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Effects of bifocals on visual acuity in children with Down syndrome: a randomized controlled trial

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ABSTRACT.

Purpose: **Children with Down syndrome (DS) typically have reduced visual acuity (VA) and accommodation lag, but it is unclear whether prescribed glasses should correct both distance VA (DVA) and near VA (NVA) due to the lack of RCTs. We therefore conducted a multicentre RCT to compare the effects of bifocals designed to correct both DVA and NVA with distance-correcting unifocal glasses in children with DS.**

Methods: **A total of 119 children with DS, aged 2–16, were randomly allocated for bifocal or unifocal glasses (with full correction of refraction error in cycloplegia) in 14 Dutch hospitals and followed during 1 year. VA data were analysed in relation to baseline VA with ANCOVA.**

Results: **Treatment groups showed no differences at baseline. Shortly after receiving new corrections (~6 weeks), uncrowded NVA (bifocals 0.18 ± 0.33 LogMar; unifocals 0.09 ± 0.19 LogMar) and crowded NVA with bifocals (bifocals 0.13 ± 0.36 LogMar; unifocals 0.08 ± 0.33 LogMar) were significantly better than at baseline, but these short-term improvements in NVA were not significantly different between the two treatments ($p > 0.151$). The 1-year treatment differences were as follows: significantly larger improvement for bifocals compared to unifocals in both uncrowded NVA (bifocals 0.23 ± 0.29 LogMar, unifocals 0.12 ± 0.30 LogMar, $p = 0.045$) and crowded NVA (bifocals 0.31 ± 0.28 LogMar; unifocals 0.16 ± 0.30 LogMar, $p = 0.017$). Improvements in DVA were comparable (bifocals 0.07 ± 0.21 LogMar, unifocals 0.08 ± 0.22 LogMar, $p = 0.565$). Children with poor baseline VA improved more. Accommodation lag stayed unchanged.**

Conclusion: **After one year, bifocals with full correction of ametropia led to significantly larger improvement of both uncrowded NVA and crowded NVA in children with DS with accommodation lag compared to unifocals.**

Key words: accommodation lag – child development – crowded near visual acuity – near addition in children – ocular accommodation – refraction error

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Introduction

Uncertainty exists about prescribing bifocals or unifocals in children with Down syndrome (DS) to correct distance visual acuity (DVA) as well as near visual acuity (NVA), because of the lack of large randomized controlled trials. In the Netherlands, the annual incidence of DS, the most common chromosomal anomaly in newborn children, is 14.6 per 10 000 (van Gameren-Oosterom et al. 2012). This is similar to the annual birth incidence of DS in the United States of 14.5 per 10 000 (Parker et al. 2010). Children with DS have well-known physical markers, specific health problems, varying degrees of intellectual impairment, and delayed cognitive and motor development (van Gameren-Oosterom et al. 2011). Their brain development differs from typically developing children. In particular, in children with DS less brain weight is found, there is dendritic atrophy, and poor maturation of the central nervous system has been described (Courage et al. 1994; Little et al. 2009a, Morton 2011; Watt et al. 2015). In recent years, research has shown that their visuospatial memory is better than their verbal memory (Lanfranchi et al. 2004; Frenkel & Bourdin 2009). Possibly they learn more by seeing than by hearing (Fidler et al. 2005; Frenkel & Bourdin 2009; Roch et al. 2012). From the youngest ages, they find their challenges in their direct surroundings. At school, most of their learning activities will be at near (Cregg et al. 2001). So for these children, visual functions are very

important, but visual functions are reduced in almost all children with DS. This may be a barrier to achieve their maximum developmental potential.

Although neural deficits at least partly constrain the visual acuity (VA) of children with DS, there are ocular disorders that further limit their visual functioning (Borstlap et al. 2011). Compared to other children, many ocular findings in DS occur more frequently and in a more severe form (Creavin & Brown 2009; Little et al. 2009b, Afifi et al. 2013; Aslan et al. 2014; Watt et al. 2015). In literature, the following prevalences have been reported: reduced visual acuity (poorer than 0.3 LogMar) in 80–100% and poor contrast sensitivity in almost all DS children (John et al. 2004; Morton 2011; Little et al. 2013; Watt et al. 2015; Zahidi et al. 2018). Accommodation deficit occurs in 50–90% of the children with DS (Woodhouse et al. 1993, 1996, 2000; Cregg et al. 2001; Nandakumar & Leat 2009, 2010; Anderson et al. 2011; Doyle et al. 2016, 2017). Indeed, most children with DS have a consistent, inappropriate lag of accommodation at all distances. This deficit does not disappear with age and occurs in all kinds of refraction errors. Additionally, refraction errors occur in 40–90% of the children with DS (Woodhouse et al. 1997; Wong & Ho 1997; Doyle et al. 1998; Haugen et al. 2001; Cregg et al. 2003; Stephen et al. 2007; Nandakumar & Leat 2009; Creavin & Brown 2009; Little et al. 2009a, Al-Bagdady et al. 2011; Ljubic et al. 2011; Watt et al. 2015). At birth, refraction errors are similar to those in typically developing children, but the refraction errors change and increase over time; the normal emmetropization mechanism does not occur. Children with DS who initially have no refraction error are at risk of developing refraction errors. Furthermore, the prevalence of strabismus in DS is 15–47% (Haugen & Hovding 2001; Cregg et al. 2003; Stewart et al. 2007; Ljubic et al. 2011; Morton 2011; Watt et al. 2015; Doyle et al. 2016), which is on average 10 times higher than in normally developing children (Bruce & Santorelli 2016; Schuster et al. 2017). In DS, the onset of strabismus occurs mostly between 3 and 6 years of age. This age could be associated with the developmental stage at which DS children become interested in visual details and consequently start to accommodate. Strabismus probably then occurs as a result of a lack of balance between accommodation and convergence (McClelland & Saunders 2003; Stewart et al. 2007; Doyle et al. 2017). Hence, there is far more esotropia than exotropia (9:1) in DS, and more acquired strabismus than congenital (7:3). In addition, nystagmus occurs in 6–33% (Creavin & Brown 2009; Afifi et al. 2013; Weiss et al. 2016).

The reduced accommodation, which results in a reduction of near vision, may be a substantial limiting factor for children with DS. Regular glasses, as prescribed to other children (mostly partial correction of hyperopia (Atkinson et al. 2000)), improve distant acuity of children with DS, but probably do not improve near acuity (Cregg et al. 2001; Stewart et al. 2007; Nandakumar & Leat 2009; Nandakumar et al. 2011). For short distances, they still have to accommodate. In myopic children with DS, near vision will be reduced more with regular glasses than without glasses because of the lack of accommodation (Cregg et al. 2001; Nandakumar & Leat 2009). So in myopia, children with DS might prefer to observe their direct surroundings at near without glasses. This may result in low compliance in the use of glasses in myopic children with DS.

Small-scale studies by Woodhouse and colleagues have shown that bifocals improve visual acuity and that in some children, accommodation accuracy through the distance portion of the lens is more accurate (Stewart et al. 2005; Al-Bagdady et al. 2009). Thereafter, Nandakumar selected 14 children with Down syndrome for their ability to read and write, and found that these selected cases had better visual acuity with bifocals, both at distance and at near, and that bifocals improved both their reading performance and their performance on visual perceptual tasks (Nandakumar & Leat 2009, 2010; Nandakumar et al. 2011). Furthermore, researchers found that compliance in wearing bifocal glasses in children with DS was the same or even better than for regular glasses (Stewart et al. 2005; Nandakumar & Leat 2010; Adyanthaya et al. 2014). However, due to the small scale of these studies, it is still unclear in which cases it may be appropriate to prescribe bifocals to children with DS, and how bifocals influence their accommodation and visual acuity.

