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Research article

Associations between the cause of amblyopia and pre-treatment contrast sensitivity, stereoacuity, fixation, and nystagmus

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A B S T R A C T

Purpose: To explore the association between the cause of amblyopia and pre-treatment contrast sensitivity, stereoacuity, fixation and nystagmus.
Design: Retrospective cohort study.
Methods: A retrospective review was conducted for 3408 patients with amblyopia who had not yet started amblyopia treatment utilizing a large amblyopia patient database maintained at Zhongshan Ophthalmic Centre. Six amblyogenic factor subtypes were identified: anisometropia, isoametropia, strabismus, anisometropia and strabismus, monocular visual deprivation, and binocular visual deprivation amblyopia. Monocular best corrected visual acuity (BCVA), the contrast sensitivity function (CSF), fixation, and stereopsis were compared between the subtypes before and after propensity score matching (PSM) for age and sex.
Results: The two deprivation groups had poorer BCVA and CSF than the other groups. There were no systematic differences in CSF between the non-deprivation groups. Nystagmus was more common in the bilateral amblyopia groups compared to the monocular amblyopia groups. Eccentric fixation was uncommon with the exception of the anisometropia and strabismus group which had an eccentric fixation rate of 20%. Distance stereoacuity measured without monocular cues was absent for almost all patients. The results were consistent when analyzed using PSM.
Conclusion: Visual deprivation causes more severe amblyopia than other amblyogenic factors. For non-deprivation amblyopia subtypes, individual differences such as variation in the severity of the amblyogenic factor might be more important in determining pre-treatment vision than whether amblyopia was caused by refractive error, strabismus or both.

1. Introduction

Amblyopia is a neurodevelopmental vision disorder caused by the presence of strabismus (eye misalignment), anisometropia (an interocular difference in refractive error), isoametropia (bilateral refractive error), visual deprivation, or a combination of these conditions during early childhood. The clinical diagnosis of amblyopia relies on reduced best-corrected visual acuity (BCVA) [1], however a broad range of other visual functions are also affected [2]. Because amblyopia is caused by an interaction between brain development and abnormal visual experience, it provides a unique model for exploring the way in which sensory input guides the

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maturation of cortical processing [3].

Strabismus, anisometropia, isoametropia and visual deprivation have distinct effects on visual input to the brain and may cause differing patterns of vision deficits when they disrupt normal visual development and cause amblyopia. Specifically, strabismus causes a spatial decorrelation of the two retinal images without affecting their spatial frequency content, anisometropia causes a mismatch in the high spatial frequency content of the two retinal images, isoametropia causes a general reduction in high spatial frequency content available to visual cortex and visual deprivation (blocked vision, typically due to cataract) can cause a loss of pattern vision in one or both eyes. Unilateral deprivation causes an extreme mismatch in the spatio-temporal content of the two retinal images, whereas bilateral deprivation, in its most extreme form, prevents any patterned visual information from reaching the brain. Any variations in a particular visual function that are associated with the cause of amblyopia would indicate that the development of that function relies on visual input that is disrupted more by some amblyogenic factors than others.

A core feature of amblyopia is reduced contrast sensitivity when viewing with the amblyopic eye, evident as abnormalities in the contrast sensitivity function (CSF). As expected, poorer visual acuity in the amblyopic eye is associated with a shift in the peak and cutoff of the contrast sensitivity function to lower spatial frequencies [4,5]. However, the contrast sensitivity deficit in amblyopia is not always limited to high spatial frequencies with deficits in sensitivity to mid and low spatial frequencies also reported [6–8].

Variations in the profile of contrast sensitivity deficits have been associated with the different sub-types of amblyopia. Pure strabismic amblyopia, where the amblyopic eye has a focused retinal image with normal contrast across the spatial frequency range, has been associated with a contrast sensitivity deficit limited to high spatial frequencies [9]. On the other hand, anisometropic amblyopia, where the retina of the amblyopic eye receives images with reduced contrast at mid to high spatial frequencies due to refractive error, has been associated with a general reduction in contrast sensitivity across the whole CSF [8–10] that becomes more pronounced when anisometropia is combined with strabismus [11]. However, this pattern has not been observed by all studies. For example, Pardhan and Gilchrist reported that strabismic amblyopia caused general contrast sensitivity deficits while anisometropic amblyopia caused only high spatial frequency contrast sensitivity losses [12]. Furthermore, Hess and Howell proposed a distinction between two types of strabismic amblyopia, one affecting high spatial frequencies and the other the whole CSF [13].

Visual deprivation amblyopia is associated with more severe vision deficits than the other sub-types and causes large and generalized reductions in contrast sensitivity [14,15]. Some studies report that these deficits are worse in the affected eye when deprivation is unilateral compared to bilateral and the unilateral cases are harder to recover [16–19]. However this may depend on the age at which the cataracts are removed [20].

Amblyopia also impairs binocular visual functions such as stereopsis. Stereoacuity in amblyopia is negatively correlated with the strength of interocular suppression [21,22] and the magnitude of fixation instability [23], both of which disrupt binocular combination. Eccentric fixation also disrupts stereopsis and predicts worse amblyopic eye vision in general [24,25]. As expected, stereopsis is less common in strabismic than in anisometropic amblyopia [26].

