

## A Randomized Clinical Trial of Asymmetric Anisometropic Correction for Anisometropic Amblyopia in Children Aged 4 to 12 Years

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### ABSTRACT

**Aims:** To compare visual acuity improvement in children with residual anisometropic amblyopia after previous treatment with spectacles and part-time patching with asymmetric anisometropic correction vs. full amblyopic-eye hyperopic correction.

**Method:** 210 participants with anisometropic amblyopia (40 to 80 letters, approximately 20/50 to 20/320). Eligible participants (mean age 7.4 years, mean baseline visual acuity of 65 letters, mean baseline interocular acuity difference of  $4.15 \pm 0.96$  lines) were randomly assigned to treatment for 24-months with asymmetric hyperopic correction ( $n = 105$ ) or full amblyopic eye hyperopic correction ( $n = 105$ ). Change in amblyopic-eye visual acuity from baseline to 3, 6, 12 and 24-month, assessed by a masked examiner until visual acuity stabilized or amblyopia resolved.

**Results:** At 3 months, mean amblyopic-eye visual acuity improved from baseline by 18 letters (95% confidence interval [CI]: 16.9 to 19.8 letters) with asymmetric anisometropic correction and by 3 letters (95% CI: 2.1 to 3.1 letters) with full amblyopic-eye hyperopic correction. After adjustment for baseline visual acuity, the letter score difference between groups was 7.9 letters (95% CI: 6.8 to 9.1 letters,  $P = 0.001$ , difference of 1.85 logMAR) at 24-months. Significant difference in letter scores was observed between groups after 24-months of treatment. Overall treatment outcome was not related to age, sex, or prior treatment history, but were related to better baseline visual acuity and the degree of anisometropia.

**Conclusion:** Visual acuity was greater improvement with asymmetric anisometropic correction treatment than full amblyopic-eye hyperopic correction treatment at 24-month in children with residual anisometropic amblyopia.

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## Keywords

Residual anisometropic amblyopia, Asymmetric anisometropic correction, Full amblyopic-eye hyperopic correction, Visual acuity, Refractive error.

## Abbreviations

ATS = Amblyopia treatment study; E-ETDRS = Electronic early treatment of diabetic retinopathy; PEDIG = Pediatric Eye Disease Investigator Group; CI = confidence interval; RCT = randomized clinical trial; SD = standard deviation; D = Diopters; logMAR = logarithm of the minimum angle of resolution.

## Introduction

Amblyopia is a visual disorder that forms due to developmental abnormalities of the brain's visual center, that is characterized by reduced spatial vision in the presence of strabismus, refractive errors, or deprivation during the visual-sensitive period [1-4]. Amblyopia is the most common cause of visual loss and is associated with a wide range of both monocular and binocular visual deficits in children, affecting 2-5% of the population [2,4-9]. Anisometropia is an unequal refractive error between the eyes when differences in refract error occur [10]. Although the refractive correction of anisometropia using spectacles improves vision in anisometropic amblyopia [3,6,11-17], it is often prescribed with therapies such as occlusion, penalization and visual training. Conventional symmetric correction of anisometropic alone is often not sufficient to completely treat anisometropic amblyopia, because previous literature suggests it is sufficient in about 25% [6,15,16,18,19].

Accommodation is the process by which the eye changes focus on an object as its distance varies to maintain a clear image[20]. During childhood and the young adulthood, the lens is malleable [21,22]. Accommodation is a reflex that has historically thought to be consciously controlled. Human changes in optical power alter the form of the elastic lens using the ciliary body up to 15 diopters [23], but children with hyperopic anisometropic amblyopia display asymmetrical aniso-accommodation [23-25]. When the visual acuity difference between the two eyes reaches a certain level, the brain is difficult to fuse, and it may inhibit the visual acuity of one eye, and the stereoscopic vision will be lost. We therefore postulated that the asymmetric hyperopic correction by increasing the plus power of the spectacles in fellow eyes and reducing the plus power of the spectacles in amblyopic eyes to reduce the visual acuity difference between two eyes, let the brain to fuse, create a need for asymmetric accommodation and restore the stereoscopic vision [24,25].

In this randomized trial, we assessed whether or not there is greater improvement in visual acuity with asymmetric anisometropic correction compared with full amblyopic-eye hyperopic correction in patients with residual anisometropic amblyopia.

## Materials and Methods

This study is listed on [www.medresman.org.cn](http://www.medresman.org.cn), under identifier ChiCTR2000030142, accessed March 4, 2020. The complete

study protocol is available on [www.medresman.org.cn](http://www.medresman.org.cn). The study was supported by the Asia Pediatric Ophthalmologist Association and was conducted by the Radiant Children's Hospital Group. Protocol and HIPAA compliance informed consent forms were approved by the ethics committee of AFGH (res) No.2010-05-pj04 (Beijing, China). The parent or guardian of each patient provided written informed consent. The study was overseen by an independent data and safety monitoring committee. Patients were randomly assigned to asymmetric anisometropic correction treatment groups or to full amblyopic-eye hyperopic correction as control groups. Eligibility criteria and exclusion criteria are listed in Table 1.

