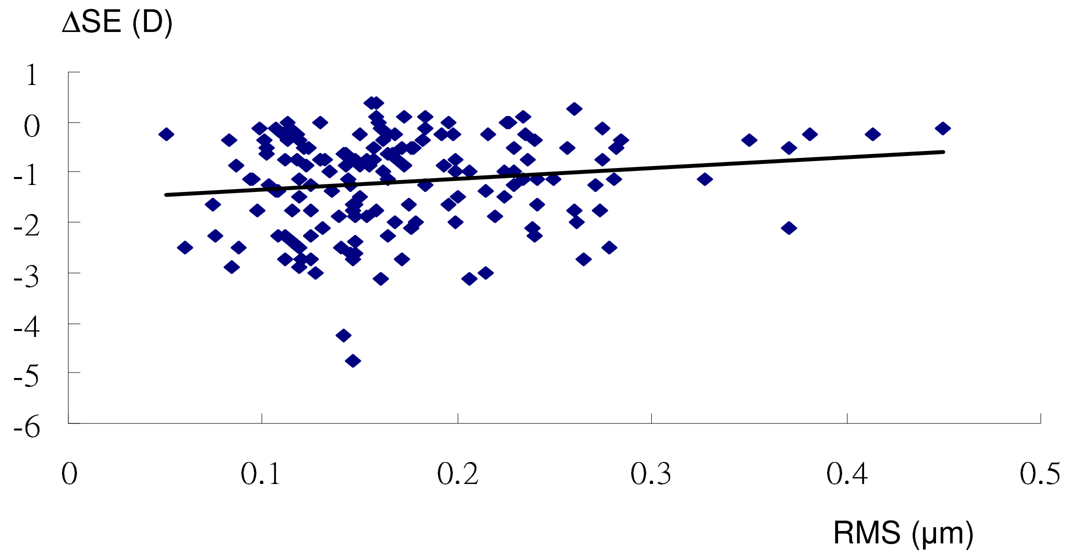


Figure 5.6

Linear regression of spherical equivalent change as function of initial C(4,0) in myopic eyes (m=5.53, p=0.037, r=0.30)

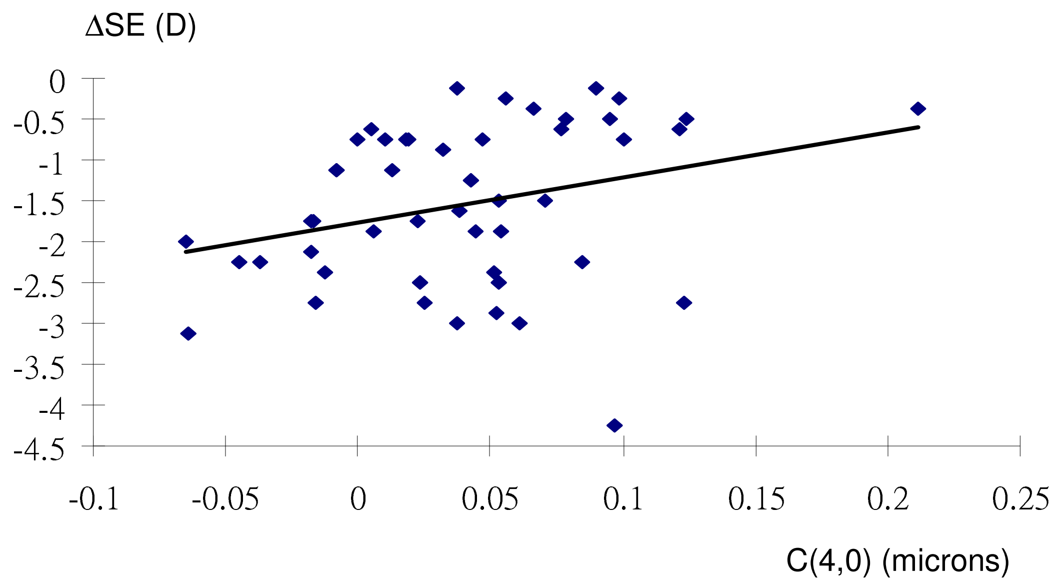


Figure 5.7

Linear regression of spherical equivalent change as function of initial C(4,0) in emmetropic eyes (m=-0.68, p=0.74, r=0.040)

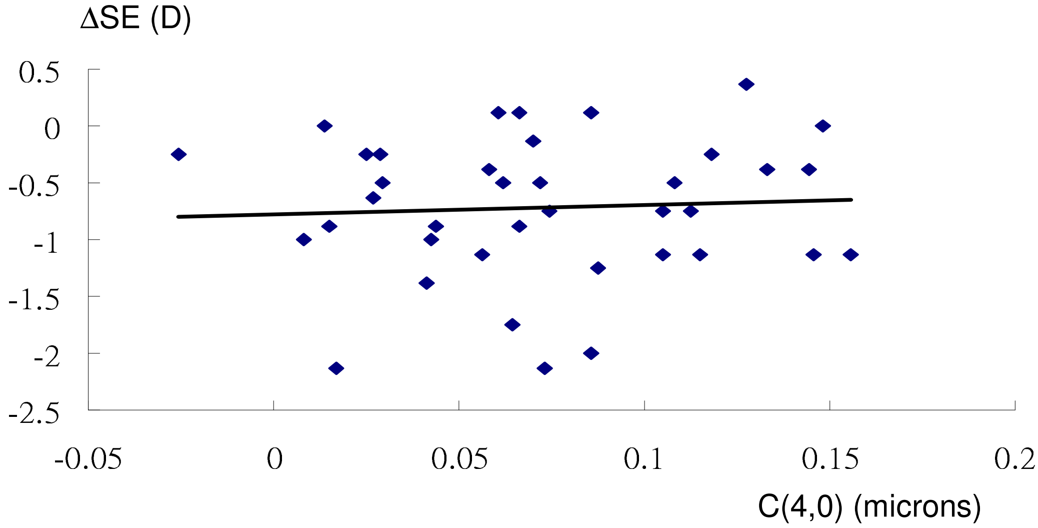
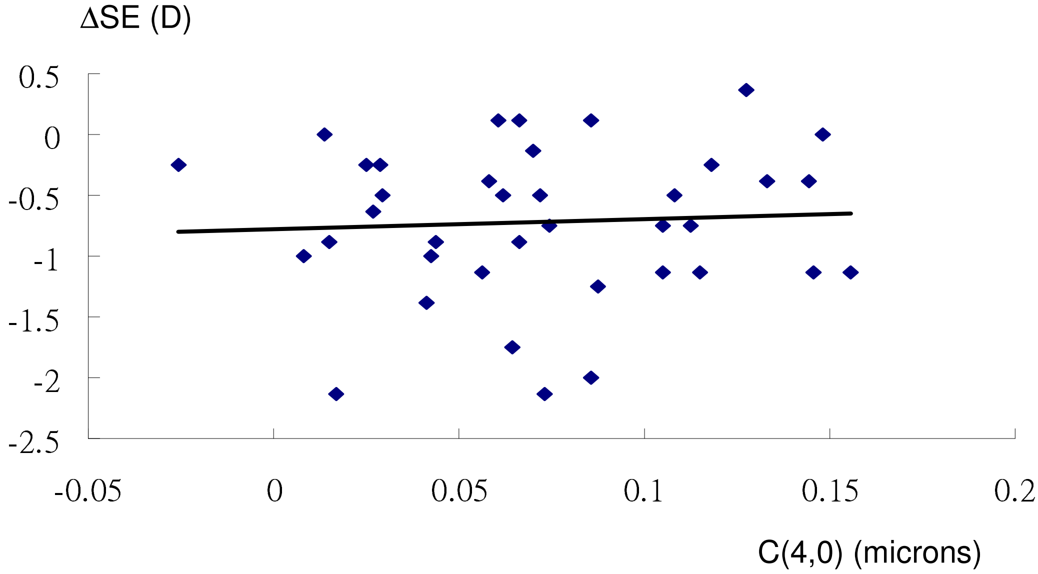


Figure 5.8

Linear regression of spherical equivalent change as function of initial C(4,0) in hyperopic eyes (m=0.86, p=0.71, r=0.062)



Subjects were divided into three different groups as shown in Table 5.1. The grouping was based on the refractive change after the five assessments. For spherical equivalent change greater than 1.50D, there were 54 subjects (Group 1); spherical equivalent change smaller than or equal to 1.50D and greater than 0.50D, 55 subjects (Group 2) and spherical equivalent change smaller than or equal to 0.50D, 53 subjects (Group 3). Spherical equivalent, axial length and corneal curvature at the beginning of the longitudinal study were not significantly different among the three refractive change groups.

Table 5.1
Distribution of refractive errors, axial lengths and corneal curvatures

	SE (D) ± SD	AXL (mm) ± SD	K (D) ± SD
SE change >1.50D (n=54)	-0.870 ± 1.605	23.742 ± 1.014	43.617 ± 1.432
SE change >0.50D and ≤1.50D (n=55)	-0.652 ± 2.292	23.590 ± 1.222	43.410 ± 1.287
SE change ≤0.50D (n=53)	-0.144 ± 2.239	23.247 ± 0.923	43.544 ± 1.622
p	0.18	0.050	0.75

SE, mean refractive spherical equivalence; AXL, mean axial length; K, mean corneal curvature; p, probability values of ANOVA
*Significant at the 0.05 level

As illustrated in Fig. 5.9, second order aberrations, third order aberrations, fourth order aberrations, spherical aberration, coma and total higher order aberrations showed no significant difference among the three refractive change groups. Table 5.2 shows the root mean square values of the monochromatic aberrations of the subjects with spherical equivalent change greater than 1.50D and subjects with spherical equivalent change smaller than or equal to 0.50D at the beginning of the longitudinal study. Subjects with spherical equivalent change smaller than or equal to 0.50D showed significant larger fourth order aberrations (unpaired t-test, p = 0.048) and spherical aberration (unpaired t-test, p = 0.019) than subjects with spherical equivalent change greater than 1.50D.

Table 5.2
Average Zernike coefficients for different refractive error groups at the beginning of the 2-year period

	2nd order	3rd order	4th order	SA	Coma	Total higher order
SE change >1.50D (n=54)	0.383 ±0.375	0.135 ±0.067	0.079 ±0.030	0.052 ±0.031	0.102 ±0.069	0.162 ±0.061
SE change ≤0.50D (n=53)	0.405 ±0.351	0.159 ±0.089	0.093 ±0.040	0.070 ±0.044	0.122 ±0.087	0.190 ±0.086
p	0.76	0.12	0.048*	0.019*	0.19	0.054

Units are microns. Errors are SD; p, probability values of unpaired t-test
*Significant at the 0.05 level

Figure 5.9

Average wavefront RMS for second order aberrations, third order aberrations, fourth order aberrations, spherical aberration, coma and total higher order aberrations *Significant at the 0.05 level (ANOVA)

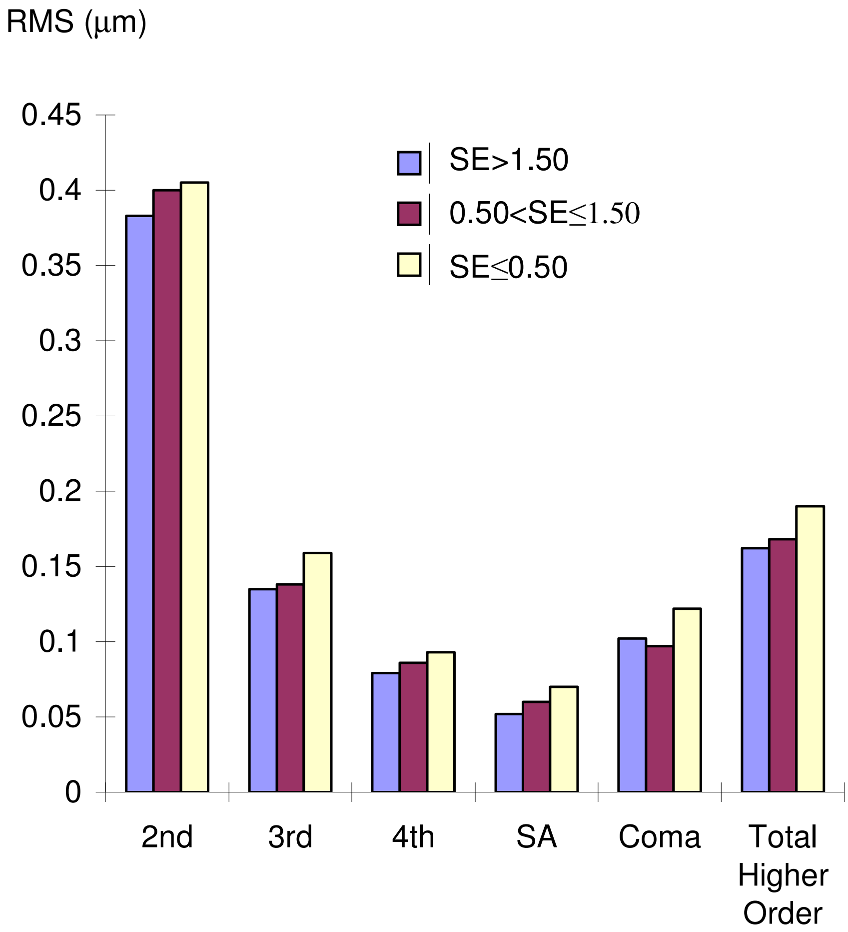


Table 5.3 shows the root mean square values of the second order aberrations, third order aberrations, fourth order aberrations, spherical aberration, coma and total higher order aberrations of all 162 subjects at the beginning and at the end of the longitudinal study. Group 1 showed significant difference for the second order aberrations (paired t-test, p = 0.0003), third order aberrations (paired t-test, p = 0.026), coma (paired t-test, p = 0.048) and total higher order aberrations (paired t-test, p = 0.019) between the beginning and the end of the study. Group 2 showed significant difference for the spherical aberration between the beginning and the end of the study (paired t-test, p = 0.0008). Group 3 showed no significant difference for the monochromatic aberrations between the beginning and the end of the study. When the tests were repeated for the subjects with no astigmatism change only (Table 5.4), no significant difference was found for Group 1. Spherical aberration of Group 2 was remaining significantly larger at the end of the study than at the beginning (paired t-test, p = 0.0038). When the astigmatism of the subjects at the beginning of the study were compared with those at the end of the study, significant difference was found in Group 1, no significant difference was found in other subjects (Table 5.5).