The aim of this study is to compare the effects of bifocal glasses with unifocals in a large cohort of children with DS. In a multicentre randomized controlled trial, we studied the effects of bifocals compared to unifocals (both with full distance correction) on NVA and distant visual acuity (DVA) in a wide range of children with DS. In this RCT, strabismus and executive functions were measured as well, but in this paper, we limit our report to VA and accommodation response.

Subjects and Methods

The project was conducted in accordance with the Declaration of Helsinki and approved by the Dutch Medical Ethics Committee of the Isala Hospitals (NL48288.75.14/METC: 14.0333). This approval was reaffirmed by the local ethics committees of the participating clinics.

Subjects

We included 119 children with DS (aged 2–16 years; 58 boys and 61 girls) recruited from the Netherlands. Informed consent was obtained from the subjects' parents or their legal guardians after explanation of the nature and possible consequences of the study.

Inclusion criteria were as follows:

(1) Diagnosed with DS, trisomy 21 as well as minority forms
(2) Accommodation lag >0.5D measured with 'modified Nott-method'
(3) Age range 2–18 years
(4) Able to understand the task instructions, and at age older than 6 able to do vision tests, preferable LEA symbols and otherwise Kay picture test, at any manner by naming, matching or gesturing the symbols or pictures
(5) Must be able to perform a task sitting on a chair and working at a table
(6) With or without strabismus, and with or without nystagmus.

Exclusion criteria were as follows:

(1) Worn bifocals before
(2) Other eye diseases that seriously hamper vision like keratoconus, colobomas, cataract
(3) Born after severe perinatal problems, and/or prematurity <36 weeks' gestational age, dysmaturity, and/or perinatal asphyxia and/or abnormalities found on MRI.

Children were included from age 2, because around this age, they reach the earliest developmental level at which they may benefit from bifocals, that is, as soon as they can sit (looking downwards) while doing a near task.

Children were recruited from the participating locations (14 hospitals in the Netherlands and one institute for visually impaired, where children with DS are examined regularly for routine examinations according to the Dutch protocol in DS) and from other locations in co-operation with: orthoptic departments in other hospitals, SDS (Stichting Down Syndrome, the Dutch Down Syndrome Foundation), DOC (Down Research Consortium), the Down teams, NVvO (Dutch Orthoptic Association), and OVN (Dutch Optometrist Association), and Dutch Working Group of Paediatric Ophthalmologists, JGZ (Dutch Youth Health Care Organizations), AJN (Dutch Youth Health Doctors), NVAVG (Dutch Doctors for Mentally Handicapped) and NVK (Dutch Association of Paediatric Medicine). The staff of those organizations (who were introduced to the study by the first author) as well as the first author provided individual or collective information to parents and those connected to the DS population, through mailings, invitation letters, flyers, posters, advertisements in paper magazines or on websites and digital newsletters or oral announcements at relevant meetings and conferences. After a first introduction to the study, parents could ask the first author, the research team or the ligated independent paediatrician for more information, oral and written, about the nature of the study (www.ClinicalTrials.gov number R0002308 and in patient information forms reviewed and approved by the Medical Ethics Committee of the Isala Hospitals). In consultation with the orthoptists, children who received care from hospitals that were not participating in our RCT could be included and followed up during the study in one of our locations.

Design

To study the difference between the effect of bifocal correction in DS and the effect of the unifocal correction in DS, both with full distance correction, we conducted a multicentre randomized controlled trial (Fig. 1).

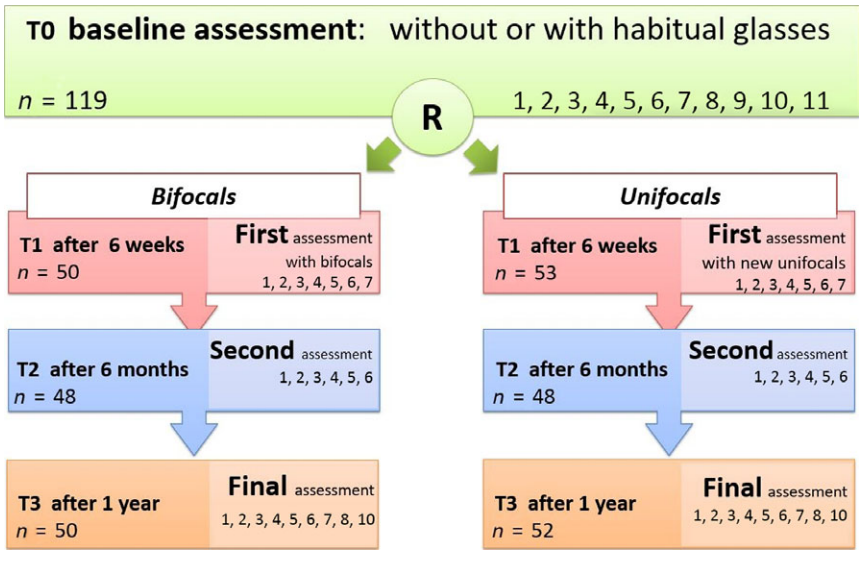

Fig. 1. Study design, timeline with applied diagnostic procedures at each visit (T0, T1, T2 and T3) and the number of children who were tested at that point in time. *R* = age and gender matched randomization. 1 = anamnesis, 2 = ocular alignment, 3 = binocularity and stereopsis, 4 = distance visual acuity, 5 = near visual acuity, uncrowded and crowded, 6 = dynamic retinoscopy, 7 = Minnesota Executive Function Scale, 8 = objective refraction error in cycloplegia and prescription of glasses, 9 = ophthalmological examination for exclusion of pathology, by the ophthalmologist of the clinic, 10 = questionnaires BRIEF-P and BRIEF, 11 = questionnaire Vineland-S.

Locations

The 15 participating locations were geographically spread over the Netherlands to increase the accessibility to our study for as many children as possible. Before the start of the inclusion, all participating orthoptists were instructed to work in a similar way in all participating centres. These instructions were given by the first author during sessions for each participating location and by the first author and by experts who explained data management and accommodation measurement during two centrally organized sessions.

Randomization

A permuted-blocks randomization schedule, stratified by gender, age and language development (parents' report: speaking in one -to three-word sentences and speaking in four word or longer sentences) was used to randomly assign a child with equal probability to one of the two treatment groups. All participating orthoptists of the participating locations could login onto the digital Web-based research data managing system, ResearchManager® (a Web-based electronic CRF, developed by Cloud9 Health Solutions and Isala Academy in Zwolle, the Netherlands, according to GCP and GCDMP guidelines and 21 CFR part one of FDA regulations) to remotely enter the data of the child, create a patient number, effectuate the randomization and thereafter enter the data of the assessments required at each visit. Blinding was not possible, because of the visibility of the near addition in bifocals. As the type of intervention was always evident to the parents, the participants, the orthoptist and the investigator, they knew to which group the child was assigned.