## Patients

The 210 participants (F=96, 47.29%) with anisometropic amblyopia were aged 4 to 12 years (mean age  $7.37 \pm 1.72$  in treated;  $7.40 \pm 1.76$  in control) with a history of full correction of the cycloplegic refractive error treatment (100% spectacle wear at least 24 months; 100% patching 4 hours per day at least 12 months; atropine 55% in the asymmetric hyperopic correction groups and 54% in full amblyopic-eye hyperopic correction groups, and 55% visual training such as visual perception, spatial localization, hand eye coordination in both groups) in Table 2. Amblyopia was defined as the best distance visual acuity with cycloplegia (instillation of one drop of cyclopentolate 1% eye drops) and ranged from 0.4 logMAR to 1.2 logMAR and limited to cases associated with anisometropia alone. Anisometropic amblyopia was characterized by an interocular acuity difference of  $\geq 3$  lines, anisometropia of  $\geq 2.00$  diopter (D) of spherical equivalent and/or  $\geq 1.50$  D difference of the cylinder, with no myopia in the amblyopic eye Table 1. Patients were excluded if they had measurable heterotropia in the primary gaze at distance, near fixation in the prescribed spectacles, or a documented history of strabismus. Prior to enrollment into the study, participants were examined and excluded for potential ocular pathological defects and strabismus. Their visual acuity was measured on each eye with cycloplegia by a study certified examiner, using the Amblyopia Treatment Study single-surround HOTV protocol [26] for subjects aged  $< 7$  years on an electronic visual acuity test system and the Electronic Early Treatment Diabetic Retinopathy study protocol [27] for subjects aged 7 to  $< 13$  years using The Specialized Products (M&S Technologies, Niles, IL, USA). The data of visual acuity was converted to letter score for statistical analyses. Full orthoptic and ophthalmic examinations were performed including intraocular pressure measurements, fundus examinations, stereopsis, visual contrast, and cycloplegic refraction. At each visit, visual acuity was assessed without cycloplegia, by an individual masked to the treatment assignment. Accommodation in each eye was measured simultaneously using a PlusOptiX PowerRef 3 (Nuremberg, Germany) as a reference only. Participants fixated on an accommodative target at 25 cm, 33 cm, 50 cm while their eyes' refractive state and gaze positions were measured with a PlusOptiX PowerRef 3. They were instructed to look at the target consisting of a scaled optotype. Data were collected in two rounds: first round; immediately after the first round which was performed without change in position of the participant or the photo refractor and was collected within

Amblyopic eye						Fellow eye	
Refractive Errors	Accommodation measured by PlusoptiX SO4 photorefractor	Accommodation at 5 years old	Spectacle correction	Refractive Errors	Spectacle correction		
8.00	0.00	3.00	6.50	1.00	1.50-2.00		
8.00	1.00	3.00	6.00	1.00	1.50-2.00		
8.00	2.00	3.00	5.50	1.00	2.00-2.50		
8.00	3.00	3.00	5.00	1.00	2.00-2.50		
8.00	4.00	3.00	4.50	1.00	2.00-2.50		
8.00	5.00	3.00	4.00	1.00	2.00-2.50		
8.00	6.00	3.00	3.50	1.00	2.50-3.00		
8.00	7.00	3.00	3.00	1.00	2.50-3.00		

**Table 1.** Study Inclusion and Exclusion Criteria

10 mins of the first round. Light level was relatively low (10 cd/m<sup>2</sup>) in order to photorefract. Corrective lenses were prescribed based on refraction, accommodation and subjective trials of lenses according to the prescription principle: asymmetric hyperopic correction by increasing plus power of spectacles in fellow eyes and decreasing plus power of spectacles in amblyopic eyes to maintain high accommodation and to reduce anisometropia, refer to details of the example in Table 1. All participants were prescribed new glasses at the initial appointment. The control group was prescribed the full hyperopic correction. The corneal light reflex test, cover-uncover test and alternated cover test were used to assess the participants' ocular alignment. The baseline demographics and the history at enrollment are listed in Table 2. All participants maintained a calendar on which treatments were logged. Calendars were reviewed at each follow-up visits. After randomization, follow-up visits were scheduled at the 3-month ( $\pm$  1 week), 6-month, 12-month and 24-month ( $\pm$  1 month).

### Asymmetric anisometric correction Methods

In the asymmetric hyperopic correction group, all participants were instructed to wear spectacles for all waking hours. Corrective lenses for anisometric amblyopia was prescribed based on their refraction with cycloplegia at the enrollment. In this groups, if the visual acuity of the fellow eye reached 0 logMAR, no refraction correction was prescribed for that eye. When the visual acuity difference between two eyes larger than 300 D, the brain is difficult to fuse, and it may inhibit the visual acuity of one eye, so if both anisometropia and hyperopic were fully corrected, the visual acuity difference between two eyes would be increased. The prescription principle of asymmetric hyperopic correction is to increase plus power of spectacles in fellow eyes and to decrease plus power of spectacles in amblyopic eyes, in order to blur the fellow eye, decrease the degree of anisometropia and stimulate accommodation in the amblyopic eye. For example (Table 1), a child at the age of 5 years old with anisometric amblyopia, accommodation 3.50 D measured by PlusOptiX SO4. In the amblyopic eye with cycloplegia, the visual acuity 1.3 logMAR, refractive errors +8.00 D; and in fellow eye with cycloplegia, visual acuity 0 logMAR, the refractive errors +1.00 D. The corrective lens power was prescribed +5.00 D in amblyopic eye, the amblyopic eye would need to accommodate +3.00 D. It blurred the amblyopic eye and worked like semi-patching. As for the fellow eye, the corrective lens power was prescribed +1.50 D, which decreased the visual acuity difference between two eyes. At the second visit (the 3-month), if the refractive errors of the amblyopic eye were improved to +5.00 D without cycloplegia (cycloplegia can cause a transient hyperopia, frequently cycloplegia can make the lens being shorter which would damage the hyperopic eye), the corrective lens was prescribed at +4.50 D to reduce the plus further if the patient can accommodate. Participants were asked to return at 3, 6, 12, and 24-month, respectively for each follow-up therapy including the visual acuity and the accommodative ability test and prescribed new corrective lens accordingly at each follow-up visiting. The recurrence induced by poor eye coordination as well as the developed diplopia would be prevented by the asymmetric hyperopic correction.

Investigators and patients were unmasked to the asymmetric anisometric correction group, but responders and non-responders were based on the visual acuity which was assessed by an individual masked to the treatment assignment. In the full amblyopic-eye hyperopic correction group, both anisometropia and hyperopia were fully corrected or symmetrically under corrected by no more than 1.50 D.