Table 5.3
Average Zernike coefficients for different refractive error groups, all subjects

		2nd order	3rd order	4th order	SA	Coma	Total higher order
SE change >1.50D (n=54)	1st visit	0.383 ±0.375	0.135 ±0.067	0.079 ±0.030	0.052 ±0.031	0.102 ±0.069	0.162 ±0.061
	5th visit	0.482 ±0.376	0.118 ±0.058	0.078 ±0.034	0.056 ±0.037	0.086 ±0.057	0.147 ±0.055
P		0.0003*	0.026*	0.68	0.29	0.048*	0.019*
SE change >0.50D and ≤1.50D (n=55)	1st visit	0.400 ±0.361	0.138 ±0.057	0.086 ±0.041	0.060 ±0.044	0.097 ±0.052	0.168 ±0.055
	5th visit	0.422 ±0.390	0.125 ±0.056	0.086 ±0.039	0.070 ±0.044	0.090 ±0.057	0.158 ±0.050
P		0.38	0.080	0.97	0.0008*	0.30	0.14
SE change ≤0.50D (n=53)	1st visit	0.405 ±0.351	0.159 ±0.089	0.093 ±0.040	0.070 ±0.044	0.122 ±0.087	0.190 ±0.086
	5th visit	0.424 ±0.358	0.163 ±0.099	0.096 ±0.038	0.077 ±0.038	0.123 ±0.094	0.195 ±0.095
P		0.47	0.73	0.18	0.14	0.94	0.62
All subjects (n=162)	1st visit	0.396 ±0.360	0.144 ±0.072	0.086 ±0.038	0.060 ±0.041	0.107 ±0.071	0.173 ±0.069
	5th visit	0.442 ±0.374	0.135 ±0.076	0.086 ±0.037	0.067 ±0.041	0.099 ±0.073	0.166 ±0.072
P		0.0020*	0.054	0.86	0.0016*	0.10	0.11

Units are microns. Errors are SD; p, probability values of paired t-test
*Significant at the 0.05 level

Table 5.4
Average Zernike coefficients for different refractive error groups, subjects with no astigmatism change (Δcyl=0D)

		2nd order	3rd order	4th order	SA	Coma	Total higher order
SE change >1.50D (n=14)	1st visit	0.284 ±0.233	0.133 ±0.063	0.066 ±0.023	0.049 ±0.024	0.096 ±0.070	0.151 ±0.062
	5th visit	0.352 ±0.234	0.116 ±0.046	0.074 ±0.032	0.051 ±0.034	0.079 ±0.046	0.141 ±0.046
P		0.11	0.22	0.22	0.79	0.19	0.47
SE change >0.50D and ≤1.50D (n=17)	1st visit	0.393 ±0.378	0.140 ±0.059	0.085 ±0.045	0.061 ±0.048	0.095 ±0.048	0.171 ±0.056
	5th visit	0.384 ±0.405	0.123 ±0.048	0.090 ±0.040	0.076 ±0.045	0.088 ±0.046	0.160 ±0.037
P		0.80	0.24	0.50	0.0038*	0.58	0.45
SE change ≤0.50D (n=13)	1st visit	0.313 ±0.262	0.142 ±0.058	0.096 ±0.030	0.075 ±0.039	0.118 ±0.058	0.176 ±0.052
	5th visit	0.337 ±0.237	0.126 ±0.069	0.094 ±0.030	0.084 ±0.034	0.099 ±0.071	0.165 ±0.056
P		0.53	0.47	0.70	0.18	0.34	0.56
All subjects (n=44)	1st visit	0.335 ±0.301	0.139 ±0.059	0.082 ±0.036	0.061 ±0.039	0.102 ±0.058	0.166 ±0.057
	5th visit	0.360 ±0.306	0.122 ±0.054	0.086 ±0.035	0.071 ±0.040	0.089 ±0.054	0.155 ±0.046
P		0.23	0.071	0.32	0.015*	0.097	0.22

Units are microns. Errors are SD; p, probability values of paired t-test
*Significant at the 0.05 level

Table 5.5
Average astigmatism for different refractive error groups at the beginning and at the end of the study

		Astigmatism (D)	p
SE change >1.50D (n=54)	1st visit	-0.620±0.480	0.0006*
	5th visit	-0.824±0.610	
SE change >0.50D and ≤1.50D (n=55)	1st visit	-0.605±0.515	0.75
	5th visit	-0.623±0.525	
SE change ≤0.50D (n=53)	1st visit	-0.722±0.544	0.21
	5th visit	-0.627±0.618	

Errors are SD; p, probability values of paired t-test
*Significant at the 0.05 level

All 162 subjects were divided into 3 groups: myopia (SE < -0.75D), 49 subjects; emmetropia (-0.75D ≤ SE ≤ 0.75D), 75 subjects and hyperopia (SE > 0.75D), 38 subjects (Table 5.6). At the beginning of the longitudinal study, spherical equivalent, axial length, corneal curvature and spherical aberration were significantly different among the three refractive groups (ANOVA, $p < 0.0001$, $p < 0.0001$, $p = 0.036$ and $p = 0.039$, respectively). Since the grouping of the subjects were dependent on the refractive errors, significant difference of spherical equivalent and axial length among groups was expected. Table 5.7 shows the change of spherical equivalent, axial length, corneal curvature and spherical aberration at the end of the study. Spherical equivalent, axial length and spherical aberration showed significant change at the end of the study (ANOVA, $p = 0.0003$, $p = 0.0066$ and $p = 0.0076$, respectively). As shown in Fig 5.10, C(4,0) change was not significantly correlated with axial length change over the 2-year study period.

Table 5.6
Distribution of refractive errors, axial lengths, corneal curvatures and spherical aberration

	SE (D)	AXL (mm)	K (D)	SA (microns)
Myopia (n=49)	-2.929 ±2.254	24.587 ±0.848	43.784 ±1.464	0.052 ±0.041
Emmetropia (n=75)	0.067 ±0.411	23.383 ±0.698	43.209 ±1.479	0.059 ±0.039
Hyperopia (n=38)	1.263 ±0.484	22.451 ±0.637	43.805 ±1.249	0.074 ±0.043
p	<0.0001*	<0.0001*	0.036*	0.039*

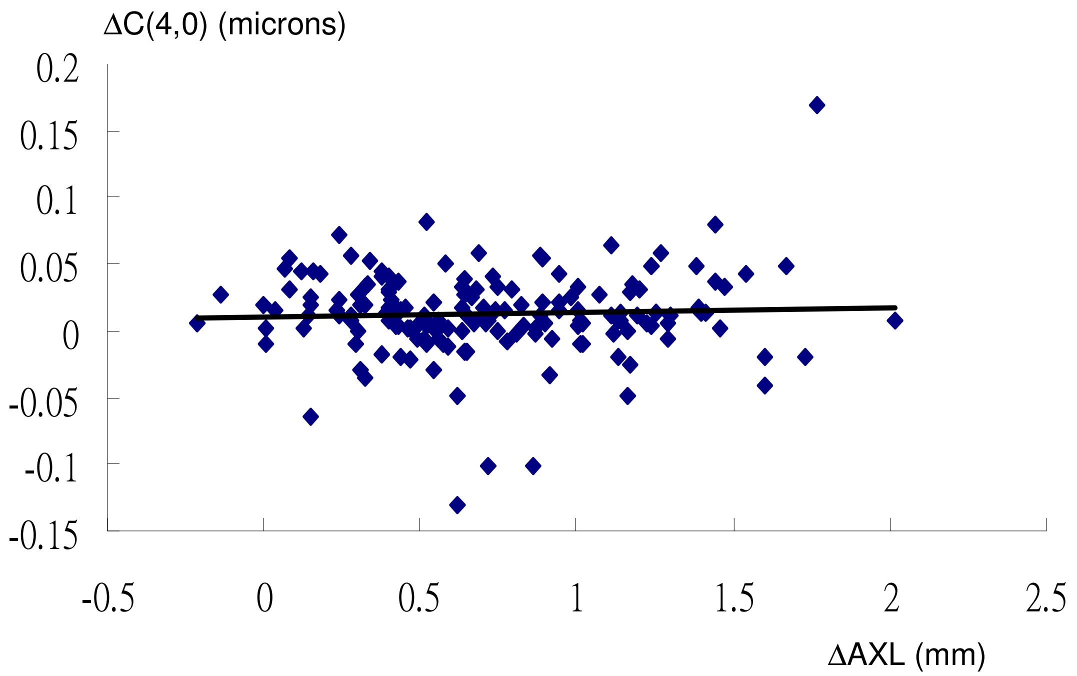
SE, mean refractive spherical equivalence; AXL, mean axial length; K, mean corneal curvature; SA, spherical aberration; Errors are SD; p, probability values of ANOVA
*Significant at the 0.05 level

Table 5.7
Distribution of change of refractive errors, axial lengths, corneal curvatures and spherical aberration at the end of the study

	ΔSE (D)	ΔAXL (mm)	ΔK (D)	ΔSA (microns)
Myopia (n=49)	-1.541 ±0.986	0.794 ±0.421	0.266 ±0.281	0.0020 ±0.0302
Emmetropia (n=75)	-1.193 ±0.992	0.775 ±0.453	0.283 ±0.428	0.0040 ±0.0269
Hyperopia (n=38)	-0.717 ±0.628	0.513 ±0.362	0.146 ±0.210	0.0186 ±0.0193
All subjects (n=162)	-1.187 ±0.961	0.720 ±0.436	0.246 ±0.348	0.0068 ±0.0271
P	0.0011*	0.0099*	0.25	0.022*

SE, mean refractive spherical equivalence; AXL, mean axial length; K, mean corneal curvature; SA, spherical aberration; Errors are SD; p, probability values of ANOVA
*Significant at the 0.05 level

Figure 5.10
Linear regression of C(4,0) change as function of axial length change (m=0.0036, p=0.54, r=0.048).



Spherical equivalent, axial length and C(4,0) in each visit was shown in Figure 5.11, Figure 5.12 and Figure 5.13 respectively. Spherical equivalent became significantly more negative ($p < 0.0001$) after the 2-year period (Table 5.8). Axial length increased significantly ($p < 0.0001$) after the 2-year period (Table 5.9). C(4,0) became significantly more positive ($p < 0.0001$) after the 2-year period (Table 5.10). When we divided the subjects into myopic, emmetropic and hyperopic groups, emmetropic and hyperopic eyes showed significantly more positive C(4,0) ($p = 0.0007$ and $p < 0.0001$, respectively), myopic eyes showed no significantly difference after the 2-year period ($p = 0.11$) (Table 5.10).