Intervention

Full correction of refraction error (measured in cycloplegia) was prescribed in both groups. In the bifocal group, we used longlines (straight-top or D segment) with addition S + 2.5 as used by Al-Bagdady et al. (2009), which led to improved accommodation through the distant part of the lens in the majority of the children while wearing bifocals. The bifocal segment top was placed at the pupillary centre as found to be useful in other trials (Stewart et al. 2005; Al-Bagdady et al. 2009; Nandakumar & Leat 2009). When the refraction error was too high to make cosmetically acceptable longlines (straight-top or D segment), we chose a wide segment S45. In both groups, participants and their parent(s) got instructions on how to get used to and wear the glasses, as in usual care. Parents were asked to encourage their child to wear the glasses as much as

possible, but, if wearing the glasses all day was not possible, to use the glasses at least in school and for all near work. Parents received financial support for the extra costs of the bifocal added to the usual costs of unifocals and the health insurance contribution. This way, costs were the same for the participants in the two intervention groups.

Timeline

After inclusion, we followed the participants for 1 year, in four visits (Fig. 1). These visits were scheduled as close as possible to routine medical check-ups. During the first visit (T0), measurements were performed to prescribe glasses. The assessments for visual acuity and accommodation lag were part of a larger suite of measures, which are not reported here.

T0: On the first visit, the following aspects were assessed in the following sequence.

(1) Questionnaire: structured questions on compliance, visual functions and strabismus
(2) Ocular alignment
(3) Binocularity and Stereopsis
(4) DVA, uncrowded
(5) NVA, uncrowded and crowded
(6) Dynamic retinoscopy
(7) Minnesota Executive Function Scale (MEFS)
(8) Objective refraction error (in cycloplegia)
(9) Ophthalmological examination by the ophthalmologist of the clinic, slit-lamp examination and fundoscopy, in order to exclude of ocular pathology
(10) Questionnaires BRIEF-P or BRIEF filled out at home (parents/caretakers)
(11) Questionnaire Vineland-S filled out at home (parents/caretakers)

(Assessments 6, 7, 10 and 11 are analysed separately and not presented in this paper.)

T0 measurements were taken with the glasses the child already wore or without glasses if he or she did not wear glasses. Some tests and orthoptic examination were applied additionally to the routine medical treatment.

For this study, the more extended structured anamnesis was performed, which included questions about compliance in wearing glasses, and near visual functions and activities. In addition, the tests for near vision and the measurement of accuracy of accommodation response were administered. Subsequently, the child was randomly assigned to either one of the two treatment groups and in accordance with the assigned group by the randomization, new glasses with full correction of distance refraction error were prescribed, with or without the addition of S + 2.5 for near vision.

T1: After 6 weeks, measurements 1, 2, 3, 4, 5, 6 and 7 were repeated with their new correction.

T2: Six months after the first assessment, follow-up measurements 1, 2, 3, 4, 5 and 6 were taken.

T3: The final assessment, after 1 year, measurements 1, 2, 3, 4, 5, 6, 7, 8 and 10 were taken.

Measurement procedures

The questionnaire [1] included structured questions addressing compliance in wearing glasses, parents' impression on visual functioning of their child.

Ocular alignment [2]: We used cover test and prism bars or Hirschberg light reflex to determine the presence and size of strabismus.

Binocularity and stereopsis [3]: Binocularity was assessed by 15 dioptre prism test. Stereopsis was measured with stereotests (TNO, Titmus Fly test or Lang test).

Visual acuity [4,5]: Visual acuity (at distance and at near) was measured with Lea symbols if possible. If a verbal reaction was not yet possible, Lea symbols were used in a nonverbal way by matching or signing. For those children for whom Lea symbols could not yet be applied, Kay pictures were used. DVA (uncrowded) was typically tested at 5 m distance with Lea linearly arranged cards or Kay pictures. If necessary, this distance could be shortened (minimal testing distance of 2 m). As our study was designed in such a way that measurements were taken at the usual ophthalmological check-ups of a child with DS, DVA was assessed binocularly and if possible monocularly.

Near vision was assessed binocularly at 40 cm with Lea symbols with absolute spacing, crowded and uncrowded (Huurneman et al. 2012b). This distance is more reliable for near vision testing (Huurneman & Boonstra 2016).

In case 40 cm was not feasible and the child insisted to keep the card at a closer distance, the actual distance (range 10–40 cm) was noted for correct calculation of visual acuity (although a shorter distance gives less accurate NVA). In case the child was unable to do both uncrowded and crowded near vision charts, we only tested uncrowded NVA. In some cases, the orthoptists skipped the uncrowded NVA test and only tested the crowded NVA. When the child became uncooperative, testing was stopped according to the Dutch code of conduct relating to expressions of objection by people who are incapable of giving consent, minors or mentally disabled participating in medical research (NVK Code of Conduct in the Netherlands 2001, Code of Conduct in the Netherlands 2002). Reasons for missed data, because of a lack of co-operation or otherwise, were noted.

Accommodation accuracy [6]: To measure the accuracy of the accommodation response, we used the 'modified Nott-method' retinoscopy (Woodhouse et al. 1993; Leat & Gargon 1996; McClelland & Saunders 2003). A small fixating object was kept at a certain close distance, and the child was encouraged to observe that near point target. Meanwhile, the streak retinoscope was moved closer or further away from the child's eyes until a neutral reflex was achieved to assess the distance of the exerted accommodation. The distance of the neutral point determined the exerted accommodation, and so the accommodation response could be calculated. We first started with the fixating object at a distance of 25 cm and in case there was no accommodation lag found at this distance, a second measurement followed at 16.7 cm distance. As this test was not routinely applied by the majority of the participating orthoptists, we first trained the orthoptists in its use. In case of bifocals, accommodation accuracy was measured through the distance portion of the glasses.

Refraction error and ophthalmological examination [8,9]: Measurement of objective refraction error was performed with streak retinoscopy and/or autorefraction in cycloplegia/mydriasis. The ophthalmologist of the clinic performed the ophthalmological examination: slit-lamp examination and retinoscopy to exclude any pathology,

in a consistent way according to chapter C1 (Visual acuity and Ophthalmological deviations in DS) of the guideline of Dutch paediatricians (Borstlap et al. 2011).

Cognitive development [7,10,11]: Cognitive development was assessed with an engaging card sorting game on an iPad (Minnesota Executive Function Scale (Carlson & Zelazo 2014)) and questionnaires for the parents or caretakers (BRIEF-P; Gioia et al. 2003; van der Heijden et al. 2013) or BRIEF (Gioia et al. 2000; Huizinga & Smidts 2009), and the Vineland-S (Sparrow et al. 1993; Scholte et al. 2014).