### Randomization

Each patient was randomly assigned with an equal probability to either asymmetric hyperopic correction as the treatment group or to full amblyopic-eye hyperopic correction as the control group. Randomization was accomplished following data entry by clinical staff using a permuted design of varying block sizes, with a separate sequence of computer-generated random numbers for each clinical site. Both children and parents were masked.

### Statistical Analyses

The sample size of 210 participants was computed to have 90% power with a 2-sided type I error rate of 5%, a 5% loss to follow-up rate, to detect a treatment group difference based on projecting a standard deviation of 7.5 letters for the 3 month amblyopic-eye visual acuity and a mean difference between groups of 7.2 letters for a subgroup analysis of patients with amblyopic-eye acuity of 20/50 to 20/320. With these assumptions, a minimum sample size of 105 patients in each group was planned.

The primary outcome was the change in amblyopic-eye visual acuity score from baseline to 3 months ( $\pm$  1 week). A modified intent-to-treat analysis of covariance was performed to estimate the treatment group difference in mean change in visual acuity at 3 months and a 2-sided 95% confidence interval (CI), adjusted for baseline visual acuity. For each patient, the difference in mean visual acuity, interocular acuity difference, refractive errors and degree of anisometropia with 95% confidence intervals were computed at the 3, 6, 12 and 24-month. The resolution of amblyopia was defined when the visual acuity in the amblyopic eye was no more than one line worse than that of the fellow eye. The proportion of patients whose amblyopia resolved was computed and 95% confidence intervals were calculated. The association of age, sex, prior treatment history (spectacles, patching, atropine and visual training), visual acuity, degree of anisometropia and type anisometropia (sphere only, cylinder only, or both) with improvements in the resolution of amblyopia and treatment days were assessed using the analysis of linear regression, paired test and one sample test. All p-values were two-tailed. SPSS version 22 was used for data analyses.

## Results and Discussion

### Baseline Characteristics

Between October 2015 and May 2020, 210 patients with a history of anisometric amblyopia, the distance amblyopia eye visual acuity with cycloplegia ranging from 20/50 to 20/320 (mean = 0.7 logMAR, approximately 20/100) and an interocular acuity difference of  $\geq$ 3 lines (mean = 4.24 lines) were assigned randomly to the asymmetric anisometric correction group (n = 105) or to full amblyopic-eye hyperopic correction alone (n = 105). The



baseline demographics, clinical history and characteristics of the study cohort are provided in Tables 2 and 3.

	Treatment Group (n = 105)		Control Group (n = 105)	
	N	%	N	%
<b>Gender, n (%)</b>				
Female	46	43.8	49	46.7
<b>Age</b>				
4 to <5 years	3	2.9	4	3.8
5 to <6 years	14	13.3	11	10.5
6 to <7 years	17	16.2	20	19.0
7 to <8 years	22	21.0	22	21.0
8 to <9 years	22	21.0	18	17.1
9 to <10 years	17	16.2	20	19.0
10 to <11 years	6	5.7	5	4.8
11 to <12 years	3	2.9	4	3.8
12 to <13 years	1	1.0	1	1.0
Mean (SD) year*	7.35(1.71)		7.38(1.75)	
<b>Prior Treatment for Amblyopia</b>				
<b>Spectacles</b>	<b>105</b>	<b>100.0</b>	<b>105</b>	<b>100.00</b>
2 years	28	26.7	23	21.9
3 years	39	37.1	42	40.0
4 years	22	21.0	25	23.8
5 years	15	14.3	13	12.4
6 years	1	1.0	2	1.9
Mean (SD) year	3.26(1.04)		3.32(1.01)	
<b>Patching</b>	<b>105</b>	<b>100.0</b>	<b>105</b>	<b>100.00</b>
1 year	2	1.9	12	11.4
2 years	55	52.4	35	33.3
3 years	30	28.6	42	40.0
4 years	9	8.6	11	10.5
5 years	9	8.6	5	4.8
Mean (SD) year	2.70(0.97)		2.64(0.98)	
<b>Atropine</b>	<b>59</b>	<b>56.2</b>	<b>58</b>	<b>55.2</b>
none	46	43.8	47	44.8
1 year	54	51.4	54	51.4
2 years	5	4.8	4	3.8
Mean (SD) year	0.61(0.58)		0.59(0.57)	
<b>Visual Training</b>	<b>60</b>	<b>57.1</b>	<b>60</b>	<b>57.1</b>
0 year	45	42.9	45	42.9
1 year	52	49.5	52	49.5
2 years	7	6.7	7	6.7
3 years	1	1.0	1	1.0
Mean (SD) year	0.66(0.65)		0.66(0.65)	

**Table 2:** Baseline Demographics and History at Enrolment (N=210).

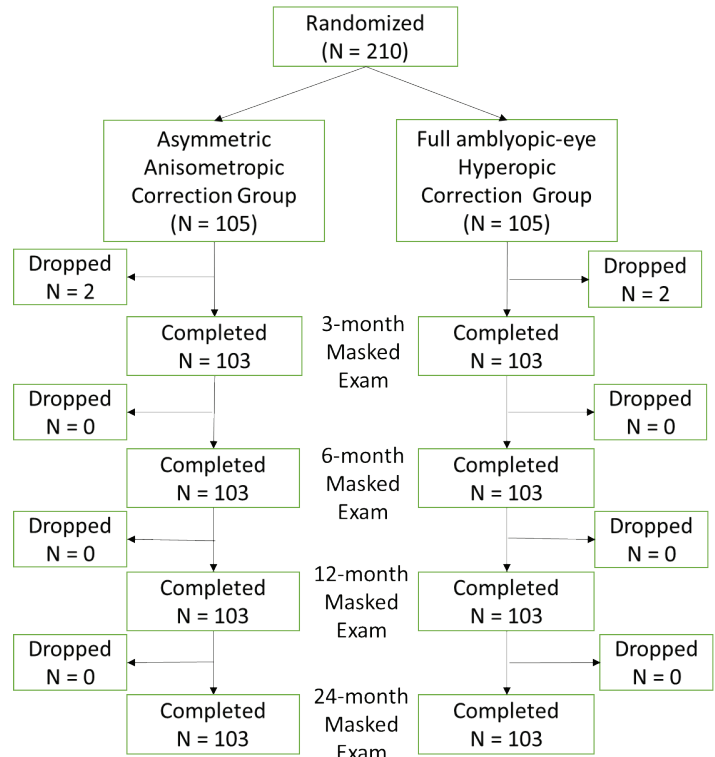
### Treatment and follow-up

The 3-month primary outcome visit, the subsequent 6, 12, and 24-month follow-up visits were completed by 103 (98%) participants in the asymmetric hyperopic correction group and the full amblyopic-eye hyperopic correction group, respectively (Figure 1). The visual acuity measurement was performed by masked testers at 98% of visits for both groups. No participant in both groups was prescribed treatment other than the randomly assigned treatment during the study.