Figure 5.11
Spherical equivalent of the subjects in each visit

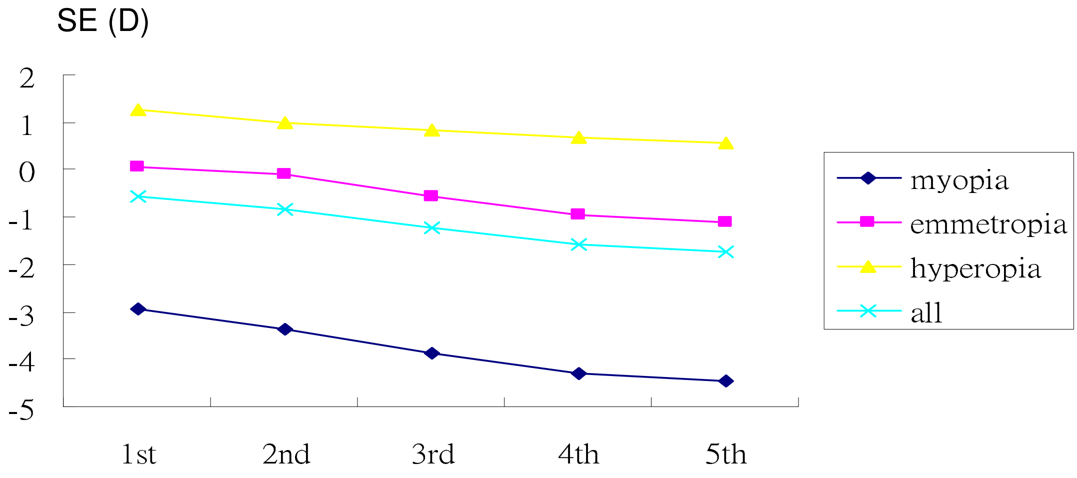


Figure 5.12

Axial length of the subjects in each visit

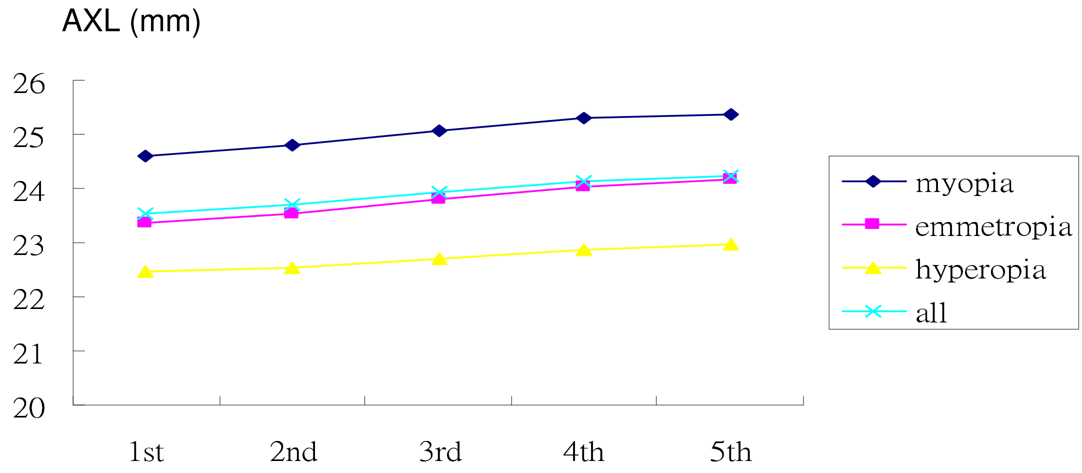


Figure 5.13

C(4,0) of the subjects in each visit

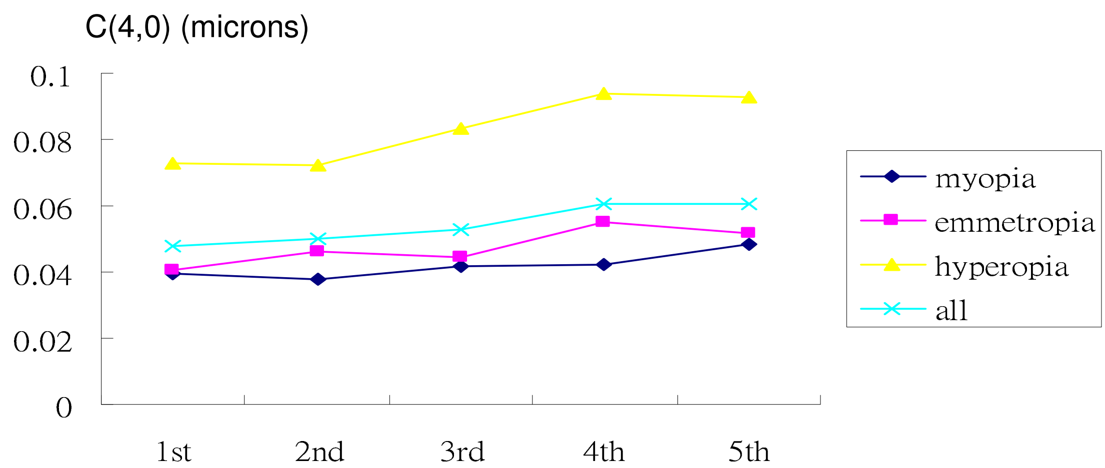


Table 5.8
Spherical equivalent of the subjects in each visit

	SE(1)(D)	SE(2)(D)	SE(3)(D)	SE(4)(D)	SE(5)(D)	P
Myopia	-2.929	-3.349	-3.865	-4.296	-4.469	<0.0001*
Emmetropia	0.0667	-0.105	-0.583	-0.937	-1.127	<0.0001*
Hyperopia	1.263	0.990	0.832	0.681	0.546	<0.0001*
All subjects	-0.559	-0.829	-1.244	-1.573	-1.745	<0.0001*

SE, spherical equivalent; (1), first visit; (2), second visit; (3), third visit; (4), fourth visit; (5), fifth visit; p, probability value of ANOVA
*Significant at the 0.05 level

Table 5.9
Axial length of the subjects in each visit

	AXL(1) (mm)	AXL(2) (mm)	AXL(3) (mm)	AXL(4) (mm)	AXL(5) (mm)	P
Myopia	24.587	24.812	25.062	25.287	25.381	<0.0001*
Emmetropia	23.376	23.535	23.805	24.049	24.151	<0.0001*
Hyperopia	22.451	22.549	22.706	22.882	22.963	<0.0001*
All subjects	23.525	23.690	23.927	24.150	24.245	<0.0001*

AXL, axial length; (1), first visit; (2), second visit; (3), third visit; (4), fourth visit; (5), fifth visit; p, probability value of ANOVA
*Significant at the 0.05 level

Table 5.10
C(4,0) of the subjects in each visit

	C(4,0)(1) (D)	C(4,0)(2) (D)	C(4,0)(3) (D)	C(4,0)(4) (D)	C(4,0)(5) (D)	P
Myopia	0.0394	0.0380	0.0416	0.0425	0.0484	0.11
Emmetropia	0.0408	0.0463	0.0446	0.0548	0.0516	0.0007*
Hyperopia	0.0728	0.0721	0.0831	0.0941	0.0928	<0.0001*
All subjects	0.0479	0.0499	0.0527	0.0603	0.0603	<0.0001*

(1), first visit; (2), second visit; (3), third visit; (4), fourth visit; (5), fifth visit; p, probability value of ANOVA
*Significant at the 0.05 level

All 3 refractive groups were sub-divided into 6 groups: myopia with refractive change larger than or equal to 1.00D (Group MH), 30 subjects; myopia with refractive change smaller than 1.00D, 19 subjects (Group ML); emmetropia with refractive change larger than or equal to 1.00D, 41 subjects (Group EH); emmetropia with refractive change smaller than 1.00D, 34 subjects (Group EL); hyperopia with refractive change larger than or equal to 1.00D, 13 subjects (Group HH), and hyperopia with refractive change smaller than 1.00D, 25 subjects (Group HL). Spherical aberration of the six refractive groups at the beginning and at the end of the study was shown in Table 5.11. Spherical aberration in Group MH was significantly smaller than that of Group ML (unpaired t-test, $p = 0.031$). No significant difference was found in other groups. When the spherical aberration at the beginning of the study was compared to that at the end of the study, Group HH and Group HL showed significantly larger spherical aberration at the end of the study (paired t-test, $p = 0.022$ and $p < 0.0001$, respectively). No significant change was found in other groups.

Table 5.11
Spherical aberration of the six refractive groups at the beginning and at the end of the study

		SA (microns) ± SD		p(2)
		1st visit	5th visit	
Myopia	SE change ≥1.00D (n=30)	0.042 ±0.028	0.044 ±0.034	0.70
	SE change <1.00D (n=19)	0.068 ±0.052	0.070 ±0.037	0.79
p(1)		0.031*		
Emmetropia	SE change ≥1.00D (n=41)	0.064 ±0.039	0.068 ±0.039	0.19
	SE change <1.00D (n=34)	0.053 ±0.038	0.057 ±0.036	0.57
p(1)		0.26		
Hyperopia	SE change ≥1.00D (n=13)	0.076 ±0.045	0.092 ±0.041	0.022*
	SE change <1.00D (n=25)	0.073 ±0.042	0.093 ±0.040	<0.0001*
p(1)		0.81		

SA, spherical aberration; Errors are SD; p(1), probability values of unpaired t-test; p(2), probability values of paired t-test
*Significant at the 0.05 level

5.4 DISCUSSION

Our results showed that spherical equivalent and axial length of the subjects at the beginning of the study have a significant impact on the refractive development (Figure 5.2 and Figure 5.3, respectively) which was in agreement with previous studies (Gwiazda et al., 2007; Saw et al., 2000) and the results of Chapter 4.Spherical equivalent, axial length and corneal curvature showed no significant difference among the three refractive groups: spherical equivalent change larger than 1.50D; spherical equivalent change smaller than or equal to 1.50D and larger than 0.50D and spherical equivalent change smaller than or equal to 0.50D (Table 5.1).This difference may due to the confounding effect of the grouping among the three refractive groups. The root mean square value of the monochromatic aberrations also showed no significant different among the three refractive groups (Figure 5.1). When the monochromatic aberrations of the subjects with spherical equivalent change larger than 1.50D were compared with those with spherical equivalent change smaller than or equal to 0.50D, fourth order aberrations and spherical aberration were found significantly smaller in the subjects with spherical equivalent change larger than 1.50D (Table 5.2). This result suggested that subjects with smaller fourth order aberrations and spherical aberration tended to be associated with more refractive change.

In agree with the results of Chapter 4, we found that the initial spherical aberration and initial total higher order aberrations had no significant impact on the degree of myopia progression. But when we divided the subjects into myopic, emmetropic and hyperopic groups, we found that myopic eyes showed significant value. This result suggests that the impact of spherical aberration on refractive development might be different among myopic, emmetropic and hyperopic eyes. Myopic eyes with less positive initial spherical aberration tended to be associated with more myopia progression.

Among the subjects with spherical equivalent change larger than 1.50D, second order aberrations, third order aberrations, coma and total higher order aberrations were significantly different between the beginning and the end of the study (Table 5.3). However, astigmatism of these subjects was also significant different between the beginning and the end of the study (Table 5.5). When the tests were repeated for subjects with no astigmatism change only, second order aberrations, third order aberrations, coma and total higher order aberrations were then not significant different between the beginning and the end of the study (Table 5.4). This suggests that the significant different of the aberrations found might be due to the change of astigmatism.

Among the subjects with spherical equivalent change smaller than or equal to 1.50D and larger than 0.50D, spherical aberration was significantly different between the beginning and the end of the study (Table 5.3). When the test was repeated for subjects with no astigmatism change only, spherical aberration remained significantly different between the beginning and the end of the study (Table 5.4). This suggests that a smaller change in spherical equivalent, within 1.50D and 0.50D, is associated with a larger change in spherical aberration.

Collins et al. (1995) reported that the spherical aberration of adult myopic subjects was less positive than that of emmetropic subjects. Llorente et al. (2004) also found that hyperopic eyes tend to have larger higher order aberrations than myopic eyes. Our results show that myopic eyes have smaller spherical aberration than emmetropic eyes and emmetropic eyes had smaller spherical aberration than hyperopic eyes. This difference is statistically significant (Table 5.6). Figure 5.1 also showed that eyes with longer axial length had less positive spherical aberration.

As shown in Table 5.11, myopic eyes with larger spherical equivalent change have a degree of smaller spherical aberration at the beginning of the study. However, this was not the case for emmetropic and hyperopic eyes. This result suggests that a smaller amount of spherical aberration in myopic eyes might be one of the risk factors for myopia progression in myopic eyes. However, this does not apply to emmetropic and hyperopic eyes. Previous studies have reported that spherical aberration always decreased and changed from positive to negative with increasing accommodation (Atchison et al., 1995; Buehren and Collins, 2005; Cheng et al., 2004; Hazel et al., 2003; He et al., 2000; Ninomiya et al., 2002; Plainis et al., 2005). Eyes with a smaller amount of positive spherical aberration at distance will tend to have a larger amount of negative spherical aberration at near. Previous studies have shown that hyperopic defocus lead to axial elongation and result in myopia development (Shaikh et al., 1999). Spherical aberration at near might play a role as a directional cue for myopia development in myopic eyes. Increased spherical aberration has been reported after orthokeratology (Berntsen et al., 2005; Hiraoka et al., 2007; Joslin et al., 2003; Joslin et al., 2004). It has also been suggested that orthokeratology can have a control effect on childhood myopia (Cho et al., 2005). The increased spherical aberration at distance after orthokeratology may enhance myopic control by reducing the negative spherical aberration at near.

Similar to the results of Chapter 4, the spherical equivalent of our subjects became more negative, axial length increased and spherical aberration became more positive after the 2-year period (Figure 5.11, Figure 5.12 and Figure 5.13, respectively). When we divide the subjects into myopic, emmetropic and hyperopic groups, spherical aberration of myopic eyes showed no significant difference after the 2-year period. In common with the suggestion in Chapter 4, eyes with different refractive error might have an effect beyond that expected from the years of age.

Our results show that change of spherical equivalent, axial length and spherical aberration after the longitudinal study are significantly different among myopic, emmetropic and hyperopic eyes (Table 5.7). Myopic eyes have the largest spherical equivalent change and axial length change while hyperopic eyes had the smallest. Myopic eyes have the smallest spherical aberration change while hyperopic eyes had the largest. A larger amount of axial elongation with a corresponding larger amount of spherical equivalent change showed a smaller spherical aberration increase. Cheng et al. (2003), using a reduced-eye model, predicted spherical aberration should increase systematically with axial elongation. Our results do not agree with the prediction of Cheng et al. (2003). From Figure 5.10, we found spherical aberration of eyes with greater axial elongation, increased by a similar amount over the 2-year period. To achieve what we have found, we suggest that the corneal positive spherical aberration may be reduced or the crystalline lens negative spherical aberration may be increased during the refractive change process.

As shown in Table 5.11, we found that the change of spherical aberration was different among myopes, emmetropes and hyperopes. Spherical aberration of the myopic and emmetropic eyes was nearly unchanged over the two year study period even though there was significant change in refractive error. However, spherical aberration of the hyperopic eyes increased significantly over the 2-year period whatever the amount of refractive error changed.

Our results show the relationship of monochromatic aberrations and refractive development for distant viewing. A smaller amount of spherical aberration at distant might play a role as a precursor to myopia. A larger amount of aberration might play a role in retarding myopia development in myopic eyes. Further investigations are required to study this relationship at near in order to find out the role of monochromatic aberrations in myopic progression.

Chapter 6
Summary and Improvements

In summary, our results suggest that higher amounts of spherical aberration in myopic eyes may reduce the risk of myopia. The possible mechanism is that eyes with higher amounts of spherical aberration at distant may remain positive value when reading. This positive spherical aberration at near might act as a directional cue for eye growth. However, one factor that should be considered is the effect of depth of focus. Depth of focus increases with spherical aberration (Cheng et al., 2004; Collins et al., 2002). Rosenfield and Abraham-Cohen (1999) reported that myopic eyes with larger depth of focus had lower subjective blur sensitivity. This result might explain why myopic eyes have a larger lag of accommodation. Higher amounts of spherical aberration might lead to increased depth of focus, as a result of increased lag of accommodation. This hyperopic retinal defocus due to increased accommodative error may play a significant role in myopia progression.

In our study, there are some improvements we could consider in order to clarify further the role of monochromatic aberrations in myopia development. First, measurement of corneal topography can give more information about the change of corneal aberration and lens aberration during refractive error development. Second, our study investigated monochromatic aberrations of the eye at distance. Monochromatic aberrations during accommodation at different gazes might reveal more information about the visual stimulus during reading. In primary gaze, monochromatic aberrations change with the effect of accommodation only. In down gaze, monochromatic aberrations change with the effect of accommodation and also lid action. Third, we analyzed our result using a fixed 5mm pupil diameter. In real life, individuals have different pupil sizes. However, much less is known about the relationship between pupil size and refractive error. Spherical aberrations increase with larger pupil size. Investigations using real pupil size might reveal more information about the role of monochromatic aberrations in refractive error development.