All previous studies comparing the pattern of contrast sensitivity, stereopsis and fixation deficits along with the presence of nystagmus between amblyopia subtypes have included participants whose amblyopia has been treated. Prior treatment may confound the results. The aim of our study was to test for associations between the cause of amblyopia and measures of contrast sensitivity, stereopsis, fixation, and nystagmus made before treatment had commenced. We utilized a large and comprehensive database to compare CSF (contrast sensitivity functions), fixation, visual acuity, and stereoacuity among strabismic, anisometropic, isoametropic, and visual deprivation amblyopia patients. Data from all patients, except those with deprivation amblyopia who underwent cataract surgery in infancy, were available prior to treatment. An understanding of the associations between the cause of amblyopia and the resulting pattern of vision deficits will help to clarify the relative importance of eye alignment and retinal image clarity on the development of spatial and binocular vision. In addition, this information can be used to inform caregivers about the pattern spatial vision deficits that a child is likely to experience during the early stages of occlusion therapy.

2. Methods

2.1. Participants

The UFOs Database [27] was searched for records of patients with amblyopia between January 2019 and April 2022. To be eligible for analysis, records for patients with anisometropic, isoametropic, strabismic, and as well as mixed anisometropic/strabismic amblyopia, had to contain monocular visual acuity (VA), contrast sensitivity, fixation and stereopsis data from the first, pre-treatment clinical visit. For visual deprivation amblyopia, we selected patients with history of cataract, all of whom had undergone cataract surgery in infancy. For these patients, data were included from the first clinical visit at which they were old enough to complete the required test battery.

Unilateral amblyopia was defined as an interocular difference in best corrected visual acuity (BCVA) of at least 0.2 logMAR. Binocular amblyopia was defined as BCVA worse than age-matched normal controls following the age-related criteria provided in the Preferred Practice Guidelines [1]. Anisometropia was defined as myopia ≥ -2.0D, hyperopia $\geq$1.5D and astigmatism $\geq$2.0 D [28]. Isoametropia was defined as having high bilateral refractive error (Myopia ≥ -3.0D, hyperopia$\geq$+4.5D, astigmatism>2.0D, and hyperopia combined with esotropia>+1.5D [28]) without anisometropia (an interocular refractive error difference for myopia < -2.0D, hyperopia <1.5D and astigmatism <2.0 D). The definition of strabismus included constant, non-alternating, or unequally alternating tropias [1]. Patients with deprivation amblyopia were labelled as monocular or binocular. For all groups, CSF data from the worse eye were used for analysis. The worse eye was identified according to criteria outlined previously [29].

Based on the database search results, six amblyopia subtypes were selected for further analysis: anisometropic, isoametropic,

strabismic, anisometropia combined with strabismus, monocular visual deprivation, and binocular visual deprivation. All participants had BCVA, fixation, and CSF data available prior to treatment (or at an appropriate age for the visual deprivation patients), and the majority had stereoacuity measurements. Contrast sensitivity was tested psychophysically using the quick contrast sensitivity function (qCSF [30]) test for older patients. Younger patients unable to complete psychophysical testing were assessed with a CSV-1000E chart. These datasets were analyzed separately.

Two sets of analyses were conducted. The first compared visual functions across the six groups using all available data. The second used propensity score matching (PSM) to eliminate the potential influence of age and sex across groups (Fig. 1).

2.2. Visual function measurements

Best Corrected Visual Acuity. High-contrast logMAR best-corrected distance VA was measured using the ETDRS tumbling E Chart (WEHEN Vision, Guangzhou, Guangdong, China), viewed from a distance of 4 m at a luminance of 200 cd per square meter (cd/m^2). The chart consisted of 5 optotypes per line for a total of 14 lines, decreasing from 1.0 to −0.3 logMAR. Visual acuity was scored per correct letter (0.02 logMAR per letter). For the patients who could not recognize the largest optotypes at 1 m (typically patients with