### Visual Acuity in the Amblyopic Eye

At the 3-month primary outcome visit, after adjusting for baseline, mean difference of visual acuity improved from baseline by 18

letters (95% CI: 16.9 to 19.8 letters) with asymmetric hyperopic correction, and by 3 letters (95% CI: 2.1 to 3.1 letters) with full amblyopic-eye hyperopic correction. Follow-up at the 6, 12 and 24 months, mean difference of visual acuity improved from baseline by 22 letters (95% CI: 21.0 to 23.8 letters), 23 letters (2-sided 95% CI: 22.1 to 24.9 letters), 25 letters (95% CI: 23.3 to 26.2 letters) with asymmetric hyperopic correction, and 6 letters (95% CI: 5.3 to 6.7 letters), 7 letters (95% CI: 6.9 to 7.9 letters), 8 letters (95% CI: 7.7 to 8.9 letters) with full amblyopic-eye hyperopic correction, respectively (Figure 2).



**Figure 1:** Flowchart showing visit completion by treatment. The 3-month primary outcome visit, the subsequent 6-month, 12-month and 24-month visits were completed by 103 (98%) participants in asymmetric anisometropic correction group and full amblyopic-eye hyperopic correction group, respectively.

### Interocular acuity difference

With asymmetric hyperopic correction, mean difference of interocular acuity difference reduced from baseline by 1.8 lines (95% CI: 1.6 to 2.1 lines) at the 3-month, and by 2.7 lines (95% CI: 2.4 to 2.9 lines) at the 24-month. In the full amblyopic-eye hyperopic correction treatment group, mean difference of interocular acuity difference reduced from baseline by 0.2 line (95% CI: 0.1 to 0.3 line) at the 3-month, by 1.0 line (95% CI: 0.8 to 1.1 line) at the 24-month (Table 4).

### Anisometropia and refractive errors

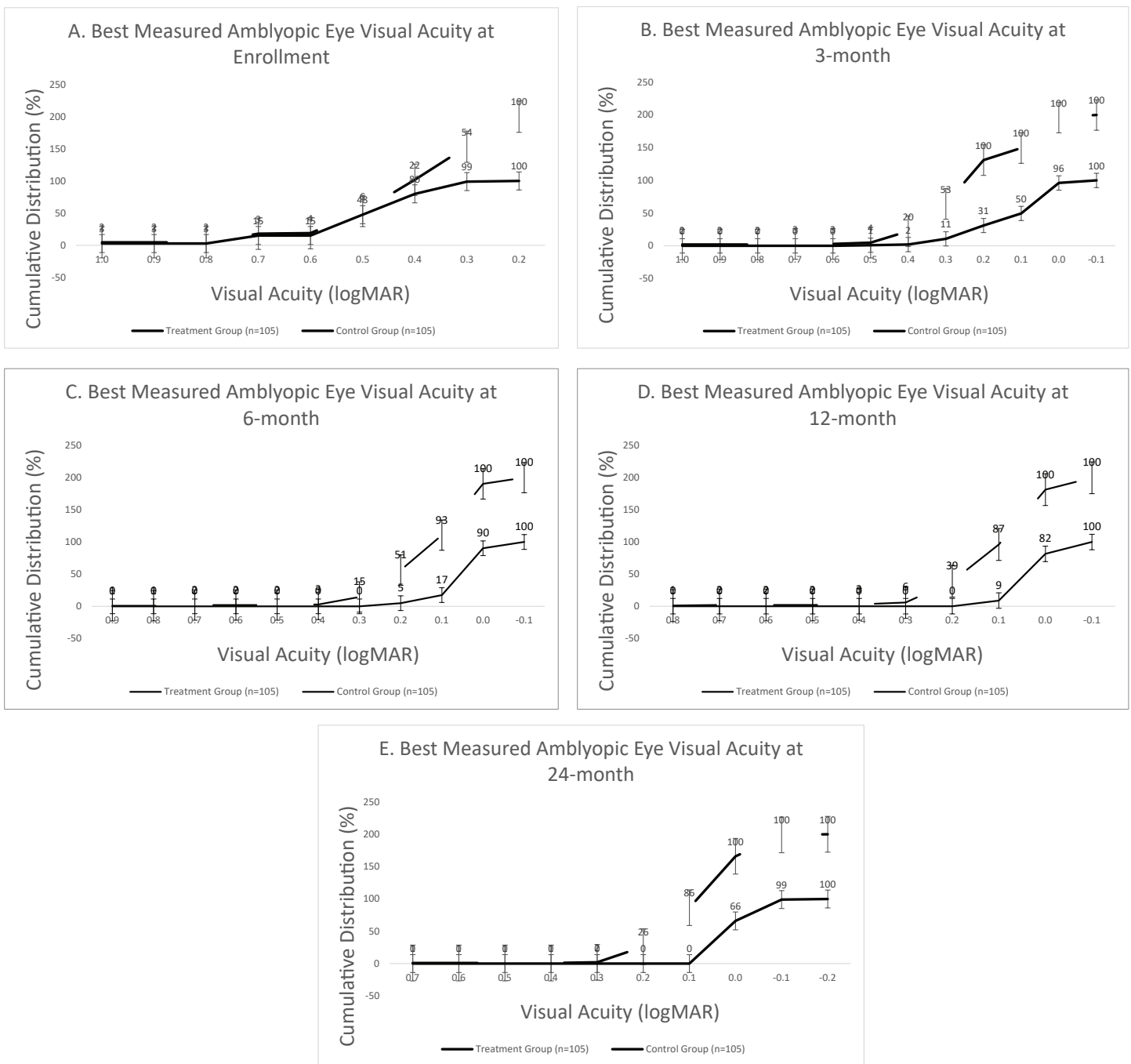
With the asymmetric hyperopic correction, the degree of anisometropia without cycloplegic refraction drastically decreased (Table 4). Mean difference of the degree of anisometropia reduced from baseline by 3.04 D (95% CI: 2.86 to 3.21 D) at the 3-month and by 3.96 D (95% CI: 3.73 to 4.18 D) at the 24-month; mean