Chapter 7
Conclusion

Our results suggest that monochromatic aberrations of the eye may be associated with refractive development. Myopic eyes tended to have less positive spherical aberration. No significant correlation was found between monochromatic aberrations change and myopia development. The reason may due to the balance effect among corneal aberrations, lens aberrations and internal aberrations. There was no evidence to support the notion that high amounts of higher order aberrations drive myopia development. On the contrary, we found that small amounts of spherical aberration may be one of the risk factors for myopia development and higher amounts of spherical aberration in myopic eyes may reduce the risk of myopia. For myopic and emmetropic eyes, spherical aberration was mostly unchanged over the two year study period even though there was significant change in refractive error. For hyperopic eyes, spherical aberration was significantly increased over the two year study period irrespective of refractive error change. More investigations are required to clarify further the role of monochromatic aberrations in myopia development.

Appendix 1

Data for the left eyes of chapter 4

Appendix 1.1
Distribution of refractive errors and axial lengths of the subjects at the beginning of the 1-year period (n=964)

		SE (D) ± SD	AXL (mm) ± SD	No. of Eyes
Low astigmatism (≥-1.00D)	Myopia (<-0.75D), (c)	-1.996 ± 1.036	24.118 ± 0.767	169
	Myopia (<-0.75D), (nc)	-1.933 ± 1.110	24.114 ± 0.715	69
	Emmetropia (-0.75 to +0.75D), (c)	-0.036 ± 0.443	23.252 ± 0.721	199
	Emmetropia (-0.75 to +0.75D), (nc)	+0.111 ± 0.344	23.065 ± 0.670	350
	Hyperopia (>+0.75D), (c)	+1.108 ± 0.182	22.893 ± 0.598	15
	Hyperopia (>+0.75D), (nc)	+1.291 ± 0.819	22.262 ± 0.763	37
High astigmatism (<-1.00D)	Myopia (<-0.75D), (c)	-3.283 ± 1.474	24.497 ± 0.885	50
	Myopia (<-0.75D), (nc)	-2.054 ± 1.434	23.494 ± 0.753	7
	Emmetropia (-0.75 to +0.75D), (c)	-0.217 ± 0.391	23.199 ± 0.894	15
	Emmetropia (-0.75 to +0.75D), (nc)	-0.165 ± 0.352	22.689 ± 0.662	34
	Hyperopia (>+0.75D), (c)	+1.438 ± 0.782	22.738 ± 0.531	6
	Hyperopia (>+0.75D), (nc)	+2.144 ± 1.589	22.016 ± 0.778	13
p			<0.0001*	

Units are microns; SE, mean refractive spherical equivalent; AXL, mean axial length; (c), SE change ≥0.50D at the end of 1-year period; (nc), SE change <0.50D at the end of 1-year period; p, probability value of ANOVA
*Significant at the 0.05 level

Appendix 1.2
Average Zernike coefficients for different astigmatism groups at the beginning of the 1-year period

	2nd order	3rd order	4th order	SA	Coma	3rd to 4th order
Low astigmatism subjects (n=839)	0.323 ± 0.223	0.134 ± 0.060	0.084 ± 0.040	0.060 ± 0.045	0.096 ± 0.060	0.163 ± 0.061
High astigmatism subjects (n=125)	1.155 ± 0.624	0.161 ± 0.084	0.088 ± 0.043	0.060 ± 0.044	0.117 ± 0.070	0.189 ± 0.081
p	<0.0001*	<0.0001*	0.27	0.90	0.0003*	<0.0001*

Units are microns; Errors are SD; p, probability values of unpaired t-test
*Significant at the 0.05 level

Appendix 1.3
Average Zernike coefficients for different refractive error groups, all subjects (low astigmatism) at the beginning and at the end of the 1-year period

		2nd order	3rd order	4th order	SA	Coma	Total higher order
Myopes (c) (n=169)	1st visit	0.342 ±0.247	0.136 ±0.079	0.079 ±0.036	0.057 ±0.040	0.100 ±0.063	0.161 ±0.063
	2nd visit	0.371 ±0.273	0.120 ±0.050	0.078 ±0.033	0.058 ±0.039	0.088 ±0.052	0.147 ±0.048
p		0.13	0.0008*	0.54	0.91	0.011*	0.0016*
Myopes (nc) (n=69)	1st visit	0.326 ±0.232	0.131 ±0.056	0.074 ±0.028	0.046 ±0.037	0.094 ±0.059	0.154 ±0.052
	2nd visit	0.361 ±0.221	0.130 ±0.066	0.077 ±0.035	0.055 ±0.041	0.090 ±0.065	0.155 ±0.066
p		0.20	0.90	0.61	0.092	0.60	0.96
Emmetropes (c) (n=199)	1st visit	0.310 ±0.227	0.138 ±0.057	0.087 ±0.037	0.064 ±0.042	0.100 ±0.059	0.167 ±0.057
	2nd visit	0.338 ±0.295	0.143 ±0.064	0.091 ±0.051	0.069 ±0.056	0.107 ±0.065	0.175 ±0.069
p		0.18	0.26	0.22	0.18	0.12	0.090
Emmetropes (nc) (n=350)	1st visit	0.305 ±0.198	0.131 ±0.062	0.084 ±0.045	0.061 ±0.048	0.091 ±0.060	0.161 ±0.065
	2nd visit	0.312 ±0.231	0.139 ±0.071	0.089 ±0.042	0.066 ±0.046	0.098 ±0.067	0.170 ±0.071
p		0.53	0.060	0.028*	0.069	0.12	0.025*
Hyperopes (c) (n=15)	1st visit	0.392 ±0.212	0.143 ±0.046	0.093 ±0.037	0.064 ±0.047	0.091 ±0.057	0.175 ±0.042
	2nd visit	0.296 ±0.195	0.126 ±0.064	0.099 ±0.037	0.077 ±0.043	0.089 ±0.070	0.168 ±0.054
p		0.013*	0.26	0.36	0.11	0.86	0.50
Hyperopes (nc) (n=37)	1st visit	0.441 ±0.264	0.141 ±0.048	0.096 ±0.041	0.069 ±0.047	0.101 ±0.051	0.175 ±0.051
	2nd visit	0.439 ±0.297	0.134 ±0.055	0.099 ±0.043	0.072 ±0.050	0.098 ±0.053	0.171 ±0.058
p		0.98	0.42	0.53	0.67	0.68	0.66
All subjects (c) (n=383)	1st visit	0.327 ±0.236	0.137 ±0.060	0.084 ±0.037	0.061 ±0.041	0.099 ±0.061	0.165 ±0.059
	2nd visit	0.351 ±0.282	0.132 ±0.059	0.086 ±0.044	0.064 ±0.050	0.098 ±0.061	0.162 ±0.062
p		0.087	0.12	0.42	0.16	0.59	0.46
All subjects (nc) (n=456)	1st visit	0.319 ±0.212	0.132 ±0.060	0.083 ±0.043	0.060 ±0.047	0.093 ±0.059	0.161 ±0.062
	2nd visit	0.330 ±0.238	0.137 ±0.069	0.088 ±0.041	0.065 ±0.046	0.097 ±0.065	0.168 ±0.069

p	0.30	0.14	0.020*	0.018*	0.25	0.049*

Units are microns. Errors are SD. (c), SE change ≥0.50D at the end of the 1-year period. (nc), SE change <0.50D at the end of the 1-year period; p, probability value of paired t-test
*Significant at the 0.05 level

Appendix 1.4
Average Zernike coefficients for different refractive error groups, all subjects (high astigmatism) at the beginning and at the end of the 1-year period

		2nd order	3rd order	4th order	SA	Coma	Total higher order
Myopes (c) (n=50)	1st visit	1.151 ±0.570	0.141 ±0.068	0.075 ±0.042	0.047 ±0.047	0.101 ±0.057	0.166 ±0.067
	2nd visit	1.082 ±0.537	0.141 ±0.070	0.082 ±0.038	0.055 ±0.044	0.106 ±0.062	0.168 ±0.069
p		0.41	0.95	0.14	0.12	0.62	0.80
Myopes (nc) (n=7)	1st visit	1.068 ±0.710	0.175 ±0.059	0.098 ±0.035	0.063 ±0.037	0.123 ±0.041	0.205 ±0.050
	2nd visit	1.025 ±0.657	0.167 ±0.097	0.066 ±0.025	0.026 ±0.022	0.127 ±0.092	0.184 ±0.092
p		0.80	0.88	0.077	0.055	0.91	0.62
Emmetropes (c) (n=15)	1st visit	0.994 ±0.496	0.146 ±0.098	0.085 ±0.032	0.068 ±0.038	0.100 ±0.094	0.176 ±0.089
	2nd visit	1.043 ±0.587	0.144 ±0.059	0.088 ±0.036	0.063 ±0.049	0.105 ±0.058	0.175 ±0.052
p		0.59	0.90	0.70	0.58	0.77	0.90
Emmetropes (nc) (n=34)	1st visit	1.059 ±0.598	0.184 ±0.096	0.105 ±0.049	0.069 ±0.042	0.134 ±0.068	0.217 ±0.097
	2nd visit	0.863 ±0.605	0.157 ±0.064	0.105 ±0.038	0.076 ±0.039	0.118 ±0.067	0.194 ±0.058
p		0.063	0.15	1.00	0.21	0.20	0.22
Hyperopes (c) (n=6)	1st visit	1.002 ±0.568	0.177 ±0.068	0.073 ±0.0306	0.054 ±0.031	0.144 ±0.053	0.195 ±0.065
	2nd visit	1.059 ±0.748	0.143 ±0.085	0.074 ±0.033	0.044 ±0.033	0.090 ±0.053	0.165 ±0.082
p		0.87	0.11	0.91	0.38	0.0094	0.16
Hyperopes (nc) (n=13)	1st visit	1.726 ±0.781	0.175 ±0.096	0.096 ±0.043	0.077 ±0.049	0.137 ±0.095	0.210 ±0.080
	2nd visit	1.771 ±0.603	0.188 ±0.102	0.108 ±0.035	0.085 ±0.045	0.149 ±0.099	0.223 ±0.094
p		0.66	0.35	0.22	0.31	0.38	0.35
All subjects (c) (n=71)	1st visit	1.105 ±0.552	0.145 ±0.075	0.077 ±0.039	0.052 ±0.044	0.105 ±0.066	0.171 ±0.071
	2nd visit	1.072 ±0.557	0.142 ±0.068	0.083 ±0.037	0.056 ±0.044	0.104 ±0.060	0.169 ±0.066
p		0.62	0.62	0.13	0.34	0.96	0.84
All subjects (nc) (n=53)	1st visit	1.221 ±0.707	0.180 ±0.091	0.102 ±0.045	0.070 ±0.043	0.134 ±0.072	0.214 ±0.087
	2nd visit	1.103 ±0.712	0.166 ±0.079	0.101 ±0.038	0.072 ±0.042	0.127 ±0.078	0.200 ±0.072

p	0.11	0.28	0.83	0.77	0.48	0.29

Units are microns. Errors are SD. (c), SE change ≥0.50D at the end of the 1-year period. (nc), SE change <0.50D at the end of the 1-year period; p, probability value of paired t-test
*Significant at the 0.05 level

Appendix 1.5
Spherical equivalent of the subjects in each visit

	SE (1) (D)	SE (2) (D)	P
Myopia	-2.201	-2.977	<0.0001*
Emmetropia	0.0389	-0.283	<0.0001*
Hyperopia	1.421	1.224	0.002*
All subjects	-0.545	-0.996	<0.0001*

SE, spherical equivalent; (1), first visit; (2), second visit; p, probability value of paired t-test
*Significant at the 0.05 level

Appendix 1.6
Axial length of the subjects in each visit

	AXL (1) (mm)	AXL (2) (mm)	P
Myopia	24.167	24.571	<0.0001*
Emmetropia	23.109	23.387	<0.0001*
Hyperopia	22.390	22.584	<0.0001*
All subjects	23.380	23.690	<0.0001*

AXL, axial length; (1), first visit; (2), second visit; p, probability value of paired t-test
*Significant at the 0.05 level

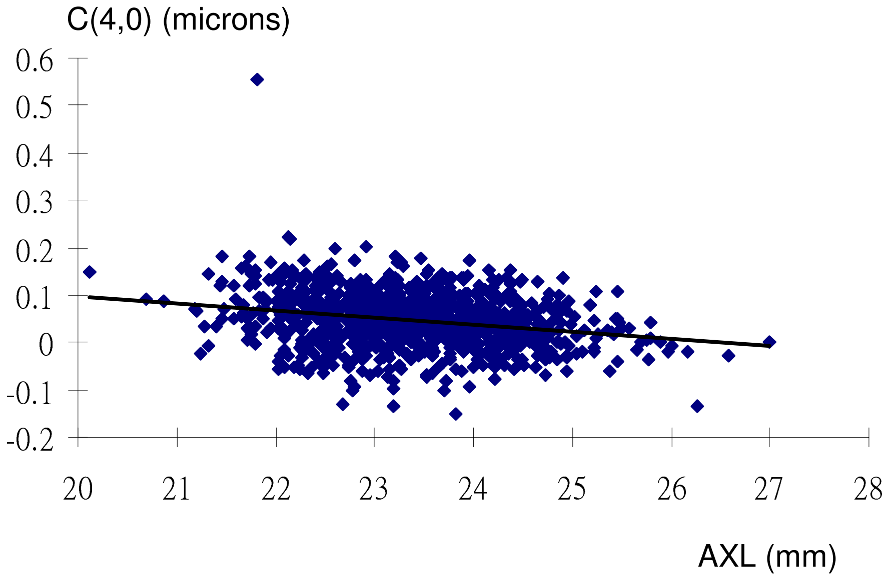
Appendix 1.7
C(4,0) of the subjects in each visit

	C(4,0) (1) (microns)	C(4,0) (2) (microns)	P
Myopia	0.0397	0.0434	0.189
Emmetropia	0.0509	0.0598	<0.0001*
Hyperopia	0.0524	0.0629	0.031*
All subjects	0.0476	0.0550	<0.0001*

(1), first visit; (2), second visit; p, probability value of paired t-test
*Significant at the 0.05 level