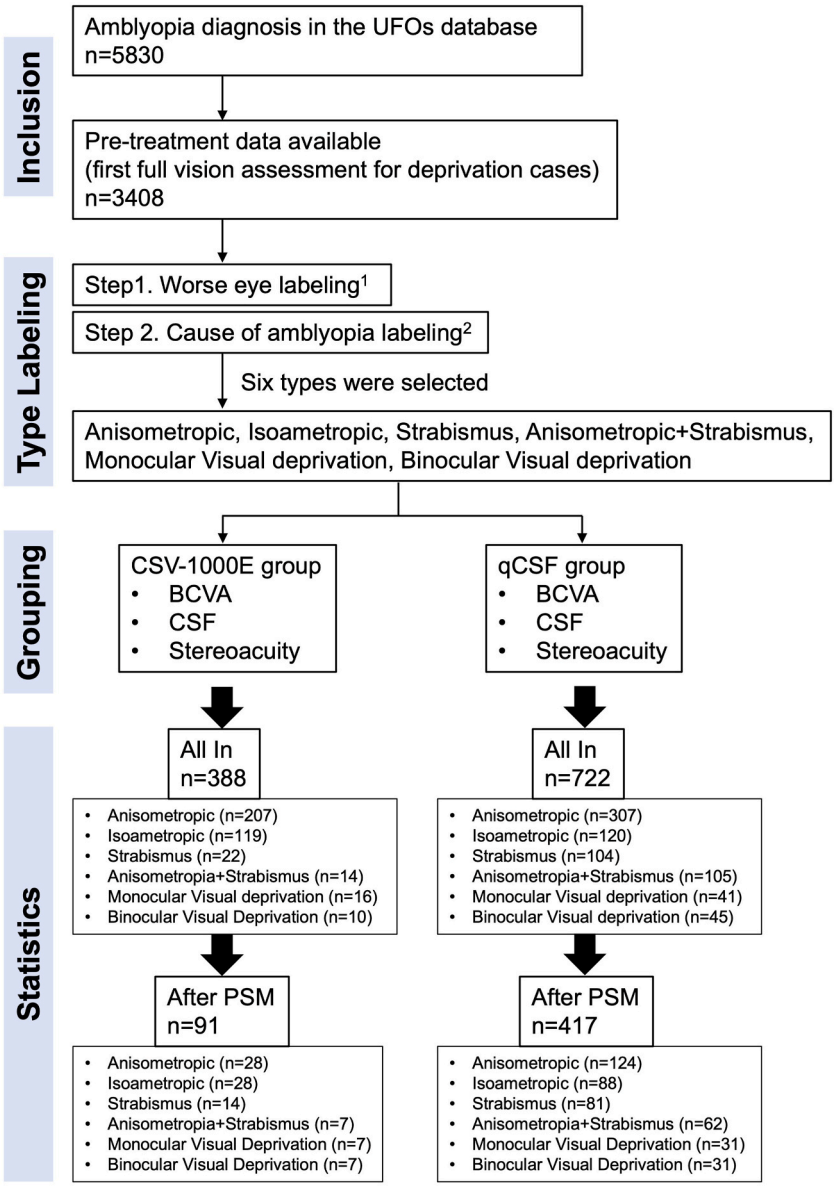

Fig. 1. Flowchart of participant selection. UFOs, uniting functions in ophthalmology and optometry. BCVA, best corrected visual acuity. CSF, contrast sensitivity function. PSM, propensity score matching.

visual deprivation amblyopia), we assigned logMAR values to finger counting (FC, 1.85 logMAR) [31], hand movement (HM, 2.90) or light perception (LP, 3.20) as suggested by the World Glaucoma Association guidelines [32].

Fixation. A direct ophthalmoscope YZ6E (66Vision. Tech, Suzhou, China) was used to screen for eccentric fixation [33].

Monocular Contrast Sensitivity Functions. If a patient older than 6 could not complete the qCSF test (Manifold Contrast Vision Meter, Adaptive Sensory Technology, Inc., SanDiego, CA, USA), they completed the CSV-1000E measurement (VectorVision, Dayton, OH, USA). The detailed procedure has been described previously [29,34]. The CSV-1000E test was administered under photopic lighting conditions (an auto-calibration was used to maintain a light level of 85 cd/m^2) at a distance of 2.5 m. The qCSF test was conducted at a distance of 4.5 m in a dark room, using a gamma-corrected 46-inch LCD monitor with a resolution of 1920 × 1080 pixels and a mean luminance of 50 cd/m^2. For the CSV-1000E test, if only the standard gratings were visible, pre specified log CS scores were assigned (Row A 0.70, Row B 0.91, Row C 0.61, and Row D 0.17) as suggested by official website of VectorVision. If a patient could not recognize the standard gratings and CS of 0 was assigned. For the qCSF test, a 0 value was assigned if a patient could not recognize any of the test stimuli.

Stereoacuity. Near stereoacuity was measured using the Random Dot Stereo Acuity Test (Vision Assessment Corporation, Elk Grove Village, IL, USA) at a distance of 40 cm with polarized glasses, and distance stereoacuity was measured using the Randot Stereoacuity Test (Stereo Optical, Inc., Chicago, IL, USA) at a distance of 3 m with polarized glasses. The near Random Dot Stereo Test has monocular cues (section B and C were tested) and the distance Randot Stereoacuity Test has no monocular cues. Age-normal performance was defined as meeting the third interquartile range or the lower limit of published normative data for the relevant age group. The detailed procedure has been described previously [29].

2.3. Statistical analysis

Statistical analyses were performed using the R Programming Language (4.1.2) and plots were produced using GraphPad Prism 9 (GraphPad Software, La Jolla, CA, USA). Descriptive statistics were used to summarize patient demographics. Categorical variables were expressed as frequencies (percentage) and continuous variables as mean and SD or median and quartiles depending on their distribution. To compare the values of the categorical variables in three or more groups, a chi-square test or a Fischer's exact test was performed with Bonferroni correction. To compare the values of the quantitative variables in three or more groups, a one-way analysis of variance (ANOVA) analysis was used if the data were normally distributed. Otherwise a Kruskal–Wallis test was used. Post-hoc analysis with Fisher's Least Significant Difference (LSD) test or Dunn's test was used to explore statistically significant effects.

As the age and sex were potential confounders and differed between the amblyopia-subgroups, we used propensity score matching (PSM) [35] to adjust for these two covariates and reduce potential selection bias. PSM was performed with a 1:1, 1:2, 1:3 or 1:4

Table 1
Demographics, nystagmus and fixation.