	Treatment Group (n = 105)		Control Group (n = 105)	
	N	%	N	%
<b>Distance amblyopia-eye visual acuity (letters)</b>				
40	1	1.0	1	1.0
45	2	1.9	2	1.9
50	29	27.6	22	21.0
65	28	26.7	41	39.0
75	31	29.5	27	25.7
80	11	10.5	10	9.5
85	3	2.9	1	1.0
90	0	0.0	1	1.0
Mean (SD) visual acuity logMAR	0.69(0.24)		0.69(0.22)	
<b>Distance fellow-eye visual acuity (letters)</b>				
90	1	1.0	0	0.0
95	11	10.5	7	6.7
100	33	31.4	35	33.3
105	44	41.9	41	39.0
110	16	15.2	22	21.0
Mean (SD) visual acuity logMAR	-0.06(0.09)		-0.07(0.09)	
<b>Best-corrected distance amblyopia-eye visual acuity (letters)</b>				
50.00	3	2.9	2	1.9
65.00	13	12.4	1	1.0
70.00	0	0.0	1	1.0
75.00	34	32.4	2	1.9
80.00	34	32.4	17	16.2
85.00	20	19.0	34	32.4
90.00	1	1.0	48	45.7
Mean (SD) visual acuity logMAR	0.47(0.15)		0.29(0.14)	
<b>Best-corrected distance fellow-eye visual acuity (letters)</b>				
85	1	1.0	0	0.0
90	6	5.7	0	0.0
95	36	34.3	4	3.8
100	56	53.3	17	16.2
105	6	5.7	59	56.2
110	0	0.0	25	23.8
Mean (SD) visual acuity logMAR	0.04(0.07)		-0.10(0.08)	
<b>Interocular Acuity Difference Lines</b>				
-3	0	0.0	1	1.0
-4	6	5.7	6	5.7
-5	18	17.1	16	15.2
-6	17	16.2	16	15.2
-7	17	16.2	15	14.3
-8	12	11.4	14	13.3
-9	9	8.6	12	11.4
-10	11	10.5	8	7.6
-11	11	10.5	13	12.4
-12	4	3.8	4	3.8
Mean (SD) lines	7.53(2.27)		7.61(2.31)	
<b>Best-corrected Interocular Acuity Difference Lines</b>				
-1	1	1.0	0	0.0
-2	20	19.1	0	0.0
-3	41	39.1	40	38.1
-4	28	26.7	42	40.0
-5	8	7.6	17	16.2
-6	6	5.7	3	2.9
-7	0	0.0	1	1.0
-8	1	1.0	2	1.9
Mean (SD) lines	3.42(1.18)		3.96(1.11)	