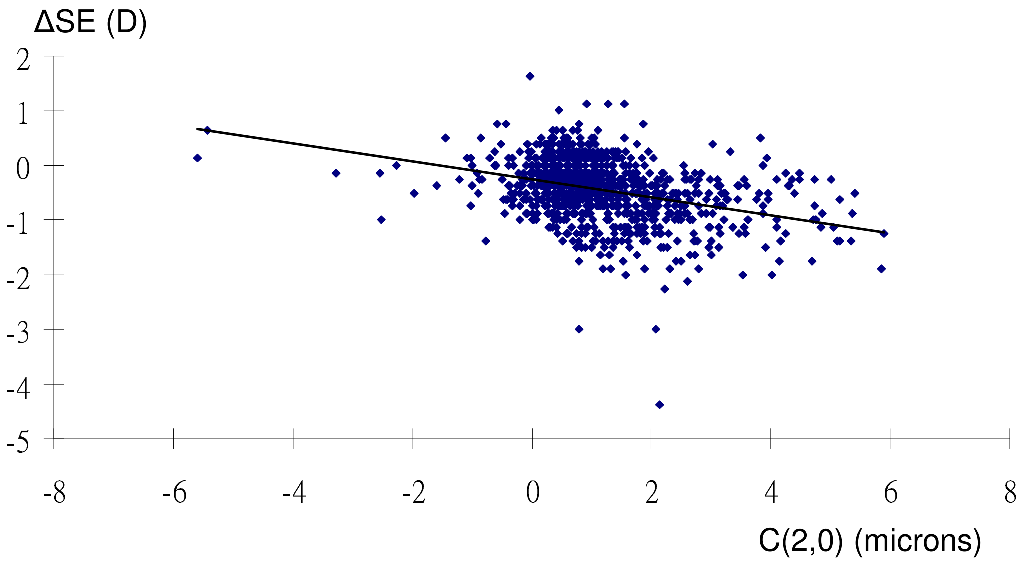
Appendix 1.8

Linear regression of C(4,0) as function of axial length (m=-0.015, p<0.0001, r=-0.24) at the beginning of the 1-year period



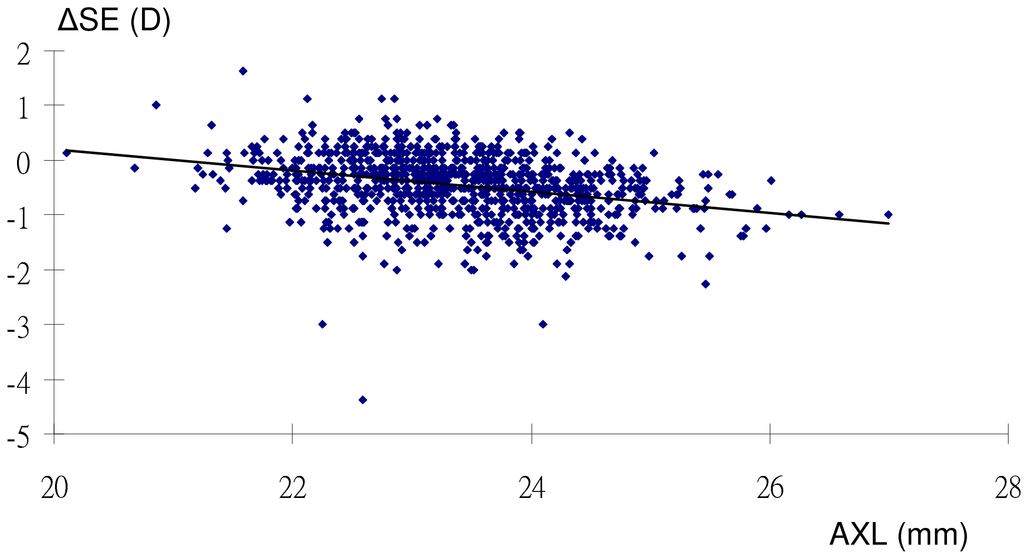
Appendix 1.9

Linear regression of spherical equivalent change as function of initial C(2,0) (m=-0.17, p<0.0001, r=-0.36)



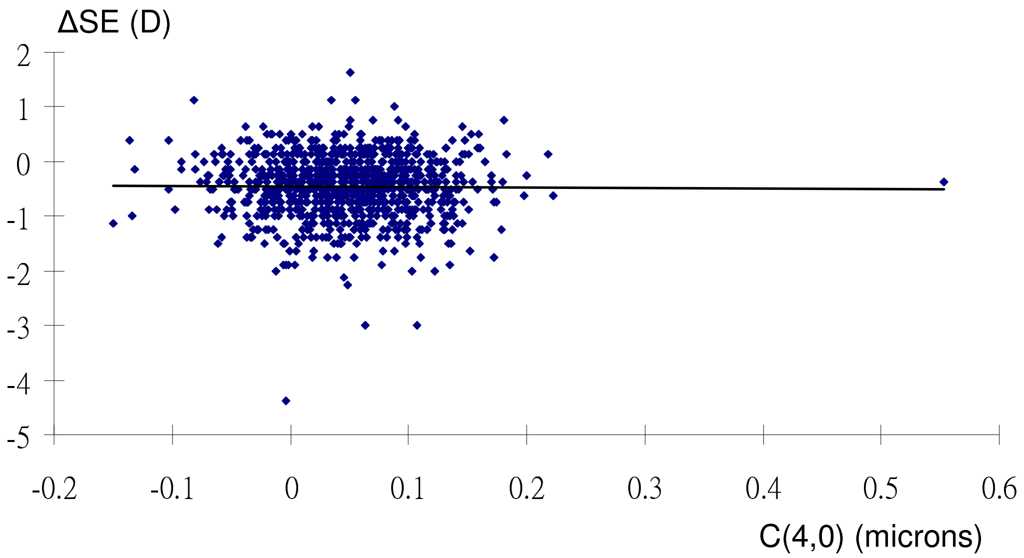
Appendix 1.10

Linear regression of spherical equivalent change as function of initial axial length (m=-0.19, p<0.0001, r=-0.32)



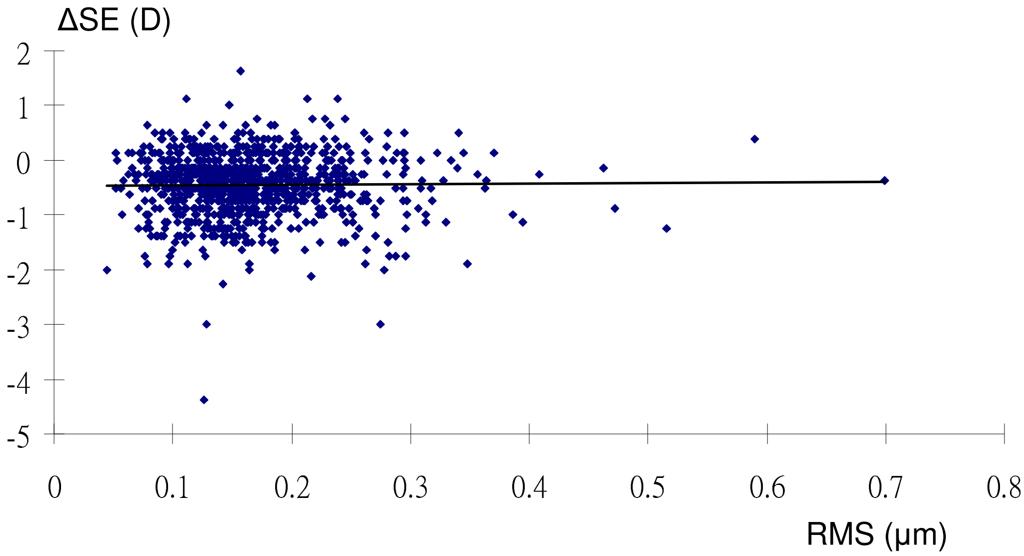
Appendix 1.11

Linear regression of spherical equivalent change as function of initial C(4,0) (m=-0.12, p=0.71, r=-0.012)



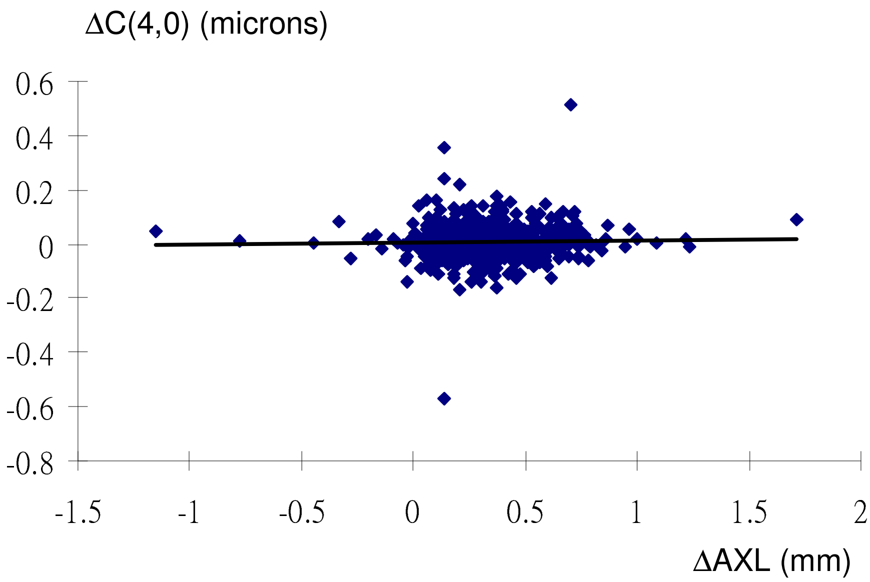
Appendix 1.12

Linear regression of spherical equivalent change as function of initial total higher order aberrations (m=0.11, p=0.71, r=0.012)



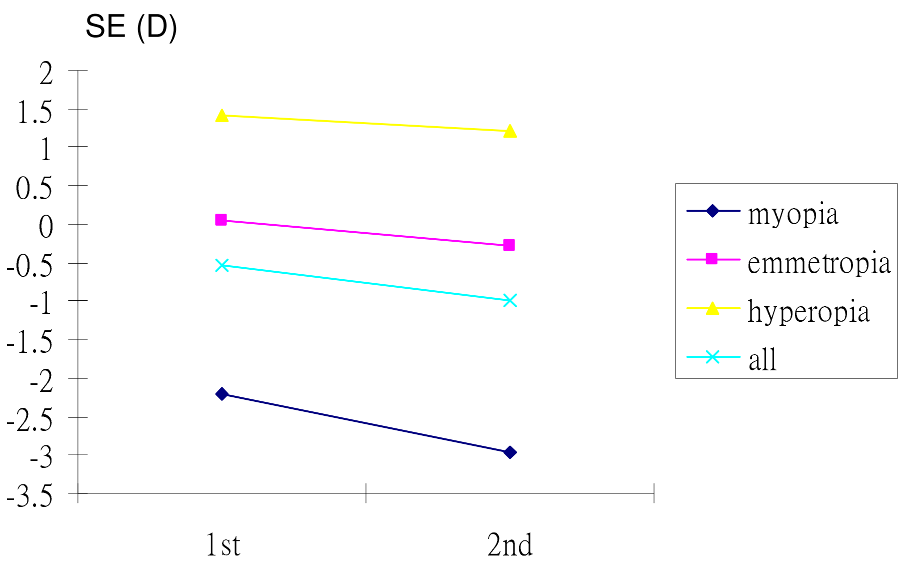
Appendix 1.13

Linear regression of C(4,0) change as function of axial length change (m=0.009, p=0.28, r=0.035)