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS version 23, IBM Inc., Chicago, IL, USA). Absolute and relative frequencies were used in categorical data. Normally distributed numerical data were summarized by their mean and standard deviations (±). Non-normally distributed variables were described with their median and interquartile scores (IQS). Either the chi-squared test or the Fisher exact test (in case of cell frequencies <5) was used to identify differences in proportions. Student's *t*-test or the Mann–Whitney *U*-test was used to compare means or medians, respectively. Pearson's correlation coefficient was used to identify correlations. Two-way ANOVA was applied to detect differences between the intervention groups at the four time-points. The difference between the pre- and post-test was determined as the observed change over time: T0–T1 is the short-term change and T0–T3 is the 1-year change (positive values indicate improvement). ANCOVA (general linear model, GLM) with baseline performance as the covariate was used to analyse the changes between the study groups. Due to the expected inattention and/or lack of co-operation in children with DS, it was not possible to administer all tests on all participants. Only those children in whom the same measurement could be done at T0 and T1 or, respectively, at T0 and T3 were entered in these analyses with ANCOVA. Correction for baseline measurement VA was applied, because changes in VA were significantly correlated with baseline measurements. The observed changes in each of the two groups are not only due to the interventions, but also include the effect of regression to the mean (RTM; the phenomenon that if a variable is extreme on its first measurement, it will tend to be closer to the average on its second measurement, and if it is extreme on its second measurement, it will tend to have been closer to the average on its first; Barnett et al. 2005).The effect of bifocals in comparison with unifocals was therefore calculated as the observed change in the bifocal group minus the observed change in the unifocal group. The per cent regression to the mean (P_{rm}) was estimated from the (partial) correlation between pre- and post-VA ($R_{pre,post}$) in the GLM using: $P_{rm} = 100 (1 - R_{pre,post})$; Trochim 2006). To test whether the correlation between change and baseline VA was in part due to a differential treatment effect (i.e. a greater or smaller treatment effect can be achieved in subjects with greater disease severity; Altman 1991), we used Oldham's method (Oldham 1962). This method is adequate for testing possible differential treatment effects in subgroups that are not selected on the basis of high (or relative low) initial values compared to the population means (Tu et al. 2005; Tu & Gilthorpe 2007). This condition was satisfied in our study; children with DS were not selected on their baseline VA, and the sample proved representative for the general population of children with DS.

For analyses of DVA, monocular DVA of the best eye was selected if binocular DVA was not available. We calculated the spherical equivalent (SER) of the refraction error of the least ametropic eye for analysis of the refraction error. Hyperopia was defined as a spherical equivalent exceeding S + 0.5 'emmetropia' between S − 0.5 and S + 0.5, and myopia was defined as a negative spherical equivalent greater than S − 0.5, including high myopia which was defined as negative spherical equivalent exceeding −6.5 D. Furthermore, we checked for anisometropia with a contralateral myopic eye in the hyperopic and 'emmetropic' children, a so-called reading eye. Astigmatism was defined as cylinder exceeding C-0.75 and classified as with the rule (wtR, horizontal), against the rule (atR, vertical), and oblique astigmatism as axis between 105–165 and 15–75.

Results

Inclusion

During 9 months of total inclusion time, 132 children were recruited. Thirteen of these children had to be excluded. The reasons for exclusion of those children were as follows: no accommodation lag ($n = 9$), insufficient co-operation during testing ($n = 1$), parents objecting to the chance of being assigned to the unifocal group ($n = 2$) or unknown reason ($n = 1$). Of the 119 children (aged 2–16 years) who could be included in our study, 103 (50 boys and 53 girls) returned for the first follow-up visit T1. One child omitted the T1 assessment, but returned for the T2 and T3 assessments. The T1 visit was planned at 6 weeks after the baseline measurement with a maximum delay of 8 weeks (for instance because of unavailability of newly prescribed glasses, illness or family circumstances). In the unifocal group, eight children stopped participating after baseline measurements because parents objected to randomization in the group of unifocals ($n = 5$) or did not respond to repeated reminders and invitations ($n = 2$). One child had to stop at T0 because of early keratoconus. In the bifocal group, a total of seven children did not finish the trial. Parents of two children gave monetary reasons for their withdrawal after repeated reminders, while parents of the other five children gave no explanation. Of the total of 104 participants whom we could re-examine with their new glasses, only one skipped the T1 assessment. Two different children missed the T3 assessment, resulting in 102 children who came for final measurements at T3.

Baseline measurements (T0)

The ocular findings (incidences, means and ranges) in our study population are listed in Table 2. The distribution and kind of refraction errors, strabismus and nystagmus closely match those of the general population of children with DS as have been reported in other studies over the last three decades (see Watt et al. 2015 and Afifi et al. 2013; for review; Table 1). Randomization resulted in groups with no statistically

Table 1. Incidences of ocular findings.

Incidences of ocular findings		
	Present study	**Review**
myopia	15%	12-25%
hyperopia	75%	56-80%
astigmatism	72%	67-74%
strabismus	32%	19-34%
nystagmus	16%	3-33%

Incidences of ocular findings at baseline (T0) in comparison with previously published incidences in reviews (Afifi et al. 2013; Watt et al. 2015).

significant differences in baseline (T0) measurements (Table 2).

Refraction errors

Analysis of frequencies of refraction errors showed that 75% of the children were hyperopic, with a median of S+2.75 not exceeding S+6.5; 15.4% myopic, with a median of S−4.06, ranging to −6.25 (except for one with high myopia of S−11.75 in the bifocal group, and one with high myopia of S−12.13 in the unifocal group; Table 2). Spherical equivalent between S−0.5 and S + 0.5 was found in nine children, but further analysis showed that all of them had an astigmatism over C−0.75. Astigmatism was assessed in 75 (72%) of the participants and was classified as with the rule in 22 (21%) children, against the rule in six (6%) and oblique astigmatism in 47 (45%).

Correction

When they first came for baseline measurements, 13 children in the bifocal group and 15 children in the unifocal group did not wear corrections (Table 2). All children had their refraction errors measured in cycloplegia. They were provided with new prescription for full correction of any refraction error.

Visual acuity

NVA. At baseline measurements, uncrowded NVA was assessed in 70% of the children in the bifocal group (in 31 children using Lea chart and four using Kay picture test) and in 76% in the unifocal group (in 34 children using Lea chart and seven using Kay picture test). NVA testing proved more difficult than DVA testing. NVA testing had to be minimized to just one test (bifocals $n = 32$, unifocals $n = 29$), either uncrowded or crowded, because of short attention span or concentration deficit, or the more engaging Kay picture chart was used instead of the Lea symbols chart. There were no significant differences in uncrowded and crowded NVAs between the two intervention groups (Table 2).

DVA. At baseline, DVA measures were obtained from 88% of the children in the bifocal group (in 41 children with Lea chart and three using Kay picture

Table 2. Baseline group averages (T0).