CSV-1000E	Anisometropic	Isoametropic	Strabismus	Anisometropic + Strabismus	Monocular Visual Deprivation	Binocular Visual Deprivation	P Value
No.	207	119	22	14	16	10	
Age (years)	5.70(5.10,6.40)	5.60 (5.10,6.00)	5.75 (5.20,6.00)	5.70(5.50,6.30)	5.60(4.70,6.55)	5.75(5.40,6.70)	0.779
Sex							0.808
Male	120(57.97)	69(57.98)	10(45.45)	7(50.00)	9(56.25)	7(70.00)	
Female	87(42.03)	50(42.02)	12(54.55)	7(50.00)	7(43.75)	3(30.00)	
Nystagmus							<0.0001*
No	206(99.52)	115(96.64)	22(100.00)	13(92.86)	16(100.00)	2(20.00)	
Yes	1(0.48)	4(3.36)	0(0.00)	1(7.14)	0(0.00)	8(80.00)	
Fixation							0.0015*
Centric	196(94.69)	119(100.00)	19(86.36)	14(100.00)	13(81.25)	10(100.00)	
Eccentric	11(5.31)	0(0.00)	3(13.64)	0(0.00)	3(18.75)	0(0.00)	
qCSF group	Anisometopic	Isometropic	Strabismus	Anisometropic+Strabismus	Monocular Visual Deprivaiton	Binocular Visual Deprivation	P Value
No.	307	120	104	105	41	45	
Age (years)	10.70 (7.90,15.90)	7.90 (6.50,13.70)	8.85 (7.35,13.10)	10.60(8.20,17.70)	8.50(6.90,11.60)	8.90(7.40,11.00)	<0.001*
Sex							0.184
Male	175(57.00)	67(55.83)	61(58.65)	55(52.38)	18(43.90)	32(71.11)	
Female	132(43.00)	53(44.17)	43(41.35)	50(47.62)	23(56.10)	13(28.89)	
Nystagmus							<0.001*
No	305(99.35)	95(79.17)	98(94.23)	101(96.19)	39(95.12)	15(33.33)	
Yes	2(0.65)	25(20.83)	6(5.77)	4(3.81)	2(4.88)	30(66.67)	
Fixation							<0.001*
Centric	292(95.11)	119(99.17)	96(92.31)	85(80.95)	37(90.24)	44(97.78)	
Eccentric	15(4.89)	1(0.83)	8(7.69)	20(19.05)	4(9.76)	1(2.22)	

Data are presented as median (quartile 1, quartile 3) for age (years), otherwise as n (%). Detailed comparisons between groups are shown in SI Tables 1 and 2 Data are split by type of contrast sensitivity measurement: CSV-1000E (top) and qCSF (bottom). * Statistically significant difference.

matching protocol without replacement (greedy-matching algorithm) with a caliper width equal to 0.5 for propensity scores. No missing data were reported for age, sex, amblyopia type, BCVA, or CSF. We did not impute missing stereoacuity data. We analyzed only the available data. Differences were considered significant at $P < 0.05$.

3. Results

The database search identified 5830 patients with an amblyopia diagnosis and 3408 with eligible data. The included dataset consisted of 388 records in the CSV-1000E group and 722 in the qCSF group before PSM, and 91 in the CSV-1000E group and 417 in the qCSF group after PSM (Fig. 1). PSM analysis was not conducted for the CSV-1000E group due to the small sample size. Demographic and clinical information for the whole group data and the PSM data for qCSF are shown in Tables 1 and 4.

4. BCVA and contrast sensitivity

4.1. Whole group analysis

Amblyopic eye BCVA distributions for each amblyopia sub-type group are shown in Fig. 2A and B. In both the CSV-1000E and qCSF groups, BCVA was worse in the deprivation groups than the anisometropic and isoametropic subtypes (Table 2 and SI Table 1).

The CSFs for the amblyopic/weaker eye for the six amblyopia sub-types are shown in Fig. 2C and D and statistical comparisons are shown in Table 2 and SI Table 1. In general, the two deprivation groups exhibited poorer contrast sensitivity than the other groups at low and medium spatial frequencies for the CSV measure and across the whole spatial frequency range for the qCSF measure. Monocular visual deprivation amblyopia (type 5) and binocular visual deprivation (type 6) showed similar contrast sensitivity profiles in both groups. There were no consistent differences in contrast sensitivity between the non-deprivation groups, although the isoametropic and combined anisometropic and strabismus groups showed a trend for poorer contrast sensitivity than the pure anisometropia group and the pure strabismus group.

4.2. PSM

Amblyopic eye BCVA distributions after PSM are shown in Fig. 3A along with median contrast sensitivity functions for each amblyopia subtype (Fig. 3B). Statistical analyses are provided in Tables 5 and SI Table 3. The results were similar to the whole group

Table 2
BCVA and CSF.