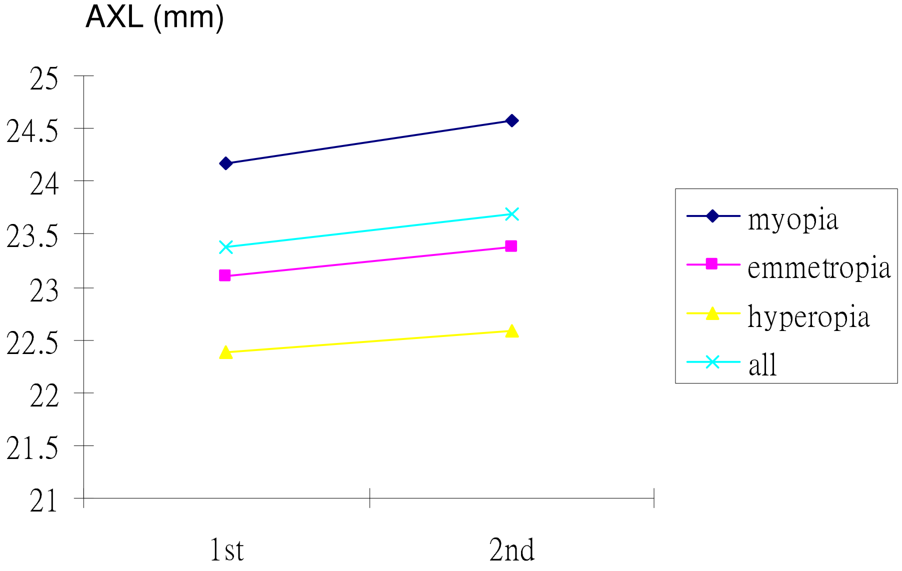
Appendix 1.14

Spherical equivalent of the subjects in each visit



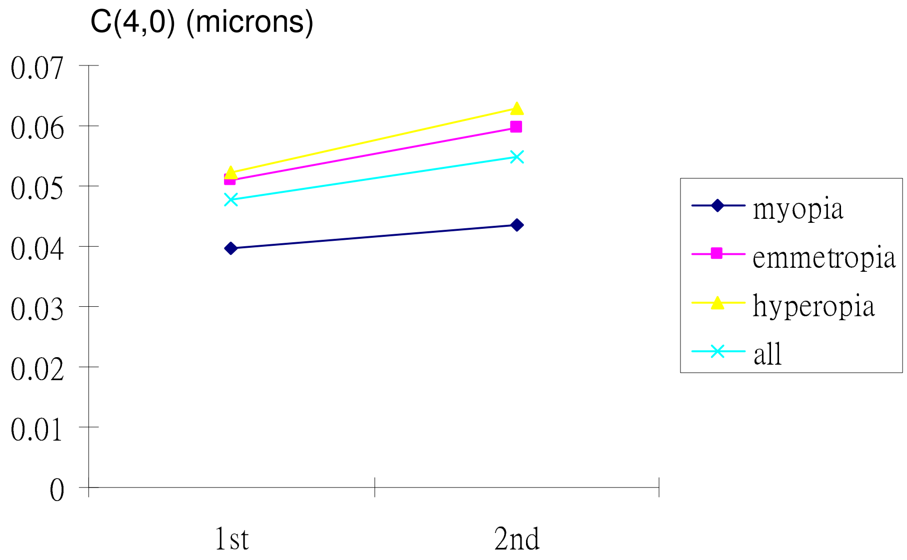
Appendix 1.15

Axial length of the subjects in each visit



Appendix 1.16

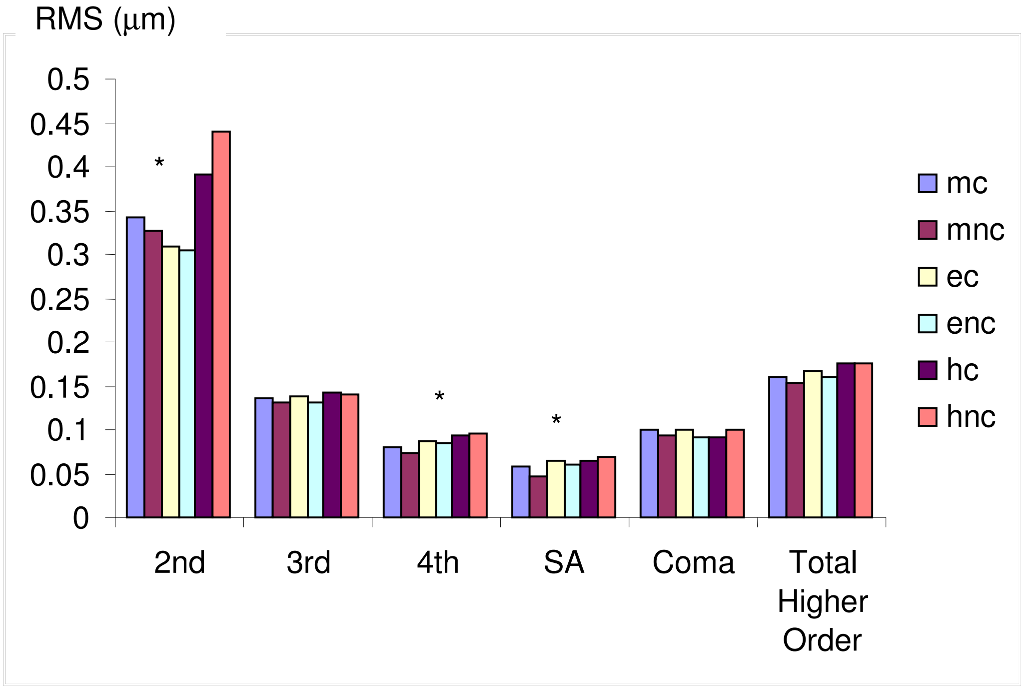
C(4,0) of the subjects in each visit



Appendix 1.17

Average wavefront RMS for second order aberrations, third order aberrations, fourth order aberrations, spherical aberration, coma and total higher order aberrations of the low astigmatism subjects at the beginning of the 1-year period

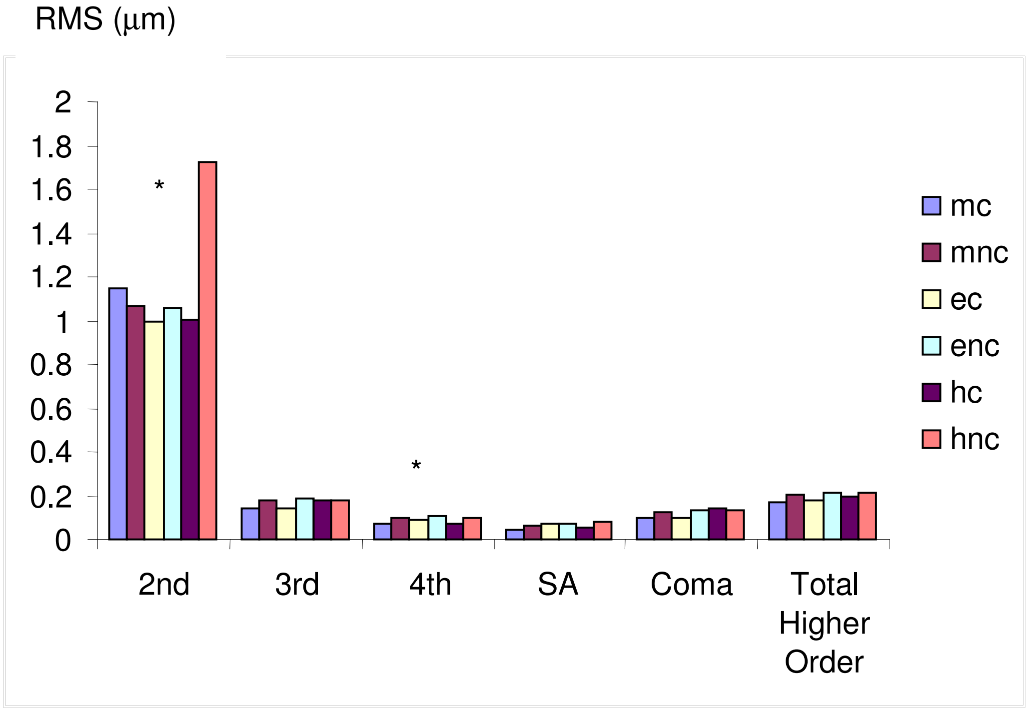
*Significant at the 0.05 level (ANOVA). (mc, myopia with refractive change; mnc, myopia without refractive change; ec, emmetropia with refractive change; enc, emmetropia without refractive change; hc, hyperopia with refractive change; hnc, hyperopia without refractive change)



Appendix 1.18

Average wavefront RMS for second order aberrations, third order aberrations, fourth order aberrations, spherical aberration, coma and total higher order aberrations of the high astigmatism subjects at the beginning of the 1-year period

*Significant at the 0.05 level (ANOVA). (mc, myopia with refractive change; mnc, myopia without refractive change; ec, emmetropia with refractive change; enc, emmetropia without refractive change; hc, hyperopia with refractive change; hnc, hyperopia without refractive change)



Appendix 2

Data for the left eyes of chapter 5

Appendix 2.1
Distribution of refractive errors, axial lengths and corneal curvatures

	SE (D) ± SD	AXL (mm) ± SD	K (D) ± SD
SE change >1.50D (n=55)	-1.298 ± 2.134	23.849 ± 1.075	43.602 ± 1.333
SE change >0.50D and ≤1.50D (n=56)	-0.420 ± 2.107	23.383 ± 1.120	43.761 ± 1.507
SE change ≤0.50D (n=51)	-0.002 ± 2.057	23.238 ± 0.969	43.470 ± 1.491
P	0.0059*	0.0087*	0.58

SE, mean refractive spherical equivalence; AXL, mean axial length; K, mean corneal curvature; p, probability values of ANOVA
*Significant at the 0.05 level

Appendix 2.2
Average Zernike coefficients for different refractive error groups

	2nd order	3rd order	4th order	SA	Coma	Total higher order
SE change >1.50D (n=55)	0.381 ±0.369	0.124 ±0.052	0.080 ±0.033	0.057 ±0.030	0.093 ±0.053	0.151 ±0.054
SE change ≤0.50D (n=51)	0.375 ±0.303	0.161 ±0.098	0.097 ±0.041	0.069 ±0.041	0.115 ±0.096	0.194 ±0.093
P	0.93	0.017*	0.029*	0.10	0.15	0.0040*

Units are microns. Errors are SD; p, probability values of unpaired t-test
*Significant at the 0.05 level

Appendix 2.3
Average Zernike coefficients for different refractive error groups, all subjects

		2nd order	3rd order	4th order	SA	Coma	Total higher order
SE change >1.50D (n=55)	1st visit	0.381 ±0.369	0.124 ±0.052	0.080 ±0.034	0.057 ±0.030	0.093 ±0.053	0.151 ±0.054
	5th visit	0.511 ±0.365	0.113 ±0.045	0.069 ±0.031	0.051 ±0.032	0.085 ±0.043	0.136 ±0.046
p		<0.0001*	0.054	0.0079*	0.086	0.29	0.0076*
SE change >0.50D and ≤1.50D (n=56)	1st visit	0.494 ±0.375	0.141 ±0.065	0.088 ±0.038	0.062 ±0.041	0.103 ±0.060	0.171 ±0.062
	5th visit	0.526 ±0.401	0.145 ±0.081	0.095 ±0.037	0.072 ±0.043	0.113 ±0.078	0.179 ±0.078
p		0.23	0.62	0.058	0.0079*	0.24	0.38
SE change ≤0.50D (n=51)	1st visit	0.375 ±0.303	0.161 ±0.098	0.097 ±0.041	0.069 ±0.041	0.115 ±0.096	0.194 ±0.093
	5th visit	0.401 ±0.282	0.155 ±0.083	0.102 ±0.047	0.084 ±0.045	0.111 ±0.086	0.192 ±0.081
p		0.37	0.46	0.32	0.0068	0.64	0.79
All subjects (n=162)	1st visit	0.418 ±0.354	0.142 ±0.075	0.088 ±0.038	0.062 ±0.038	0.104 ±0.072	0.172 ±0.073
	5th visit	0.481 ±0.357	0.137 ±0.074	0.089 ±0.041	0.069 ±0.042	0.103 ±0.072	0.168 ±0.073
p		0.0002*	0.34	0.90	0.015*	0.88	0.44

Units are microns. Errors are SD; p, probability values of paired t-test
*Significant at the 0.05 level

Appendix 2.4
Average Zernike coefficients for different refractive error groups, subjects with no astigmatism change (∆cyl=0D)

		2nd order	3rd order	4th order	SA	Coma	Total higher order
SE change >1.50D (n=12)	1st visit	0.382 ±0.460	0.122 ±0.045	0.074 ±0.025	0.051 ±0.025	0.099 ±0.039	0.146 ±0.040
	5th visit	0.412 ±0.440	0.111 ±0.048	0.069 ±0.034	0.047 ±0.034	0.081 ±0.033	0.133 ±0.052
p		0.35	0.35	0.67	0.68	0.18	0.28
SE change >0.50D and ≤1.50D (n=18)	1st visit	0.532 ±0.424	0.120 ±0.047	0.098 ±0.038	0.075 ±0.047	0.081 ±0.040	0.159 ±0.047
	5th visit	0.527 ±0.431	0.125 ±0.053	0.102 ±0.034	0.081 ±0.046	0.080 ±0.045	0.167 ±0.044
p		0.91	0.70	0.51	0.42	0.93	0.41
SE change ≤0.50D (n=10)	1st visit	0.390 ±0.141	0.185 ±0.173	0.099 ±0.038	0.081 ±0.049	0.147 ±0.167	0.224 ±0.157
	5th visit	0.400 ±0.224	0.168 ±0.105	0.106 ±0.044	0.092 ±0.047	0.135 ±0.099	0.207 ±0.095
p		0.85	0.56	0.51	0.23	0.65	0.57
All subjects (n=40)	1st visit	0.451 ±0.385	0.137 ±0.096	0.091 ±0.035	0.069 ±0.043	0.103 ±0.091	0.171 ±0.090
	5th visit	0.461 ±0.388	0.132 ±0.070	0.093 ±0.039	0.074 ±0.046	0.094 ±0.063	0.167 ±0.066
p		0.70	0.57	0.72	0.37	0.32	0.60

Units are microns. Errors are SD; p, probability values of paired t-test
*Significant at the 0.05 level

Appendix 2.5
Average astigmatism for different refractive error groups at the beginning and at the end of the study

		Astigmatism (D)	p
SE change >1.50D (n=55)	1st visit	-0.650±0.506	<0.0001*
	5th visit	-0.905±0.576	
SE change >0.50D and ≤1.50D (n=56)	1st visit	-0.759±0.495	0.24
	5th visit	-0.701±0.609	
SE change ≤0.50D (n=51)	1st visit	-0.613±0.382	0.17
	5th visit	-0.534±0.439	

Errors are SD; p, probability values of paired t-test
*Significant at the 0.05 level

Appendix 2.6
Distribution of refractive errors, axial lengths, corneal curvatures and spherical aberration

	SE (D)	AXL (mm)	K (D)	SA (microns)
Myopia (n=53)	-2.922 ±2.214	24.487 ±0.875	43.840 ±1.377	0.062 ±0.035
Emmetropia (n=77)	0.179 ±0.421	23.226 ±0.759	43.496 ±1.514	0.060 ±0.037
Hyperopia (n=32)	1.44 ±0.679	22.503 ±0.733	43.530 ±1.360	0.067 ±0.043
p	<0.0001*	<0.0001*	0.38	0.70

SE, mean refractive spherical equivalence; AXL, mean axial length; K, mean corneal curvature; SA, spherical aberration; Errors are SD; p, probability values of ANOVA
*Significant at the 0.05 level

Appendix 2.7
Distribution of change of refractive errors, axial lengths, corneal curvatures and spherical aberration at the end of the study

	ΔSE (D)	ΔAXL (mm)	ΔK (D)	ΔSA (microns)
Myopia (n=53)	-1.573 ±1.008	0.867 ±0.459	0.245 ±0.399	-0.0042 ±0.0254
Emmetropia (n=77)	-1.146 ±0.952	0.769 ±0.442	0.108 ±0.482	0.0112 ±0.0401
Hyperopia (n=32)	-0.711 ±0.696	0.513 ±0.379	0.2 ±0.240	0.0122 ±0.0205
All subjects (n=162)	-1.200 ±0.971	-0.750 ±0.451	0.171 ±0.419	0.0064 ±0.0332
p	0.0009*	0.0055*	0.31	0.046*

SE, mean refractive spherical equivalence; AXL, mean axial length; K, mean corneal curvature; SA, spherical aberration; Errors are SD; p, probability values of ANOVA
*Significant at the 0.05 level

Appendix 2.8
Spherical equivalent of the subjects in each visit

	SE(1)(D)	SE(2)(D)	SE(3)(D)	SE(4)(D)	SE(5)(D)	P
Myopia	-2.922	-3.382	-3.920	-4.302	-4.495	<0.0001*
Emmetropia	0.179	-0.018	-0.425	-0.799	-0.968	<0.0001*
Hyperopia	1.441	1.211	1.047	0.832	0.730	<0.0001*
All subjects	-0.586	-0.876	-1.278	-1.623	-1.786	<0.0001*