		Bifocals									Unifocals											
		mean	std dev	median	range min	range max	interq 25	interq 75	n	%	missing	mean	std dev	median	range min	range max	interq 25	interq 75	n	%	missing	p Value	Test statistic
T0	**T0**																						
	N = 104								50										54				
	male								25	50	0								26	48	0	0.850 †	$X^2(1) = 0.036$
	age (years)	7.68	3.21	9.00	1	12			50		0	8.57	3.74	8.50	3	13			54		0	0.219 ‡	$t(102) = -1.237$
	mainstream school education								11		7								19		6	0.332 †	$X^2(2) = 2.207$
	nystagmus								5	10	1								12	22	0	0.151 †	$X^2(2) = 3.781$
	strabismus								13	26	0								20	37	0	0.227 †	$X^2(1) = 1.460$
	wearing habitual glasses								33	66	8								36	66	13	0.295 †	$X^2(4) = 4.925$
	no glasses								13	26	0								15	28	0	0.838 †	$X^2(1) = 0.042$
	SER of habitual glasses of least ametropic eye	1.11	2.61	1.31	−8.50	6.50	0.00	2.91	50		0	0.72	2.52	0.13	−7.13	5.25	0.00	2.56	54		0	0.448 ‡	$t(102) = 0.762$
	Visual acuity (LogMar) with habitual correction																						
	uncrowded NVA	0.58	0.34	0.52	0.00	1.40	0.30	0.82	35		15	0.55	0.31	0.52	0.00	1.22	0.30	0.70	41		13	0.699 ‡	$t(74) = 0.388$
	crowded NVA	0.64	0.31	0.64	0.10	1.22	0.43	0.92	23		27	0.65	0.28	0.62	0.18	1.30	0.42	0.85	22		32	0.941 ‡	$t(43) = -0.075$
	DVA	0.43	0.27	0.40	−0.30	1.10	0.28	0.60	44		6	0.44	0.26	0.40	−0.80	1.52	0.28	0.51	47		7	0.920 ‡	$t(89) = -0.100$
	Accommodation lag (dioptres) at 25cm with habitual correction	2.17	0.91	2.00	0.70	4.00	1.50	3.00	44		6	2.25	0.88	2.10	0.30	4.00	1.50	3.00	50		4	0.673 ‡	$t(92) = -0.423$
	Refraction in cycloplegia: SER (in dioptres) of the least ametropic eye																						
	SER of the least ametropic eye	1.68	3.28	2.25	−11.75	6.50	1.00	3.78	50		0	1.32	3.14	1.75	−12.13	5.25	0.44	3.75	54		0	0.579 ‡	$t(102) = 0.572$
	Hyperopia SER> S+0.5	3.14	1.35	2.75	1.25	6.50	2.09	4.16	38	76	0	2.67	1.41	2.69	0.63	5.25	1.31	3.88	40	74	0	0.141 ‡	$t(76) = 1.529$
	SER (S−0.5 to S+0.5)								3	6	0								7	13	0	0.417 †	$X^2(2) = 0.958$
	SER (S−0.5 to S+0.5) without astigmatism								0		0								0		0		
	Myopia SER < S−0.5	−3.93	3.33	−4.00	−11.75	−0.88	−4.75	−1.38	9	18	0	−5.05	3.50	−4.13	−12.13	−1.13	−6.25	−3.00	7	13	0	0.523 ‡	$t(14) = 0.654$
	Astigmatism < C−0.75	−1.79	0.70	−1.75	−3.50	−1.00	−2.00	−1.25	35	70	0	−1.95	1.08	−1.75	−4.50	−1.00	−2.56	−1.00	40	74	0	0.442 ‡	$t(73) = 0.774$
	Axis																					0.759 †	$X^2(2) = 0.552$
	with the rule								9		0								13		0		
	against the rule								3		0								3		0		
	oblique (105-165) or (15-75)								23		0								24		0		
	SER change in new prescription	0.57	1.45	0.50	−3.35	4.13	−0.13	1.53	50		0	0.60	1.30	0.69	−5.00	3.88	0.00	1.25	54		0	0.931 ‡	$t(102) = -0.087$
	SER change in hyperopic new prescription	1.13	1.09	0.94	−0.25	4.13	0.22	1.85	38		0	0.97	0.92	1.00	−0.38	3.88	0.25	1.50	40		0	0.413 ‡	$t(76) = 0.683$
	SER change in myopic new prescription	−1.46	0.90	−1.13	−3.25	−0.37	−2.19	−0.94	9		0	−1.37	1.95	−0.25	−5.00	0.00	−3.00	0.00	7		0	0.401 ‡	$t(14) = -0.119$

% = per cent of children in that group; DVA = distance visual acuity; Interq = interquartile; Max = maximum; Min = minimum; NVA = near visual acuity; SER = spherical equivalent of refraction error; Std dev = standard deviation.

† χ^2 test.

‡ Student's *t*-test.

test) and 87% of the children in the unifocal group (in 40 children using Lea chart and seven using Kay picture test). There was no significant difference in DVA scores between the two intervention groups (Table 2).

Accommodation response

The accommodation lag at 25 cm distance measured through the distance-correcting unifocals, or the distance-correcting top section of the bifocals could be quantified in 94 (87%) children. The average lag was 2.21 ± 0.89 dioptres with no significant difference between the intervention groups (Table 2).

Follow-up measurements

The differences between the two intervention groups were analysed at T1, T2 and T3 with two-way ANOVA and subsequent *t*-tests (Table 3). Then, the observed changes over time (short-term change: T0–T1 and 1-year change: T0–T3) were analysed with ANCOVA. The observed change was defined as the difference between the pre- and post-test of each subject.

Near visual acuity

The average NVAs of the two treatment groups at T1, T2 and T3 are summarized in Table 3 and Fig. 2. Two-way ANOVAs indicated significant differences in uncrowded NVA between the two interventions (F = 4.893, p = 0.028) and between the four time-points (F = 6.830, p < 0.001; Fig. 2A). A significant difference was also observed for the crowded NVA between the four time-points (F = 2.719, p = 0.045; Fig. 2B).

Post hoc *t*-tests of the average NVA at the four assessment time-points indicated that the average uncrowded NVA and the average crowded NVA were not significantly different between the two interventions at T0, T1 and T2. However, at T3, after the 1-year follow-up, the average uncrowded NVA as well as the crowded NVA was significantly better in the bifocal group compared with the unifocal group (mean difference in uncrowded NVA: 0.14 [SEM: 0.49], and in crowded NVA: 0.14 [SEM: 0.05]).

As expected for our study population, there was considerable variability between children within each group, a variability that was already present at baseline. To better account for this large variability between subjects, we have analysed the changes by comparing the measurements at the different time-points within subjects adjusting for baseline VA. The resulting baseline-adjusted mean changes are displayed in Table 4, Fig. 3C,D. The number of children for whom changes could be determined varied between time-points

Table 3. Group averages at first assessment with newly prescribed glasses (T1); second assessment with new glasses (T2) and final assessment (T3).

		Bifocals									Unifocals										
		mean	std dev	median	range min	range max	interq 25	interq 75	n	missing	mean	std dev	median	range min	range max	interq 25	interq 75	n	missing	p Value	Test statistic
T1	T1																				
	N=103								50	0								53			
	Visual acuity (LogMar) with newly prescribed glasses																				
	uncrowded NVA	0.41	0.31	0.40	−0.12	1.05	0.18	0.63	36	14	0.51	0.37	0.40	0.00	1.70	0.26	0.60	37	17	0.213 ‡	t(71) = −1.258
	crowded NVA	0.49	0.30	0.46	0.00	1.15	0.30	0.70	28	22	0.57	0.35	0.50	0.18	1.30	0.30	0.88	24	30	0.377 ‡	t(50) = −0.891
	DVA	0.38	0.22	0.30	0.08	1.22	0.20	0.50	44	6	0.43	0.23	0.39	0.08	1.22	0.28	0.59	47	7	0.348 ‡	t(89) = −0.943
	Accommodation lag (dioptres)at 25cm through distance segment of bifocals, or through unifocals	1.74	0.99	1.50	0.50	4.00	1.00	2.00	39	11	2.00	1.05	2.00	0.50	4.00	1.00	2.60	40	14	0.313 ‡	t(79) = −1.015
T2	T2																				
	N=96								48	2								48	6		
	Visual acuity (LogMar) with newly prescribed glasses																				
	uncrowded NVA	0.40	0.29	0.30	0.00	1.30	0.18	0.62	34	16	0.48	0.29	0.43	0.00	1.30	0.30	0.60	40	14	0.187 ‡	t(72) = −1.332
	crowded NVA	0.51	0.29	0.46	0.00	1.30	0.30	0.68	32	18	0.55	0.31	0.52	0.10	1.30	0.30	0.81	33	21	0.632 ‡	t(63) = −0.481
	DVA	0.38	0.25	0.28	−0.10	1.10	0.20	0.55	41	9	0.36	0.21	0.39	−0.30	0.89	0.28	0.48	43	11	0.789 ‡	t(82) = 0.269
	Accommodation lag (dioptres) at 25cm through distance segment of bifocals, or through unifocals	1.79	0.88	2.00	0.00	4.00	1.00	2.00	33	17	1.94	0.95	2.00	0.25	4.00	1.50	2.50	40	14	0.499 ‡	t(71) = −0,680
T3	T3																				
	N=102								50	0								52	2		
	Visual acuity (LogMar) with newly prescribed glasses																				
	uncrowded NVA	0.29	0.20	0.30	−0.08	0.74	0.12	0.40	43	7	0.42	0.26	0.40	0.03	1.40	0.27	0.54	45	9	0.006 ‡	t(86) = −2.796
	crowded NVA	0.42	0.25	0.40	0.00	1.05	0.24	0.52	40	10	0.56	0.24	0.52	0.10	1.10	0.40	0.78	40	14	0.010 ‡	t(78) = −2.641
	DVA	0.39	0.24	0.39	−0.02	1.10	0.18	0.51	47	3	0.36	0.17	0.39	−0.20	0.82	0.28	0.48	44	10	0.577 ‡	t(89) = 0.560
	Accommodation lag (dioptres) at 25cm through distance segment of bifocals, or through unifocals	2.10	1.10	2.00	0.50	4.00	1.00	3.00	35	15	1.99	0.88	2.00	0.50	4.00	1.40	2.75	37	17	0.570 ‡	t(70) = −0570