CSV-1000E	Anisometropic	Isoametropic	Strabismus	Anisometropic + Strabismus	Monocular Visual Deprivation	Binocular Visual Deprivation	P Value
No.	207	119	22	14	16	10	
BCVA	0.40	0.40	0.50	0.50(0.50,0.70)	0.95(0.45,1.35)	0.85(0.70,0.90)	<0.001*
LogMAR	(0.30,0.70)	(0.30,0.50)	(0.30,0.90)				
CS-3 cpd	1.17	1.17	1.17	1.00(0.00,1.17)	0.70(0.00,1.17)	0.85(0.70,1.17)	<0.001*
	(1.00,1.34)	(1.00,1.34)	(1.00,1.34)				
CS-6 cpd	1.38	1.38	1.21	1.38(0.00,1.38)	0.91(0.00,1.38)	0.91(0.00,1.21)	0.01*
	(1.21,1.55)	(0.91,1.55)	(0.91,1.38)				
CS-12 cpd	0.91	0.91	0.76	0.61(0.00,0.91)	0.61(0.00,1.08)	0.61(0.00,0.91)	0.078
	(0.61,1.08)	(0.61,1.08)	(0.61,0.91)				
CS-18 cpd	0.47	0.17	0.17	0.17(0.00,0.47)	0.17(0.00,0.47)	0.17(0.00,0.47)	0.051
	(0.17,0.64)	(0.17,0.64)	(0.00,0.47)				
qCSF	**Anisometropic**	**Isoametropic**	**Strabismus**	**Anisometropic + Strabismus**	**Monocular Visual Deprivation**	**Binocular Visual Deprivation**	**P Value**
No.	307	120	104	105	41	45	
BCVA	0.50	0.40	0.50	0.70(0.40,1.00)	0.70(0.40,1.00)	0.80(0.70,1.00)	<0.001*
LogMAR	(0.30,0.80)	(0.35,0.70)	(0.30,0.95)				
CS-3 cpd	1.21	1.01	1.16	0.99(0.01,1.42)	0.44(0.00,1.29)	0.20(0.00,0.73)	<0.001*
	(0.70,1.57)	(0.13,1.40)	(0.17,1.66)				
CS-6 cpd	0.27	0.06	0.27	0.00(0.00,0.71)	0.00(0.00,0.47)	0.00(0.00,0.00)	<0.001*
	(0.00,0.84)	(0.00,0.69)	(0.00,1.00)				
CS-12 cpd	0.00	0.00	0.00	0.00(0.00,0.00)	0.00(0.00,0.00)	0.00(0.00,0.00)	0.001*
	(0.00,0.02)	(0.00,0.01)	(0.00,0.18)				
CS-18 cpd	0.00	0.00	0.00	0.00(0.00,0.00)	0.00(0.00,0.00)	0.00(0.00,0.00)	0.028*
	(0.00,0.00)	(0.00,0.00)	(0.00,0.00)				
Cutoff SF	0.80	0.73	0.80	0.70(0.40,0.92)	0.54(0.22,0.86)	0.47(0.30,0.60)	<0.001*
	(0.60,0.97)	(0.44,0.93)	(0.46,1.02)				
AULCSF	0.73	0.61	0.73	0.61(0.21,0.99)	0.36(0.12,0.87)	0.26(0.09,0.48)	<0.001*
	(0.44,1.04)	(0.20,0.93)	(0.23,1.14)				

Data are presented as median (quartile 1, quartile 3). Comparisons between the groups were made using the Kruskal-Wailis H test. Detailed between group comparisons are shown in SI Table 1. Data are split by type of contrast sensitivity measurement: CSV-1000E (top) and qCSF (bottom). CS, contrast sensitivity (showed with log units); SF, spatial frequency. * Statistically significant difference.

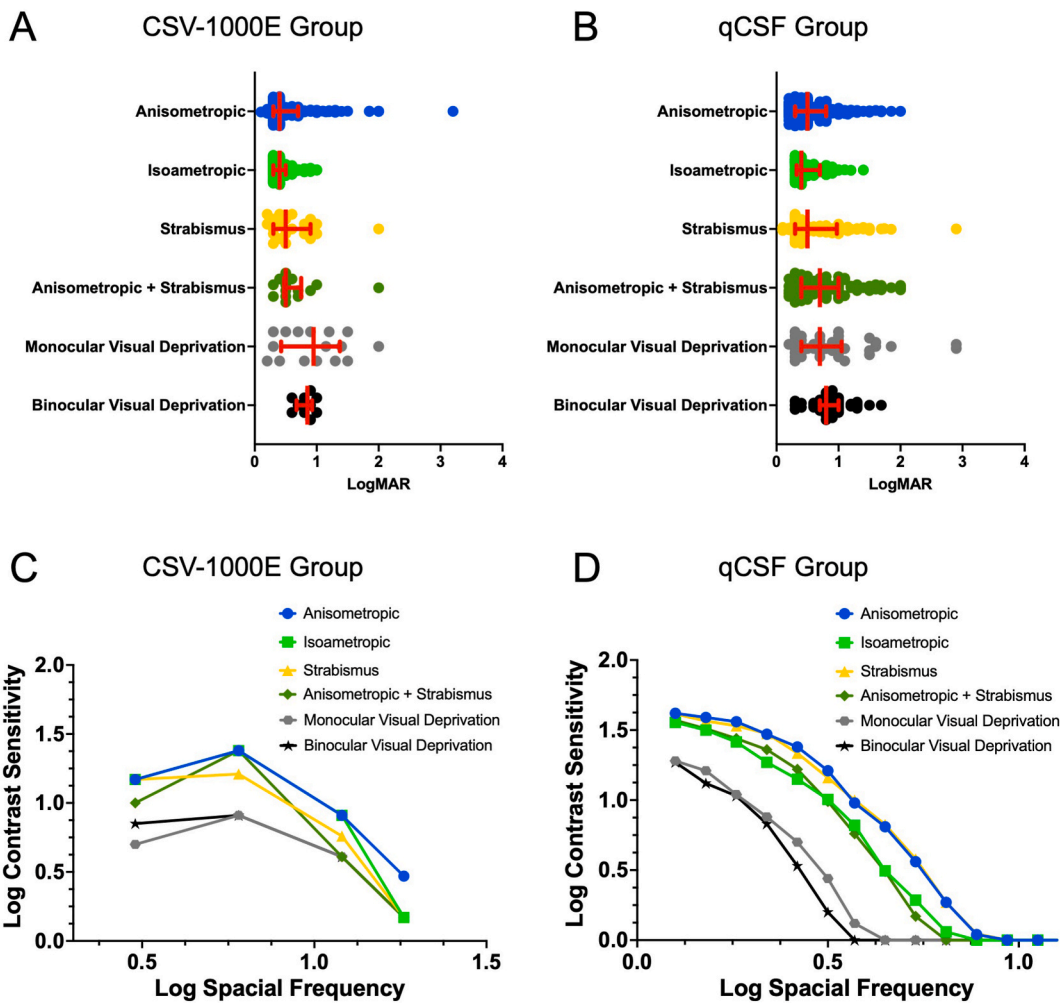

Fig. 2. Amblyopic eye BCVA and CSF. BCVA distributions are shown in panels A and B for the CSV-1000E and qCSF groups. Red lines show the median and IQR. Median CSF for each amblyopia subtype are shown in panels C and D for the CSV-1000E and qCSF groups. IQRs for each spatial frequency are provided in Table 2. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

analyses whereby the visual deprivation groups had poorer visual acuity and exhibited a general reduction in CSF compared to the other amblyopia sub-types. Other amblyopia sub-types had comparable median CSFs.