SE, spherical equivalent; (1), first visit; (2), second visit; (3), third visit; (4), fourth visit; (5), fifth visit; p, probability value of ANOVA
*Significant at the 0.05 level

Appendix 2.9
Axial length of the subjects in each visit

	AXL(1) (mm)	AXL(2) (mm)	AXL(3) (mm)	AXL(4) (mm)	AXL(5) (mm)	P
Myopia	24.487	24.783	25.063	25.272	25.353	<0.0001*
Emmetropia	23.226	23.395	23.666	23.898	23.995	<0.0001*
Hyperopia	22.503	22.611	22.763	22.944	23.017	<0.0001*
All subjects	23.496	23.694	23.945	24.159	24.246	<0.0001*

AXL, axial length; (1), first visit; (2), second visit; (3), third visit; (4), fourth visit; (5), fifth visit; p, probability value of ANOVA
*Significant at the 0.05 level

Appendix 2.10
C(4,0) of the subjects in each visit

	C(4,0)(1) (microns)	C(4,0)(2) (microns)	C(4,0)(3) (microns)	C(4,0)(4) (microns)	C(4,0)(5) (microns)	P
Myopia	0.0410	0.0434	0.0474	0.0481	0.0493	0.095
Emmetropia	0.0444	0.0509	0.0538	0.0590	0.0616	<0.0001*
Hyperopia	0.0551	0.0590	0.0674	0.0777	0.0740	<0.0001*
All subjects	0.0454	0.0500	0.0544	0.0591	0.0600	<0.0001*

(1), first visit; (2), second visit; (3), third visit; (4), fourth visit; (5), fifth visit; p, probability value of ANOVA
*Significant at the 0.05 level

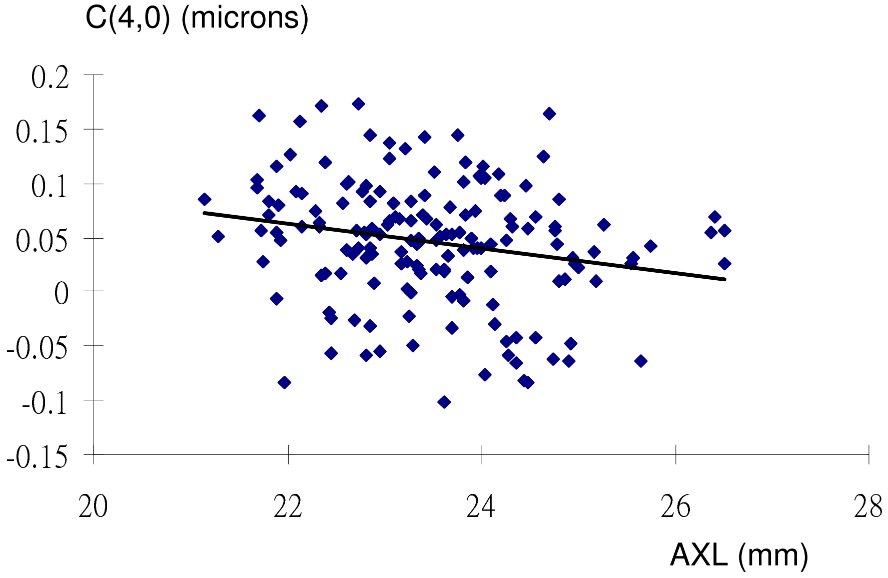
Appendix 2.11
Spherical aberration of the six refractive groups at the beginning and at the end of the study

		SA (microns) ± SD		p(2)
		1st visit	5th visit	
Myopia	SE change ≥1.00D (n=36)	0.055 ±0.029	0.046 ±0.031	0.056
	SE change <1.00D (n=17)	0.078 ±0.043	0.083 ±0.040	0.47
p(1)		0.0208*		
Emmetropia	SE change ≥1.00D (n=35)	0.065 ±0.033	0.068 ±0.043	0.63
	SE change <1.00D (n=42)	0.056 ±0.040	0.074 ±0.048	0.0085*
p(1)		0.2899		
Hyperopia	SE change ≥1.00D (n=8)	0.045 ±0.031	0.065 ±0.024	0.0006*
	SE change <1.00D (n=24)	0.074 ±0.045	0.084 ±0.042	0.049*
p(1)		0.099		

SA, spherical aberration; Errors are SD; p(1), probability values of unpaired t-test; p(2), probability values of paired t-test
*Significant at the 0.05 level

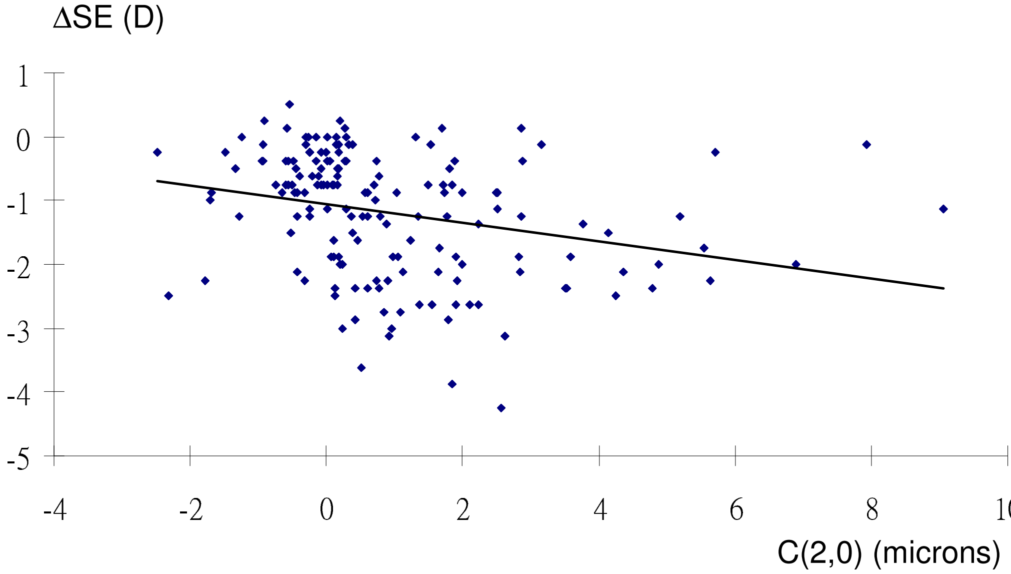
Appendix 2.12

Linear regression of C(4,0) as function of axial length (m=-0.011, p=0.005, r=-0.22) at the beginning of the 2-year period



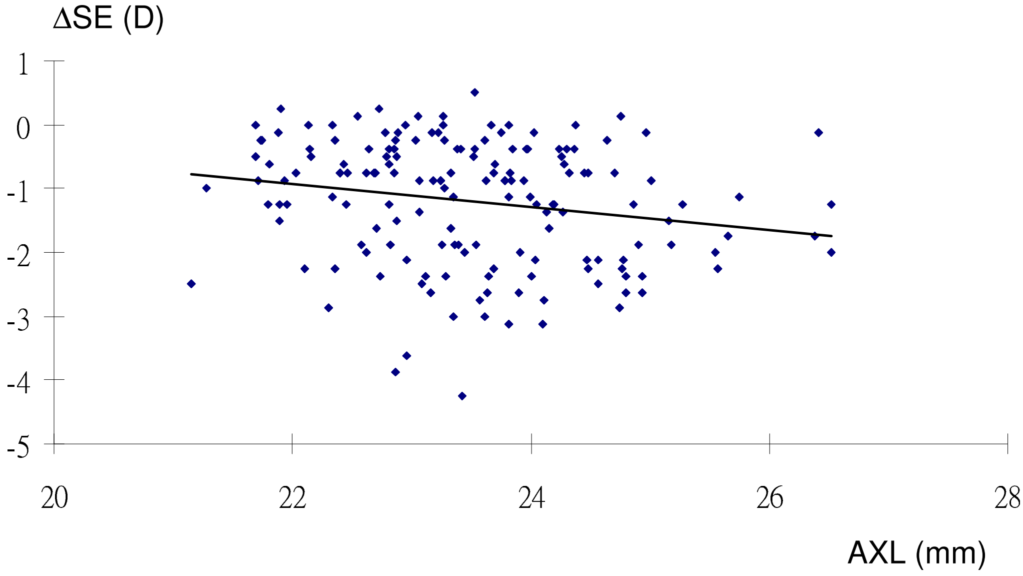
Appendix 2.13

Linear regression of spherical equivalent change as function of initial C(2,0) (m=-0.15, p<0.0001, r=-0.28)



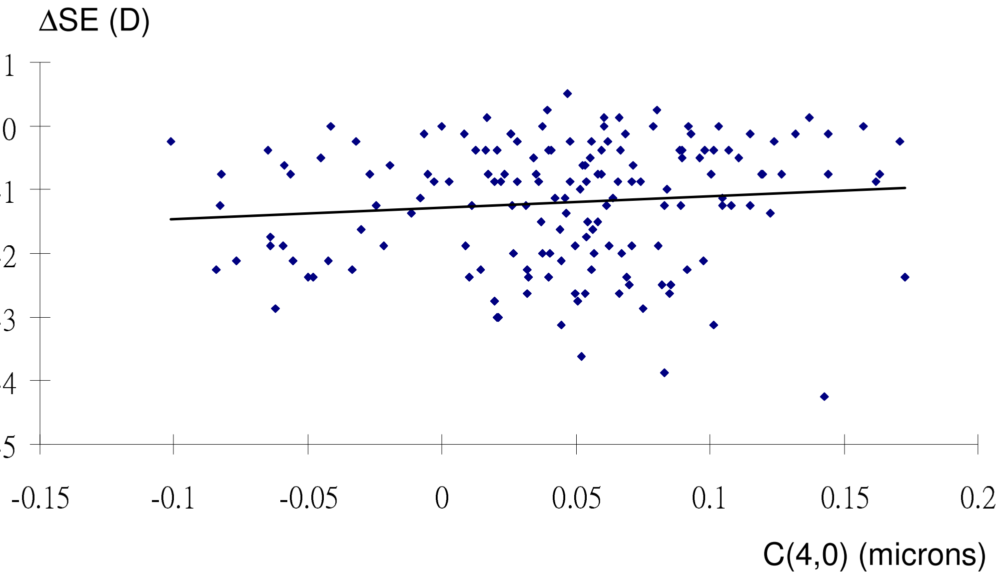
Appendix 2.14

Linear regression of spherical equivalent change as function of initial axial length (m=-0.18, p=0.011, r=-0.20)



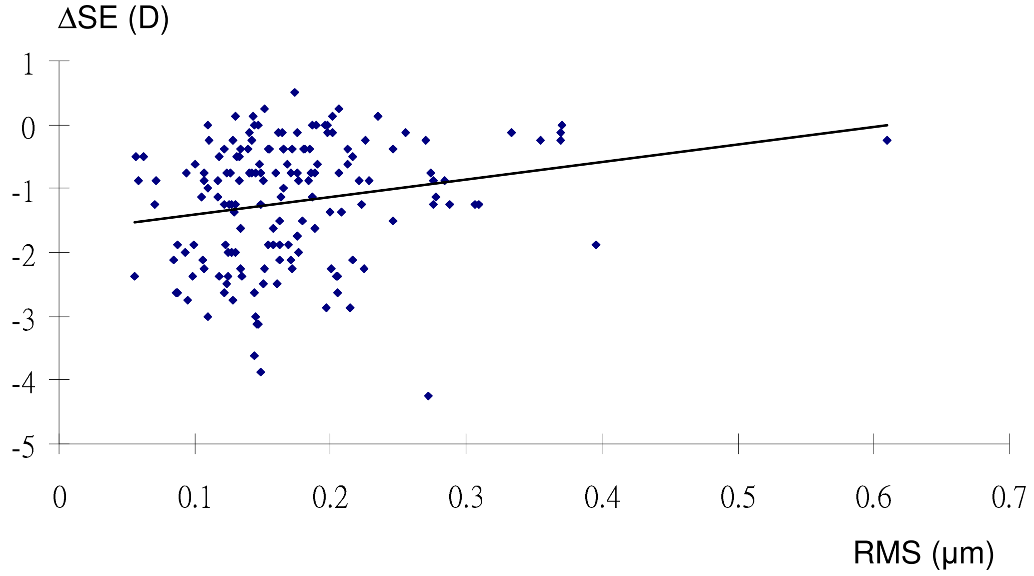
Appendix 2.15

Linear regression of spherical equivalent change as function of initial C(4,0) (m=1.82, p=0.18, r=0.11)



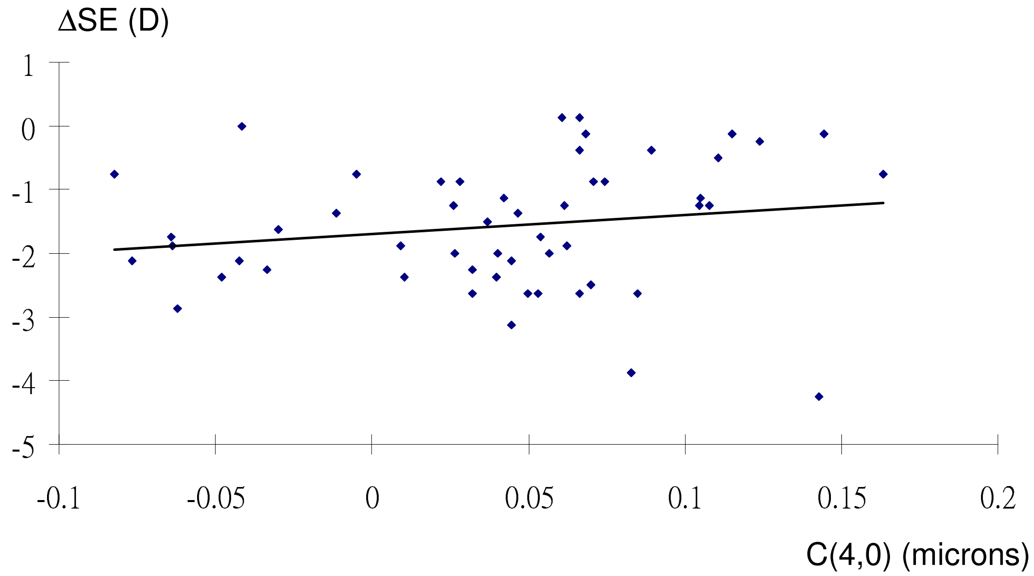
Appendix 2.16

Linear regression of spherical equivalent change as function of initial total higher order aberrations (m=2.74, p=0.009, r=0.21)