DVA = distance visual acuity; Interq = interquartile; Max = maximum; Min = minimum; NVA = near visual acuity; SER = spherical equivalent of refraction error; Std dev = standard deviation.
‡ Student's *t*-test.

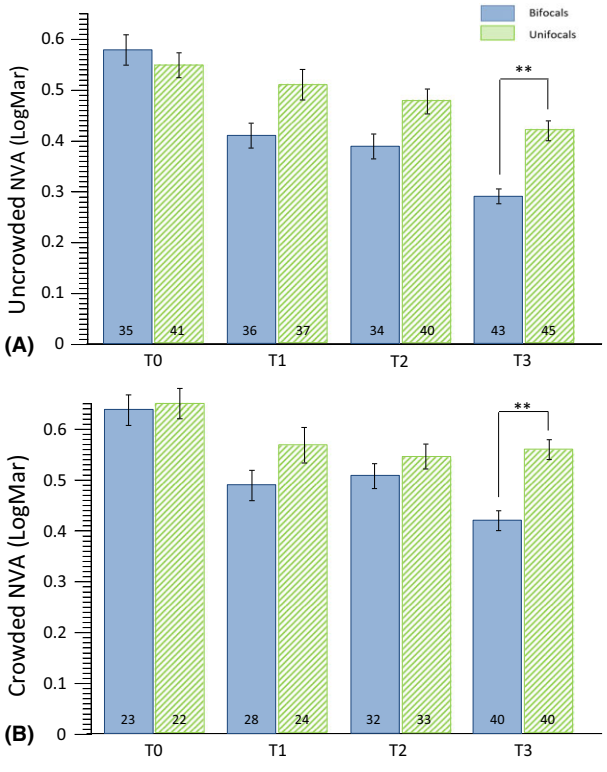

Fig. 2. (A and B) Group averages of uncrowded NVA (A) and crowded NVA (B) in the bifocal and unifocal group at baseline (T0); first assessment with newly prescribed glasses (T1); second assessment with the new glasses (T2); final assessment (T3). Significance of differences between the intervention groups is indicated above the bars. **Student's *t*-test $p < 0.01$. The number in each bar represents the number of children measured in that group at that time-point. NVA = near visual acuity; SEM = standard error of the mean. Whiskers indicate ±1 SEM.

and acuity measure because not all visual acuity measures could be collected at all time-points. This was primarily due to the limited attention span of the children. We omitted the within-subject analysis for T0–T2 because of the limited number of participants for whom the crowded and uncrowded NVA could be determined at both of these time-points. As illustrated in Fig. 3A,B, we found that the changes depended significantly on the subjects' baseline scores. Partial correlation coefficients of the change (T0–T3) with the corresponding baseline measure (DVA, uncrowded NVA or crowded NVA) ranged from $R = 0.759$ to $R = 0.509$, all with p-values ≤0.037. By contrast, the partial correlation of the pre–post change in VA with age was weak and not statistically significant ($-0.447 \leq R \leq 0.214$, $p \geq 0.072$). Therefore, our analysis of the within-subject changes only included the T0 baseline measurement as covariate.

Note that the significantly positive correlations with baseline could be due to RTM, a notorious epiphenomenon induced by measurement error and test–retest variability, as well as a true dependence of the treatment effects on baseline VA. In our study, it is quite likely that RTM had a substantial influence on the measured changes because a high within-subject variability can be expected in children with DS due to their large fluctuations in attention and performance (although this was not explicitly quantified in our study). Indeed, the percentage of RTM estimated from the correlation between T0 and T3 measurements (Trochim 2006) was 61.5% for uncrowded NVA and 59.1% for crowded NVA (partial correlation coefficients, uncrowded NVA: $R_{\text{final,baseline}} = 0.385$, crowded NVA: $R_{\text{final,baseline}} = 0.409$). It is also plausible that the children with truly low and truly high baseline VAs respond differently to the treatment (i.e. differential treatment effect) as there is less room for improvement in children with high VAs (ceiling effect) and as baseline VA might be a proxy for the developmental age of a child. Following Oldham's method to analyse the possible differential treatment effect (Oldham 1962), we found that the changes from T0 to T3 were significantly correlated with the average of the two values for uncrowded NVA ($R_{\text{change, average baseline and final}} = 0.378$, $t(68) = 3.317$, $p = 0.001$). This indicates that treatment effects of uncrowded NVA increased significantly with decreasing baseline performance. In contrast, there was no evidence that treatment effects on crowded NVA truly depend on baseline ($R_{\text{change, average baseline and final}} = 0.239$, $t(40) = 1.518$, $p = 0.137$).

In the following sections, we concentrate on the average changes reflected in the offsets of the regression lines.

T0 to T1, short-term change in NVA

The difference between the changes of uncrowded NVA in the two treatments groups was only 0.088 [SEM: 0.061] LogMar (ANCOVA, $F(59) = 2.115$, $p = 0.151$), indicating an equally strong change in the bifocal group compared with the change in the unifocal group (i.e. change due to RTM and any change due to the treatment with unifocals; Table 4, Fig. 3C,D).

The difference between the short-term changes of crowded NVA in the two intervention groups was also not significant (0.066 [SEM: 0.100] LogMar; ANCOVA, $F(36) = 0.441$, $p = 0.511$).

T0 to T3, 1-year change in NVA

The difference between the changes in uncrowded NVA in the two treatment groups was 0.095 [SEM: 0.047] LogMar (ANCOVA, $F(66) = 4.180$, $p = 0.045$), indicating a statistically significant difference in uncrowded NVA between the two treatment effects after 1 year.

The difference in crowded NVA between the intervention groups was 0.168 [SEM: 0.068] LogMar. Bifocals show a significantly larger improvement in crowded NVA (ANCOVA, $F(38) = 6.194$, $p = 0.017$).