**Table 3:** Baseline Clinical Characteristics at Enrolment (N=210).

Refractive Error in Treatment Group	At Enrolment		3-month		6-month		12-month		24-month	
	n	%	n	%	n	%	n	%	n	%
0.00 to < +1.00D	0	0.0	0	0.0	0	0.0	2	1.9	3	2.9
+1.00 to < +2.00D	0	0.0	13	12.4	34	32.4	50	47.6	58	55.2
+2.00 to < +3.00D	6	5.7	47	44.8	39	37.1	33	31.4	33	31.4
+3.00 to < +4.00D	19	18.1	24	22.9	19	18.1	13	12.4	7	6.7
+4.00 to < +5.00D	21	20.0	13	12.4	9	8.6	4	3.8	1	1.0
+5.00 to < +6.00D	22	21.0	6	5.7	2	1.9	1	1.0	1	1.0
+6.00 to < +7.00D	22	21.0	0	0.0	0	0.0	0	0.0	0	0.0
+7.00 to < +8.00D	9	8.6	0	0.0	0	0.0	0	0.0	0	0.0
+8.00 to < +9.00D	6	5.7	0	0.0	0	0.0	0	0.0	0	0.0
Mean (SD) spherical equivalent diopter in treatment group	5.20(1.54)		2.79(1.07)		2.32(0.97)		1.96(0.89)		1.68(0.79)	
Mean (SD) spherical equivalent diopter in control group	5.14(1.34)		4.37(1.34)		4.20(1.28)		4.17(1.28)		4.13(1.28)	
<b>Anisometropia (Calculated Difference in spherical equivalent in treatment group)</b>										
0.00 to < +0.50D	0	0.0	20	19.0	39	37.1	59	56.2	79	75.2
0.50 to < +1.00D	0	0.0	23	21.9	27	25.7	24	22.9	17	16.2
+1.00 to < +2.00D	0	0.0	39	37.1	30	28.6	18	17.1	6	5.7
+2.00 to < +3.00D	28	26.7	17	16.2	7	6.7	2	1.9	1	1.0
+3.00 to < +4.00D	29	27.6	4	3.8	0	0.0	0	0.0	0	0.0
+4.00 to < +5.00D	17	16.2	0	0.0	0	0.0	0	0.0	0	0.0
+5.00 to < +6.00D	21	20.0	0	0.0	0	0.0	0	0.0	0	0.0
+6.00 to < +7.00D	8	7.6	0	0.0	0	0.0	0	0.0	0	0.0
+7.00 to < +8.00D	2	1.9	0	0.0	0	0.0	0	0.0	0	0.0
Mean (SD) in Treatment Group	3.98(1.38)		1.10(0.82)		0.68(0.64)		0.40(0.50)		0.18(0.34)	
Mean (SD) in Control Group	3.97(1.14)		3.92(1.19)		3.84(1.18)		3.83(1.17)		3.80(1.17)	
<b>Best-corrected Interocular Acuity Difference Lines in Treatment Group</b>										
0	0	0.0	0	0.0	0	0.0	0	0.0	1	1.0
-1	1	1.0	15	14.3	30	28.6	31	29.5	40	38.1
-2	20	19.1	48	45.7	58	55.2	65	61.9	62	59.0
-3	41	39.1	25	23.8	13	12.4	7	6.7	0	0.0
-4	28	26.7	13	12.4	2	1.9	0	0.0	0	0.0
-5	8	7.6	1	1.0	0	0.0	0	0.0	0	0.0
-6	6	5.7	1	1.0	0	0.0	0	0.0	0	0.0
-7	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
-8	1	1.0	0	0.0	0	0.0	0	0.0	0	0.0
Mean (SD) in Treatment Group	3.42(1.18)		2.42(0.99)		1.87(0.70)		1.77(0.56)		1.59(0.51)	
Mean (SD) in Control Group	3.96(1.11)		3.92(1.10)		3.52(1.14)		3.33(1.05)		3.19(0.95)	
<b>Improvement Lines from Baseline to Best Measured Acuity</b>										
2	0	0.0	26	24.8	3	2.9	1	1.0	0	0.0
3	0	0.0	26	24.8	22	21.0	15	14.3	13	12.4
4	0	0.0	23	21.9	35	33.3	38	36.2	28	26.7
5	0	0.0	18	17.1	27	25.7	29	27.6	37	35.2
6	0	0.0	3	2.9	4	3.8	6	5.7	10	9.5
7	0	0.0	6	5.7	8	7.6	10	9.5	10	9.5
8	0	0.0	1	1.0	3	2.9	1	1.0	2	1.9
9	0	0.0	0	0.0	0	0.0	2	1.9	0	0.0
10	0	0.0	0	0.0	1	1.0	1	1.0	3	2.9
Mean (SD) in Treatment Group	0.00(0.00)		3.69(1.47)		4.84(1.34)		4.72(1.44)		4.97(1.48)	
Mean (SD) in Control Group	0.00(0.00)		0.52(0.54)		1.19(0.70)		1.48(0.54)		1.66(0.62)	

**Table 4:** Distribution of Amblyopic Eye Refractive Error and Anisometropia Outcomes at Randomization and Follow-up Visits (n = 210).



**Figure 2:** Cumulative distribution of best measured amblyopic eye visual acuity. A. at enrolment; B. at 3-month; C. at 6-month; D. at 12-month; and E. at 24-month.

difference of spherical equivalent diopter in amblyopic eye decreased from baseline by 2.39 D (95% CI: 2.22 to 2.56 D) at the 3-month and by 3.50 D (95% CI: 3.28 to 3.72 D) at the 24-month (Table 4).

In the full amblyopic-eye hyperopic correction group, mean difference of the degree of anisometropia reduce from baseline by 0.16 D (95% CI: 0.10 to 0.21 D) at the 3-month and by 0.28 D (95% CI: 0.20 to 0.35 D) at the 24-month; mean difference of spherical equivalent diopter in amblyopic eye decreased from baseline by 0.17 D (95% CI: 0.12 to 0.22 D) at the 3-month and by

0.78 D (95% CI: 0.72 to 0.83 D) at the 24-month. The distribution of amblyopic eye refractive error outcomes at randomization and follow-up visits was show in Table 4.

Treatment outcome was not related to age, sex, or prior treatment history, but were related to better baseline visual acuity and the degree of anisometropia.

### Discussion

This randomized trial was carried out by Radiant Children’s Hospital Group and designed according to “Designing Clinical



Trials for Amblyopia” by Holmes JM [28]. The manuscript was prepared according to the Pediatric Eye Disease Investigator Group (PEDIG).

In this randomized trial of 210 children with residual anisometropic amblyopia aged from 4 to 12 years old, we found that mean difference of visual acuity between the asymmetric hyperopic correction group and the full amblyopic-eye hyperopic correction group was 7.2 letters (95% CI: 5.7 to 8.7 letters,  $t=9.7$ ;  $p=0.001$ ) at the 3 months, and 7.9 letters (95% CI: 6.8 to 9.0 letters;  $t=14.6$ ;  $p=0.001$ ). The improvements in visual acuity were initiated at the 3 months which was later than the report by PEDIG (PEDIG[6] reported that the visual acuity improvement was initiated at the 5 weeks), because patients in this trial had been treated for much longer prior to enrollment. The visual acuity in amblyopic eyes was  $\leq 1$  lines worse than that of the fellow eye in 15 (14.6%), 30 (29.1%), 32 (31.1%) and 41 (39.8%) at the 3, 6, 12 and 24-month, respectively with asymmetric anisometropic correction treatment. The interocular acuity differences in 63 (61.2%) patients were smaller than 3 lines at 3-month. Acuity gains were observed over an average of 3-month. Steward et al. reported previously untreated visual acuity improvements of 15.6 weeks [19]. With the asymmetric hyperopic correction treatment, the visual acuity gains were over an average of 3-month in patients who had been treated for much longer prior to enrollment, and visual acuity stabilization occurred after 12-month and was sustained up until 24-month. Compare to literatures, acuity gains with refractive correction in children with anisometropic amblyopia have been reported in retrospective, prospective studies [6,11,12,29,30] and randomized trials [31,32], the long-term improvements of visual acuity have not reported.