5. Nystagmus and fixation

5.1. Whole group data

For the CSV-1000E group, nystagmus was most common in the bilateral visual deprivation amblyopia group than all the other groups and eccentric fixation was uncommon. Detailed statistics are shown in SI Table 2 (Left).

Similarly, in the qCSF group, nystagmus was more common in the bilateral amblyopia groups (isoametropic as well as bilateral visual deprivation amblyopia) compared to the monocular amblyopia groups (anisometropic, strabismus, and anisometropic + strabismus). Eccentric fixation was uncommon with the exception of the anisometropia + strabismus group which had an eccentric fixation rate of 20%. Detailed statistics are shown in SI Table 2 (Right).

5.2. PSM

PSM did not change the general pattern of results for the qCSF group.

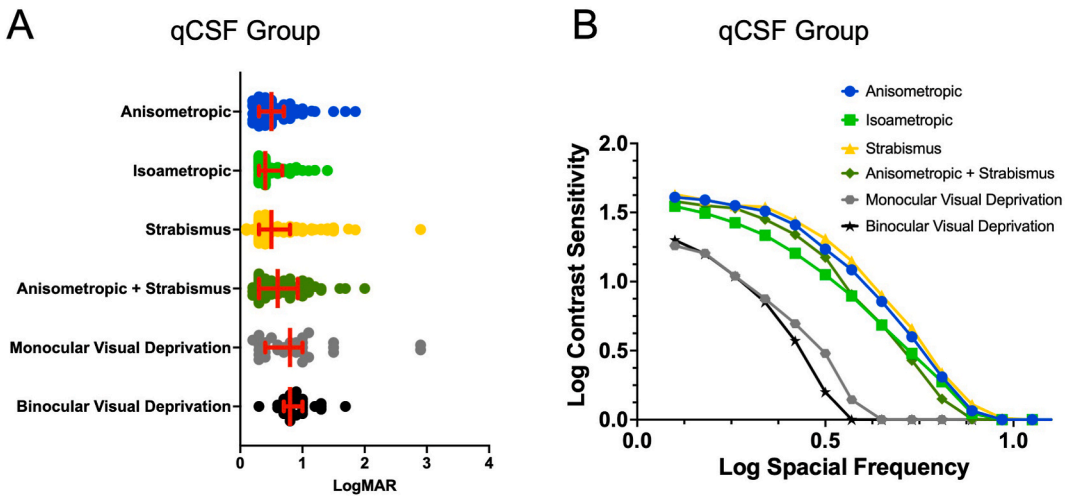

Fig. 3. Amblyopic eye BCVA and CSF after PSM. BCVA distributions are shown in panels A for qCSF groups. Red lines show the median and IQR. Median CSF for each amblyopia subtype are shown in panels B. IQRs for each spatial frequency are provided in Table 5. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Table 3
Stereoacuity.

CSV-1000E	Anisometropic	Isoametropic	Strabismus	Anisometropic + Strabismus	Monocular Visual Deprivation	Binocular Visual Deprivation	P Value
randomdot	181	111	21	12	16	10	
1	17(9.39)	14(12.61)	1(4.76)	0(0.00)	0(0.00)	0(0.00)	0.0054*
2	58(32.04)	50(45.05)	5(23.81)	3(25.00)	3(18.75)	0(0.00)	
3	106(58.56)	47(42.34)	15(71.43)	9(75.00)	13(81.25)	10(100.00)	
randot	203	114	22	14	15	9	0.8351
1	3(1.48)	5(4.39)	0(0.00)	0(0.00)	0(0.00)	0(0.00)	
2	12(5.91)	4(3.51)	1(4.55)	0(0.00)	1(6.67)	0(0.00)	
3	188(92.61)	105(92.11)	21(95.45)	14(100.00)	14(93.33)	9(100.00)	
qCSF	**Anisometropic**	**Isoametropic**	**Strabismus**	**Anisometropic + Strabismus**	**Monocular Visual Deprivation**	**Binocular Visual Deprivation**	**P Value**
randomdot	292	117	100	101	37	44	<0.001*
1	10(3.42)	9(7.69)	5(5.00)	1(0.99)	1(2.70)	0(0.00)	
2	93(31.85)	45(38.46)	15(15.00)	17(16.83)	8(21.62)	5(11.36)	
3	189(64.73)	63(53.85)	80(80.00)	83(82.18)	28(75.68)	39(88.64)	
randot	300	117	94	105	39	44	0.5178
1	2(0.67)	1(0.85)	1(1.06)	0(0.00)	0(0.00)	0(0.00)	
2	6(2.00)	0(0.00)	3(3.19)	0(0.00)	0(0.00)	0(0.00)	
3	292(97.33)	116(99.15)	90(95.74)	105(100.00)	39(100.00)	44(100.00)	

Data are presented as n (%). Between group comparisons were made using the Kruskal-Wailis H test. Detailed between group comparisons are shown in SI Table 2. Data are split by type of contrast sensitivity measurement: CSV-1000E (top) and qCSF (bottom). * Statistically significant difference.