We checked the comparability of the smaller groups in which the within-subject analyses of NVA (uncrowded and crowded) could be determined. These were the limited number of children in whom the same measurement of VA could be collected at both points in time. We found no statistically significant differences in baseline group averages between these subgroups. We checked on baseline measurements of: gender, age, nystagmus, wearing glasses

Table 4. Group averages of those children in whom changes could be calculated, that is the children in whom the same visual acuity measure could be obtained at two points in time. A: short-term changes computed as the within-subject differences between T0–T1 and B: changes after 1-year follow-up obtained from the difference between T0 and T3 measurements. Differences in changes between the unifocal and bifocal group were determined with ANCOVA. Positive values indicate improvement.

T1: Within subject comparison of VA's (LogMar)

	Group average T0		Group average T1		Changes (paired difference T0-T1)		Intervention difference		
Visual Acuity	bifocals	unifocals	bifocals	unifocals	bifocals	unifocals	offset	P value	Test statistic
	n = 29	*n = 33*	*n = 29*	*n = 33*	*n = 29*	*n = 33*			
uncrowded NVA	0.60 (0.36)	0.57 (0.30)	0.42 (0.30)	0.49 90.32)	0.18 (0.33)	0.09 (0.19)	0.088 [0.061]	0.151 §	F = 2.115
	n = 21	*n = 18*	*n = 21*	*n = 18*	*n = 21*	*n = 18*			
crowded NVA	0.63 (0.32)	0.65 (0.30)	0.49 (0.32)	0.57 (0.36)	0.13 (0.36)	0.08 (0.33)	0.066 [0.100]	0.511 §	F = 0.441
	n = 42	*n = 44*	*n = 42*	*n = 44*	*n = 42*	*n = 44*			
DVA	0.44 (0.24)	0.44 (0.27)	0.39 (0.22)	0.40 (0.20)	0.05 (0.18)	0.04 (0.19)	0.012 [0.033]	0.721 §	F = 0.128

T3: Within subject comparison of VA's (LogMar)

	Group averages T0		Group averages T3		Changes (paired difference T0-T3)		Intervention difference		
Visual Acuity	bifocals	unifocals	bifocals	unifocals	bifocals	unifocals	offset	P value	Test statistic
	n = 33	*n = 36*	*n = 33*	*n = 36*	*n = 33*	*n = 36*			
uncrowded NVA	0.55 (0.33)	0.53 (0.28)	0.32 (0.19)	0.41 (0.22)	0.23 (0.29)	0.12 (0.30)	0.095 [0.047]	0.045 §	F = 4.180
	n = 21	*n = 20*	*n = 21*	*n = 20*	*n = 21*	*n = 20*			
crowded NVA	0.66 (0.31)	0.68 (0.27)	0.35 (0.23)	0.53 (0.24)	0.31 (0.28)	0.16 (0.30)	0.168 [0.068]	0.017 §	F = 6.194
	n = 43	*n = 42*	*n = 43*	*n = 42*	*n = 43*	*n = 42*			
DVA	0.45 (0.24)	0.43 (0.27)	0.38 (0.24)	0.35 (0.17)	0.07 (0.21)	0.08 (0.22)	0.021 [0.037]	0.565 §	F = 0.334

() = standard deviation; [] = standard error of the mean; § = ANCOVA with baseline as covariate; DVA = distance visual acuity; NVA = near visual acuity; VA = visual acuity.

before the present study, SER, change in SER from habitual glasses to the new prescriptions at T0, strabismus, accommodation lag, uncrowded NVA, crowded NVA, DVA, hypermetropia, myopia and astigmatism (Student's *t*-tests, all $p > 0.128$, chi-squared tests, all $p > 0.146$).

Distance visual acuity

The average DVAs at T1, T2 and T3 are summarized in Table 3 and Fig. 4. Two-way ANOVA indicated neither significant differences in DVA between the two interventions ($F(1) = 0.015$, $p = 0.902$) nor between the four time-points ($F(3) = 1.402$, $p = 0.242$) with no Group x Time-point interaction ($F(3) = 0.388$, $p = 0.762$; Fig. 4).

We measured and analysed DVA as well to test whether the near addition to improve NVA is to the detriment of DVA. Also for the change in DVA, a significant correlation with baseline DVA was found ($R = 0.614$, $p < 0.001$). This correlation resulted from 41.2% RTM (Trochim 2006; partial correlation coefficient DVA: $R_{final,baseline} = 0.588$). There was also evidence for a differential treatment effect (Oldham 1962; partial correlation coefficient, $R_{change,\ average\ baseline\ and\ final\ DVA} = 0.238$, $t(84) = 2.215$, $p = 0.030$). For this analysis, we excluded one child from the bifocals group because the baseline DVA of this child proved implausibly good (−0.30 LogMar; cross Fig. 5A) in view of his NVA (0.22 LogMar) at T0 and DVAs at later time-points, presumably due to measurement inaccuracy or a clerical error. The child in the unifocal group with an exceptionally poor baseline DVA of 1.52 LogMar, on the other hand, was not excluded because this 3-year-old child had an uncorrected hyperopia of S + 4.00 and accommodation lag of three dioptres at T0, and showed a plausible development in VA after receiving unifocals with full correction of refraction error. The overall result with or without either one of these outliers remained the same: no significant difference in change in DVA between the two treatment groups.

T0 to T1 change in DVA

The difference in the within-subject change in DVA between the groups, 0.012 [SEM: 0.033] LogMar, was not statistically significant (ANCOVA, $F(83) = 0.128$, $p = 0.721$; Table 4, Fig. 5).

T0 to T3 change in DVA

We also found no significant difference in change in DVA between the groups, 0.021 [SEM: 0.037] LogMar (ANCOVA, $F(82) = 0.334$, $p = 0.565$).

Accommodation response

At T1, when the children wore their newly updated and full distance correction, all showed an accommodation lag through the distance correction or