In this trial, relatively long-term clinically, statistically significant improvements in the refractive errors of the amblyopic eyes with asymmetric anisometropic correction treatment were observed from baseline by 2.39 D (95% CI: 2.22 to 2.56 D) at the 3-month, by 3.50 D (95% CI: 3.28 to 3.72 D) at the 24-month, respectively. The refractive errors decreased over the 24-month period due to the treatment of both amblyopic eyes and fellow eye. To assess the long-term benefits of the treatment, follow up trials will be needed. The resolution of amblyopia was related to improved baseline acuities of amblyopic eyes and fellow eyes and the degree of anisometropia, but not related to age, sex, a prior history of spectacles, patching, atropine, or visual training. The improved acuity in both amblyopic eyes and fellow eyes in addition to the degree of anisometropia were related to an increased likelihood of a resolution of amblyopia. More than 92.2% of residual patients with anisometropia  $\leq 0.50$  D of the spherical equivalent met the resolution criteria after 24-month treatment with asymmetric anisometropic correction.

Anti-accommodation in anisometropic amblyopia is associated with a poorer treatment outcome [21,22,33-38]. Asymmetric anisometropic correction treatment decreases plus power of the spectacles in amblyopic eyes, it increases increasing plus power of the spectacles in the fellow eyes to maintain the ability to adjust

the lens in patients. For a more rapid reduction in the degree of anisometropia and maximal relaxation of the lens, the increased plus power of spectacles can be prescribed for fellow eyes to reduce the degree of Low- and higher-order aberration [2]. At the initiation of asymmetric anisometropic correction treatment, the decreased plus power of the spectacles was relatively higher which may have inhibited the effects of visual acuity in the fellow eye. Blurred fellow eyes by decreased plus power of the spectacles work like patching effects. With the treatment of both amblyopic eyes and fellow eye, the visual acuity of both eyes improved gradually to reduce the degree of anisometropia to  $\leq 0.5$  D of the spherical equivalent. In this trial, the degree of anisometropia was  $< 0.50$  D of the spherical equivalent at the 24-month in 76.7% of patients by treated both amblyopic eye and fellow eye simultaneously. At the end of this study, there was no data on the cycloplegic refraction, because cycloplegia cause a transient hyperopia in amblyopic eye, frequently cycloplegia make the lens being shorter which damage the hyperopic eye.

These results confirmed that gains in the visual acuity and reductions in the degree of anisometropia were attributable to asymmetric anisometropic correction as an effective treatment for residual anisometropic amblyopia. The asymmetric hyperopic correction led to dramatic improvements in visual acuity. The resolution of anisometropia is mediated by increasing plus power of the spectacles in fellow eye and decreasing plus power of the spectacles in amblyopic eyes to maintain ocular accommodation and decrease anisometropia [2]. Asymmetric anisometropic correction treatment reduces the degree of anisometropia more rapidly and maximally relaxes the lens and reduces anti-accommodation in anisometropic amblyopia.

Several studies have reported that higher-order aberration influences amblyopia treatment [39-44]. Ocular and internal spherical aberrations were higher in children who failed amblyopia treatment. The low-order aberration is a major factor determining vision quality and higher-order aberration should be considered in amblyopic patients [24,25]. It is possible that asymmetric anisometropic correction treatment reduces the degree of anisometropia more rapidly and maximally relaxes the lens. It is possible that spectacles with an increased plus power were prescribed for the fellow eye to reduce the degree of both low-order and high-order aberrations.

## Conclusions

In translating our results to clinical practice, the following suggestions should be noted: 1: For the resolution of anisometropia, a decreased plus power of spectacles should be prescribed in amblyopic eyes and an increased plus power of spectacles should be prescribed in fellow eyes; 2: Both amblyopic eyes and fellow eyes must be treated simultaneously.

In conclusion, our results demonstrate that asymmetric anisometropic correction is an effective amblyopia therapy to accelerate improvement in children with residual anisometric amblyopia.