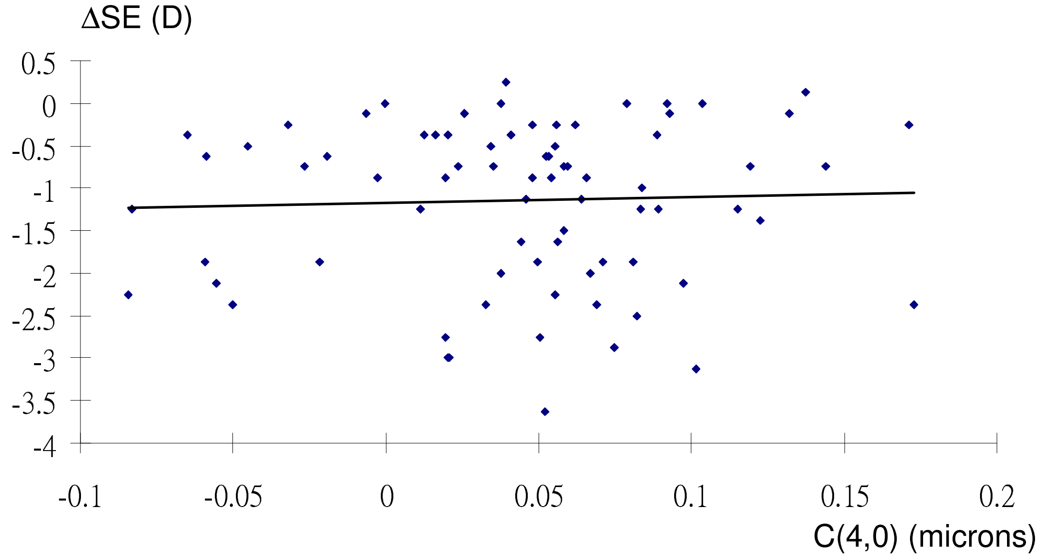
Appendix 2.17

Linear regression of spherical equivalent change as function of initial C(4,0) in myopic eyes (m=2.91, p=0.22, r=0.17)



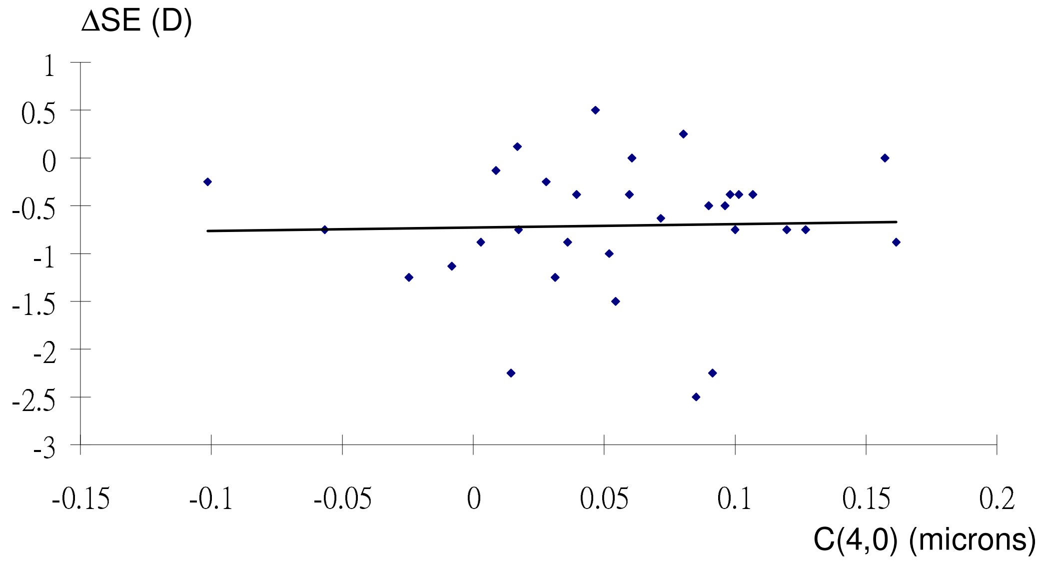
Appendix 2.18

Linear regression of spherical equivalent change as function of initial C(4,0) in emmetropic eyes (m=0.66, p=0.74, r=0.038)



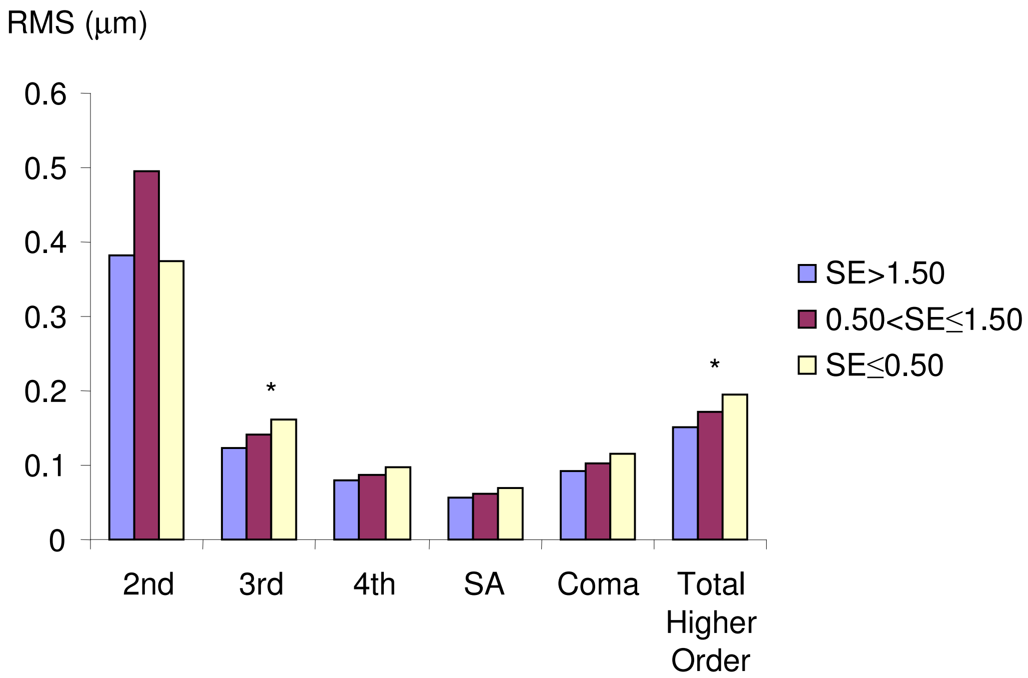
Appendix 2.19

Linear regression of spherical equivalent change as function of initial C(4,0) in hyperopic eyes (m=0.35, p=0.87, r=0.029)



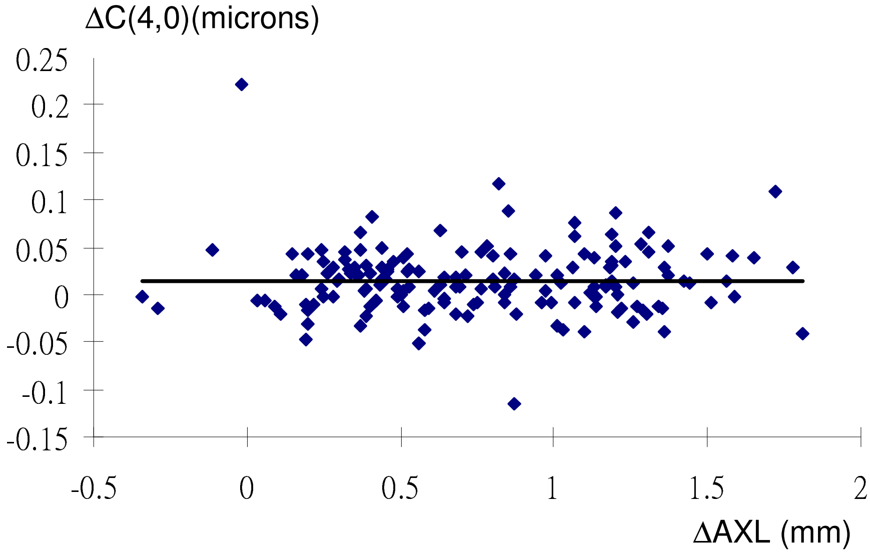
Appendix 2.20

Average wavefront RMS for second order aberrations, third order aberrations, fourth order aberrations, spherical aberration, coma and total higher order aberrations *Significant at the 0.05 level (ANOVA)



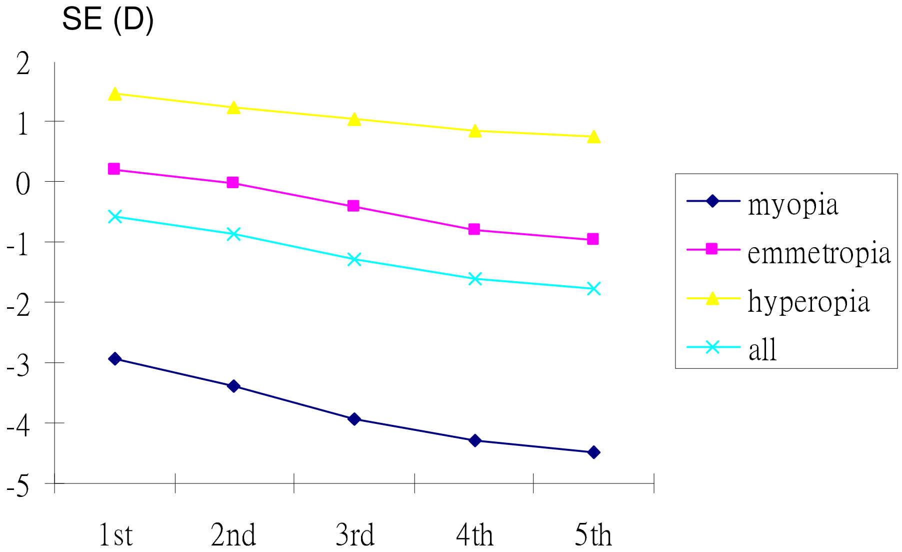
Appendix 2.21

Linear regression of C(4,0) change as function of axial length change (m=0.00, p=0.94, r=0.006)



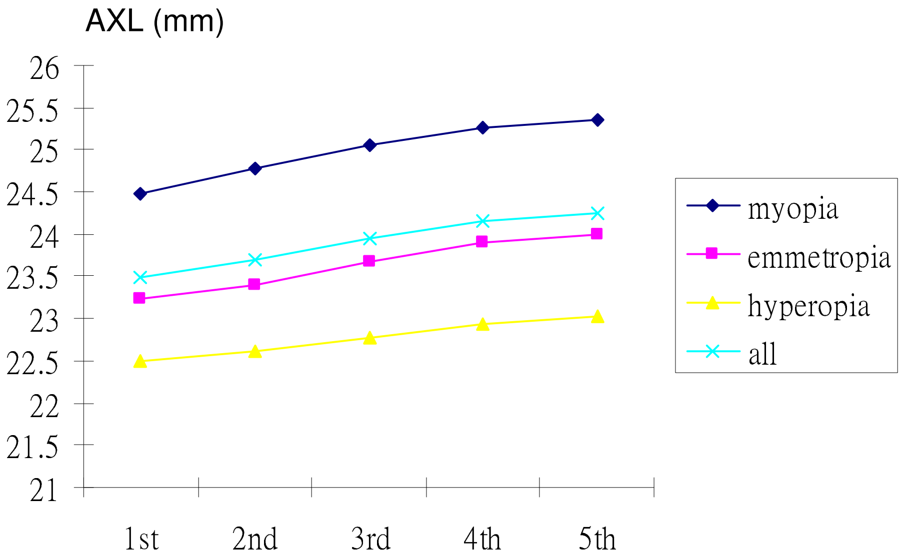
Appendix 2.22

Spherical equivalent of the subjects in each visit



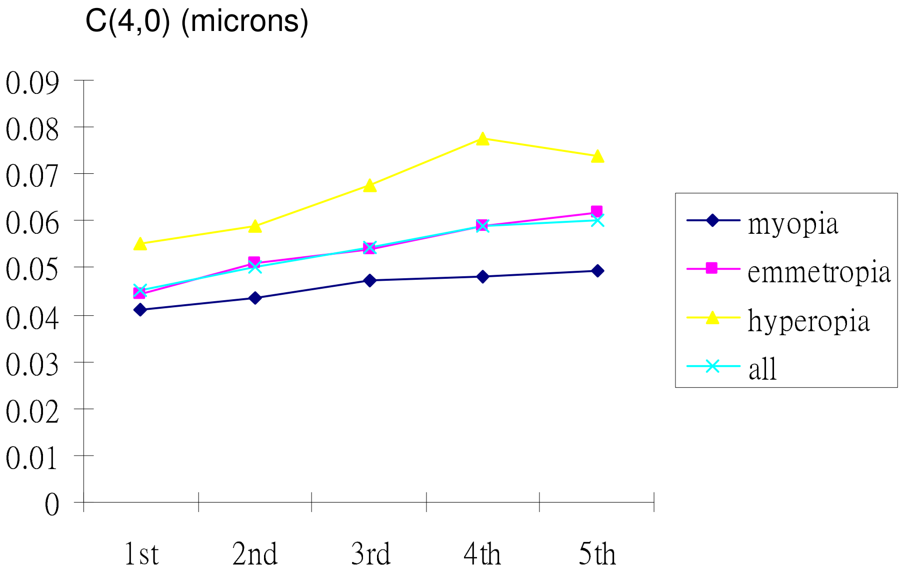
Appendix 2.23

Axial length of the subjects in each visit



Appendix 2.24

C(4,0) of the subjects in each visit



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