6. Stereoacuity

6.1. Whole group data

Near and distance stereoacuity measurements are shown in Tables 3 and SI Table 2. In both the CSV-1000E and qCSF datasets, the anisometropic and isoametropic groups had the highest proportion of age-normal near stereoacuity, although there was considerable inter-individual variability and the near stereoacuity test has monocular cues. Distance stereoacuity measured without monocular cues was absent for almost all patients.

6.2. PSM

Stereoacuity (Table 6and SI Table 4) remained poor for all amblyopia sub-types in the PSM analysis, particularly for distance stereopsis measured without monocular cues.

Table 4
Demographics, nystagmus and fixation after PSM.

qCSF group	Anisometropic	Isoametropic	Strabismus	Anisometropic + Strabismus	Monocular Visual Deprivation	Binocular Visual Deprivation	P Value
No.	124	88	81	62	31	31	
Age (years)	7.85 (6.75,11.20)	7.20 (6.40,10.40)	8.50 (7.00,10.70)	8.50(7.30,11.00)	7.30(6.10,11.20)	9.20(6.90,11.50)	0.202
Sex							1
Male	72(58.06)	52(59.09)	49(60.49)	36(58.06)	18(58.06)	18(58.06)	
Female	52(41.94)	36(40.91)	32(39.51)	26(41.94)	13(41.94)	13(41.94)	
Nystagmus							<0.001*
No	122(98.39)	72(81.82)	76(93.83)	61(98.39)	30(96.77)	7(22.58)	
Yes	2(1.61)	16(18.18)	5(6.17)	1(1.61)	1(3.23)	24(77.42)	
Fixation							0.002*
Centric	119(95.97)	88(100.00)	77(95.06)	54(87.10)	27(87.10)	31(100.00)	
Eccentric	5(4.03)	0(0.00)	4(4.94)	8(12.90)	4(12.90)	0(0.00)	

Data are presented as median (quartile 1, quartile 3) for age (years), otherwise as n (%). Detailed comparison between groups are shown in SI Tables 3 and 4 * Statistically significant difference.

Table 5
BCVA and CSF after PSM.

qCSF	Anisometropic	Isoametropic	Strabismus	Anisometropic + Strabismus	Monocular Visual Deprivation	Binocular Visual Deprivation	P Value
No.	124	88	81	62	31	31	
BCVA LogMAR	0.50 (0.30,0.70)	0.40 (0.30,0.65)	0.50 (0.30,0.80)	0.60(0.30,0.90)	0.80(0.40,1.00)	0.80(0.70,1.00)	<0.001*
CS-3 cpd	1.23 (0.71,1.58)	1.05 (0.05,1.44)	1.31 (0.71,1.68)	1.17(0.47,1.46)	0.44(0.00,1.25)	0.20(0.00,0.65)	<0.001*
CS-6 cpd	0.31 (0.00,0.87)	0.28 (0.00,0.77)	0.34 (0.00,1.07)	0.15(0.00,0.77)	0.00(0.00,0.47)	0.00(0.00,0.00)	<0.001*
CS-12 cpd	0.00 (0.00,0.05)	0.00 (0.00,0.04)	0.00 (0.00,0.24)	0.00(0.00,0.01)	0.00(0.00,0.00)	0.00(0.00,0.00)	<0.001*
CS-18 cpd	0.00 (0.00,0.00)	0.00 (0.00,0.00)	0.00 (0.00,0.00)	0.00(0.00,0.00)	0.00(0.00,0.00)	0.00(0.00,0.00)	0.085
Cutoff SF	0.82 (0.61,0.99)	0.81 (0.42,0.96)	0.82 (0.60,1.03)	0.77(0.53,0.94)	0.54(0.26,0.86)	0.47(0.30,0.58)	<0.001*
AULCSF	0.76 (0.46,1.06)	0.67 (0.18,0.95)	0.76 (0.44,1.16)	0.68(0.36,1.01)	0.31(0.12,0.77)	0.26(0.09,0.43)	<0.001*

Data are presented as median (quartile 1, quartile 3). Comparisons between the groups were made using the Kruskal-Wailis H test. Detailed between group comparisons are shown in SI Table 3. CS, contrast sensitivity (showed with log units); SF, spatial frequency. * Statistically significant difference.

7. Discussion

The UFOs database provided access to unique set of contrast sensitivity and clinical measurements made prior to treatment in a large number of children with amblyopia. Our aim was to assess whether any systematic differences in these data could be explained by the cause of amblyopia without any potentially confounding effects of amblyopia treatment. As expected, the patients with deprivation amblyopia caused by early cataract (either unilateral or bilateral) exhibited poorer contrast sensitivity and visual acuity than the other amblyopia subtypes along with a higher proportion of nystagmus. However, in contrast to some previous studies, we did not detect consistent differences in visual acuity or contrast sensitivity between patients with anisometropic, isoametropic, strabismic and mixed anisometropic and strabmismic amblyopia. This indicates that the different effects each of these amblyogenic factors had on binocular input to the visual cortex during early development did not lead to distinct patterns of vision deficits.