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## References

1. [https://nei.nih.gov/health/amblyopia/amblyopia\\_guide](https://nei.nih.gov/health/amblyopia/amblyopia_guide).
2. Li ZS. Children Ocular Refraction and Amblyopia. Hong Kong: Hong Kong New Youth Press. 2013.
3. Jefferis JM, Connor AJ and Clarke MP. Amblyopia. *BMJ*. 2015; 351: h5811.
4. Zhisheng Li, Geng Li, Xueqiang Li, et al. Treatment of Anisometropic Amblyopia in Children with Automatic Frequency Conversion Laser. *J Clin Exp Ophthalmol*. 2020; 10: 1-8.
5. Williams C, Northstone K, Howard M, et al. Prevalence and risk factors for common vision problems in children: data from the ALSPAC study. *Br J Ophthalmol*. 2008; 92: 959-964.
6. Beck RW. The Pediatric Eye Disease Investigator Group. *J AAPOS*. 1998; 2: 255-256.
7. Rahi J, Stuart Logan, Christine Timms, et al. Risk, causes, and outcomes of visual impairment after loss of vision in the non-amblyopic eye: a population-based study. *Lancet*. 2002; 360: 597-602.
8. Jakobsson P, Gun Kvarnström, Mariann Abrahamsson, et al. The frequency of amblyopia among visually impaired persons. *Acta Ophthalmol Scand*. 2002; 80: 44-46.
9. Duan XR, Yuan Bo Liang, David S Friedman, et al. Prevalence and associations of epiretinal membranes in a rural Chinese adult population: the Handan Eye Study. *Invest Ophthalmol Vis Sci*. 2009; 50: 2018-2023.
10. Kutschke PJ, Scott WE, and Keech RV. Anisometropic amblyopia. *Ophthalmology*. 1991; 98: 258-263.
11. Moseley MJ, Meir Neufeld, Bernadette McCarry, et al. Remediation of refractive amblyopia by optical correction alone. *Ophthalmic Physiol Opt*. 2002; 22: 296-299.
12. Nordlow W. Anisometropia, amblyopia, induced aniseikonia and estimated correction with iseikonic lenses in 4 year-olds. *Acta Ophthalmol (Copenh)*. 1970; 48: 959-970.
13. Steele AL, Yasmin S Bradfield, Burton J Kushner, et al. Successful treatment of anisometropic amblyopia with spectacles alone. *J AAPOS*. 2006; 10: 37-43.
14. Chen PL, Jiann-Torng Chen, Ming-Cheng Tai, et al. Anisometropic amblyopia treated with spectacle correction alone: possible factors predicting success and time to start patching. *Am J Ophthalmol*. 2007; 143: 54-60.
15. Cotter SA, Allison R Edwards, David K Wallace, et al. Treatment of anisometropic amblyopia in children with refractive correction. *Ophthalmology*. 2006; 113: 895-903.
16. Writing Committee for the Pediatric Eye Disease Investigator G, Susan A Cotter, Nicole C Foster, et al. Optical treatment of strabismic and combined strabismic-anisometropic amblyopia. *Ophthalmology*. 2012; 119: 150-158.
17. Norris JH, Pilling RF, and Hook J. An audit of the Royal College of Ophthalmologists strabismic amblyopia treatment protocol: a departmental review. *Strabismus*. 2009; 17: 78-81.
18. Stewart CE, Alistair R Fielder, David A Stephens, et al. Treatment of unilateral amblyopia: factors influencing visual outcome. *Invest Ophthalmol Vis Sci*. 2005; 46: 3152-3160.
19. Stewart CE, Moseley MJ, Fielder MJ, et al., Refractive adaptation in amblyopia: quantification of effect and implications for practice. *Br J Ophthalmol*. 2004; 88: 1552-1556.
20. <https://www.aao.org/bcscsnippetdetail.aspx?id=0554ca9e-b088-4bfe-91ab-2fc77bb0ea67>.
21. Campbell FW. Correlation of accommodation between the two eyes. *J Opt Soc Am*. 1960; 50: 738.
22. Ball EA. A study of consensual accommodation. *Am J Optom Arch Am Acad Optom*. 1952; 29: 561-574.
23. Glasser A, Croft MA, Kaufman PL. Accommodation and presbyopia. *Int Ophthalmol Clin*. 2001; 41: 33-46.
24. Toor S, Horwood A and Riddell P. The effect of asymmetrical accommodation on anisometropic amblyopia treatment outcomes. *J AAPOS*. 2020; 23: e1-203.
25. Toor S, Horwood AM and Riddell P. Asymmetrical accommodation in hyperopic anisometropic amblyopia. *Br J Ophthalmol*. 2018; 102: 772-778.
26. Holmes JM, Beck RW, Repka MX, et al. The amblyopia treatment study visual acuity testing protocol. *Arch Ophthalmol*. 2001; 119: 1345-1353.
27. Moke PS, Turpin AH, Beck RW, et al. Computerized method of visual acuity testing: adaptation of the amblyopia treatment study visual acuity testing protocol. *Am J Ophthalmol*. 2001; 132: 903-909.
28. Holmes JM. Designing clinical trials for amblyopia. *Vision Res*. 2015; 114: 41-47.
29. Kivlin JD and Flynn JT. Therapy of anisometropic amblyopia. *J Pediatr Ophthalmol Strabismus*. 1981; 18: 47-56.
30. Krumholtz I and FitzGerald D. Efficacy of treatment modalities in refractive amblyopia. *J Am Optom Assoc*. 1999; 70: 399-404.
31. Scheiman MM, Richard W Hertle, Roy W Beck, et al. Randomized trial of treatment of amblyopia in children aged 7 to 17 years. *Arch Ophthalmol*. 2005; 123: 437-447.
32. Clarke MP, Wright CM, Hrisos S, et al. Randomised controlled trial of treatment of unilateral visual impairment detected at preschool vision screening. *BMJ*. 2003; 327: 1251.
33. Campbell FW and Westheimer G. Dynamics of accommodation responses of the human eye. *J Physiol*. 1960; 151: 285-295.
34. Flitcroft DI, Judge SJ and Morley SJ. Binocular interactions in accommodation control: effects of anisometropic stimuli. *J Neurosci*. 1992; 12: 188-203.
35. Bharadwaj SR and Candy TR. The effect of lens-induced anisometropia on accommodation and vergence during human visual development. *Invest Ophthalmol Vis Sci*. 2011; 52: 3595-3603.

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36. Koh LH and Charman WN. Accommodative responses to anisoaccommodative targets. *Ophthalmic Physiol Opt.* 1998; 18: 254-262.
  37. Rutstein RP. Contemporary issues in amblyopia treatment. *Optometry.* 2005; 76: 570-578.
  38. Ciuffreda KJ, Hokoda SC, Hung GK, et al. Accommodative stimulus/response function in human amblyopia. *Doc Ophthalmol.* 1984; 56: 303-326.
  39. Yoon GY and Williams DR. Visual performance after correcting the monochromatic and chromatic aberrations of the eye. *J Opt Soc Am A Opt Image Sci Vis.* 2002; 19: 266-275.
  40. Rossi EA, Pinky Weiser, Janice Tarrant, et al. Visual performance in emmetropia and low myopia after correction of high-order aberrations. *J Vis.* 2007; 7: 14.
  41. Artal P, Esther Berrio, Antonio Guirao, et al. Contribution of the cornea and internal surfaces to the change of ocular aberrations with age. *J Opt Soc Am A Opt Image Sci Vis.* 2002; 19: 137-143.
  42. Hickenbotham A, Tiruveedhula P and Roorda A. Comparison of spherical aberration and small-pupil profiles in improving depth of focus for presbyopic corrections. *J Cataract Refract Surg.* 2012; 38: 2071-2079.
  43. Guo H, Atchison DA and Birt BJ. Changes in through-focus spatial visual performance with adaptive optics correction of monochromatic aberrations. *Vision Res.* 2008; 48: 1804-1811.
  44. Kirwan C and O'Keefe M. Higher order aberrations in children with amblyopia. *J Pediatr Ophthalmol Strabismus.* 2008; 45: 92-96.