Congenital cataracts severely disrupt visual development, and the resulting deprivation amblyopia is typically denser than amblyopia caused by refractive error and/or strabismus [1,36] and associated with nystagmus, perhaps due to a severe disruption of binocular visual development [37,38]. For our contrast sensitivity measures, deprivation amblyopia caused a general decrease in sensitivity across the whole spatial frequency range compared to other amblyopia subtypes, as has previously been reported [39]. Previous studies [2,40] have reported more pronounced acuity and contrast sensitivity losses in the worse eye of patients with monocular deprivation amblyopia compared to those with binocular deprivation. An early interocular competition for cortical territory could explain this difference because monocular deprivation causes a greater interocular imbalance. However, we did not observe this pattern in our data. The effects of congenital cataracts on visual development are critically dependent on the duration of deprivation and variation in deprivation duration within our sample may have masked any differences between monocular and binocular deprivation. In Zhongshan Ophthalmic Centre, children with severe congenital monocular cataract received surgery within 6 weeks after birth, and children with severe congenital binocular cataract received surgery within 10 weeks after birth. The operations for each eye are conducted separately within 7 days of one another. It is possible that this early treatment protocol reduces differences

Table 6
Stereoacuity after PSM.

qCSF	Anisometropic	Isoametropic	Strabismus	Anisometropic + Strabismus	Monocular Visual Deprivation	Binocular Visual Deprivation	P Value
Random dot near	116	86	77	60	27	30	<0.001[a]
Age-normal	6(5.17)	8(9.30)	3(3.90)	1(1.67)	1(3.70)	0(0.00)	
Reduced for age	39(33.62)	39(45.35)	11(14.29)	13(21.67)	3(11.11)	4(13.33)	
Unmeasurable	71(61.21)	39(45.35)	63(81.82)	46(76.67)	23(85.19)	26(86.67)	
Randot distance	118	86	71	62	29	30	0.6889
Age-normal	0(0.00)	1(1.16)	1(1.41)	0(0.00)	0(0.00)	0(0.00)	
Reduced for age	3(2.54)	0(0.00)	1(1.41)	0(0.00)	0(0.00)	0(0.00)	
Unmeasurable	115(97.46)	85(98.84)	69(97.18)	62(100.00)	29(100.00)	30(100.00)	

Data are presented as n (%). Between group comparisons were made using the Kruskal-Wailis H test. Detailed between group comparisons are shown in SI Table 4.

[a] Statistically significant difference.

in vision loss between unilateral and bilateral patients.

Our observation that contrast sensitivity and visual acuity were comparable between the non-deprivation amblyopia subtypes contrasts with some previous studies that identified differences between amblyopia subtypes [9,10]. The interquartile ranges associated with our contrast sensitivity and acuity data indicate that in a large, real-world clinical sample, interindividual differences within an amblyopia subtype, perhaps related to variables such as magnitude of anisometropia or angle of strabismus, are more important in determining visual function than amblyopia subtype. In addition, our data were collected pre-treatment which may have provided a wider variation of contrast sensitivities and visual acuities than previous studies of treated amblyopia. The qCFS is an emerging vision testing technology that may soon be available clinically [30,34]. In the future, qCSF technology has the potential to enable more accurate phenotyping of amblyopia patients within clinical practice.

Stereopsis was poor for all amblyopia subtypes, especially when monocular cues were not available. A loss of binocular visual function may be the most functionally relevant aspect of amblyopia as it can impact the development of motor function [41–43] and reading [44,45]. Amblyopia treatments that target binocular visual function have been developed [46–48] and there is evidence that binocular treatment may improve motor function [42]. Our results highlight the need for therapies that improve binocular function irrespective of amblyopia subtype.

Our study had several limitations. These include the retrospective study design and the use of two different contrast sensitivity tests; the qCSF for most participants and the CSV-1000E chart for children who were too young to complete the qCSF test. We have previously reported that the CSV-1000E chart provides higher contrast sensitivity estimates than the qCSF when both tests are administered to the same participants [49]. This is why we analyzed the two datasets separately. We also did not have a large enough sample size for the CSV-1000E measurements to enable PSM. In addition, a small proportion of participants were missing stereoacuity data. Because this was a retrospective study, we were not able to determine why these data were missing.

Our study also had a number of strengths. These included a large sample extracted from an internationally unique database of amblyopia patient data, rigorous database search criteria including precise definitions of amblyopia sub-type and the use of PSM to remove sampling bias from our results. These strengths enhance the reliability and generalizability of our findings.

Together, our results indicate that, with the exception of visual deprivation, amblyopia subtype is not strongly associated with contrast sensitivity or the extent of visual acuity loss in amblyopia prior to treatment. Amblyopia subtype differences that have been reported previously may have been influenced by smaller sample sizes or an interaction between amblyopia subtype and amblyopia treatment response, an effect that has been reported by some studies [50] but not others [51–54].

Ethics statement

This study was reviewed and approved by the Institutional Ethics Committee of Zhongshan Ophthalmic Center, Sun Yat-sen University, with the approval number: 2017KYPJ006.

Data availability statement

The data associated with this study have not been deposited into a publicly available repository. The data associated with this study will be made available on request.

CRediT authorship contribution statement

Yu Jia: Writing – original draft, Validation, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Qingqing Ye:** Writing – original draft, Validation, Software, Resources, Project administration, Methodology, Data curation, Conceptualization. **Jing Liu:** Validation, Software, Formal analysis, Data curation, Conceptualization. **Lei Feng:** Validation, Software, Methodology, Investigation. **Zixuan Xu:** Validation, Methodology, Investigation. **Yunsi He:** Validation, Methodology,

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e28857.

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