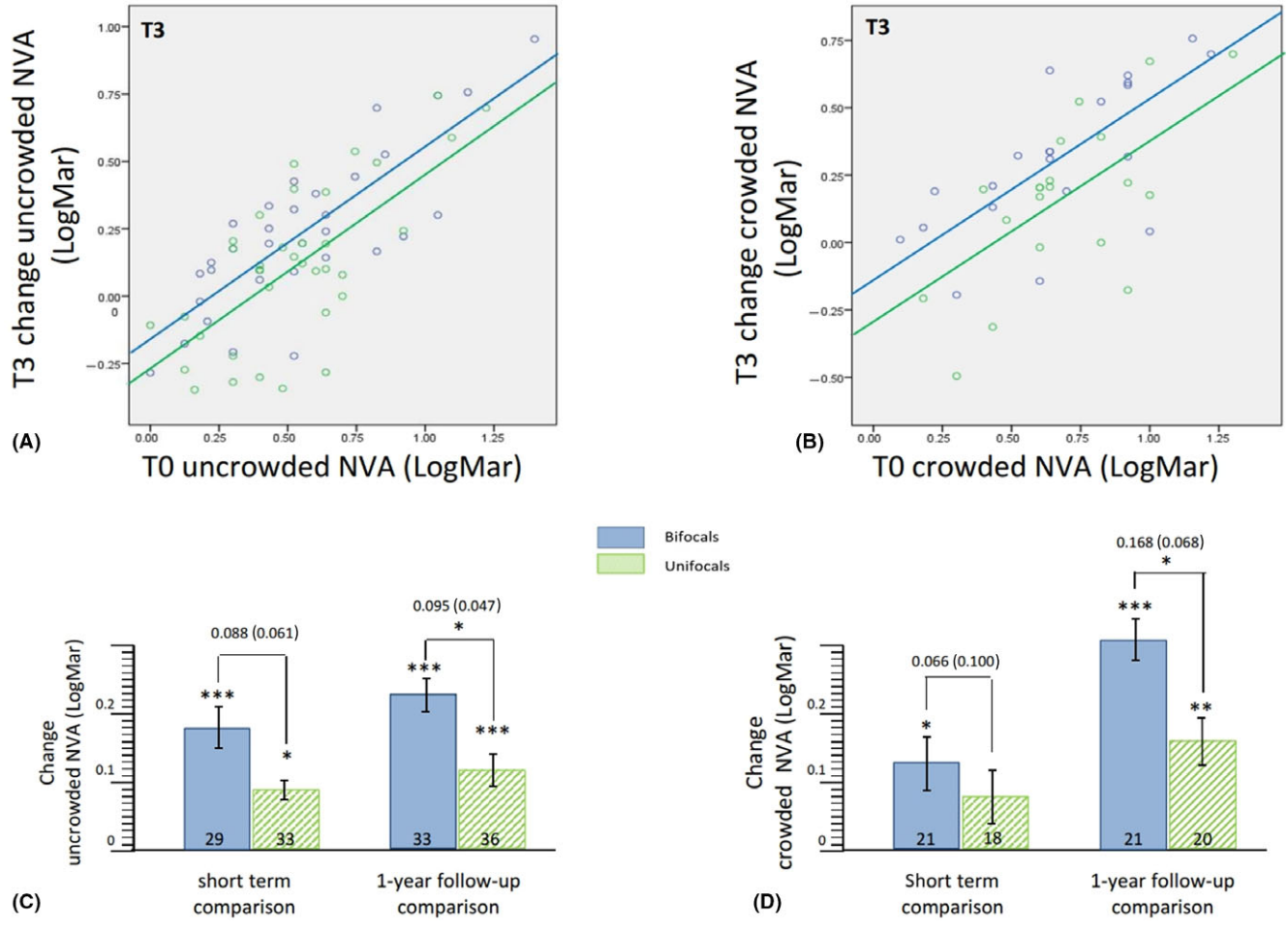

Fig. 3. (A and B) Scatterplots of the 1-year change (i.e. the within-subject difference between T0 and T3) as a function of baseline performance (T0) for uncrowded near visual acuity (A) and crowded near visual acuity (B) in the two treatment groups. Positive values indicate improvement. Solid lines are regression lines through the data. Regression line equations uncrowded NVA, bifocals $Y = -0.173 + 0.734 \times x$, unifocals $Y = -0.268 + 0.734 \times x$; Regression line equations crowded NVA, bifocals $Y = -0.135 + 0.673 \times x$, unifocals $Y = -0.303 + 0.673 \times x$. Note that the change depended significantly on the baseline scores (Partial correlation: uncrowded NVA $R = 0.685$, $p < 0.001$; crowded NVA $R = 0.626$, $p < 0.001$): children with high acuity thresholds at baseline tend to have large positive changes while children with low thresholds at baseline tend to have lower or even negative changes. This positive correlation may represent differential treatment effects for the different baseline levels (uncrowded NVA: $p = 0.001$, crowded NVA: $p = 0.137$), but also includes the effect of regression to the mean (RTM). (C and D) Average short term (T0–T1) and 1-year follow-up (T0–T3) changes in the two treatment groups. The number in each bar represents the number of children in that intervention group for whom the change could be calculated. Comparison of the changes between the two treatment groups, as quantified by the offset difference between the two parallel regression lines, is indicated above the bars. Note, significantly improved acuities at T1 and T3. Bifocals produced the largest benefit in uncrowded and crowded NVA at T3. NVA = near visual acuity. Asterisks indicate significant differences analysed with ANCOVA using baseline as covariate: *Significance $p < 0.05$; **Significance $p < 0.01$; ***Significance $p < 0.001$; SEM = standard error of the mean; [] = SEM; Whiskers indicate ±1 SEM.

distance part of bifocals (Table 3). The average accommodation lag at 25 cm distance through the distance part of the bifocals and the distance-correcting unifocals showed no significant difference at T1, T2 and T3. The within-subject changes in accommodation accuracy through distance correction in their glasses were also not significantly different between the two interventions (T1–T0: −0.038 [SEM: 0.219] dioptres; ANCOVA, $F(74) = 0.030$, $p = 0.862$, and T3–T0: 0.253 [SEM: 0.220] dioptres; ANCOVA, $F(67) = 1.325$, $p = 0.254$).

Discussion

This multicentre randomized controlled trial compared the effect of bifocals to unifocals in children with DS. We could include an extended age range and refraction error range in children with DS compared to the existing studies on prescribing bifocals to children with DS (Stewart et al. 2005; Al-Bagdady et al. 2009; Nandakumar & Leat 2009). After the 1-year follow-up, we found a larger improvement in uncrowded NVA as well as in crowded NVA with bifocals compared with unifocals. In contrast, at the short term, this was just after starting to wear the newly prescribed glasses, we found no difference between the two interventions in either NVA measures; NVAs improved equally. Accommodation response showed no change in either intervention group, neither at the short term nor after 1-year follow-up.

Strengths

Strengths of our study compared to previous studies (Stewart et al. 2005;

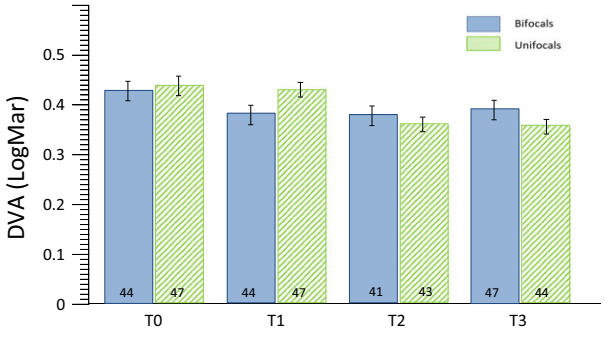

Fig. 4. Group averages DVA in the bifocal and unifocal group at baseline (T0); first assessment with newly prescribed glasses (T1); second assessment with the new glasses (T2); final assessment (T3). The number in each bar represents the number of children measured in that group at that time-point. DVA = distance visual acuity; SEM = Standard error of the mean; Whiskers indicate ± 1 SEM.

Al-Bagdady et al. 2009; Nandakumar & Leat 2009, 2010; Nandakumar et al. 2011) are the representation of the general population of children with DS, prospective study design, randomized treatment groups with no significant differences at baseline, the analyses taking into account the statistical phenomenon of RTM, the number of participating locations, the number of participants, the follow-up of 1 year, the few participants lost to follow-up and the various aspects of VA assessed. The wide geographical spread of the participating locations including rural as well as urban areas of the Netherlands resulted in participants from all social communities and school levels. The widespread of locations, the wide inclusion criteria and very few exclusion criteria contributed to include a representative sample of the general population of children with DS. The co-operation with a large number of organizations involved in health care of children with DS enabled us to reach that large number of families with a child with DS, and contributed to the number of included children. In previous studies by Nandakumar (Nandakumar & Leat 2009, 2010; Nandakumar et al. 2011) on VA with bifocals in children with DS (n = 12, age 8–18), only a selective group of children was included from the surroundings of Waterloo, Canada. Only children who could do some reading and other academic pursuits were enrolled in that longitudinal cohort study, and were followed up for 5 months with single vision glasses, and subsequently for 6 months with bifocals. Further strengths of our study include the highly motivated orthoptists of the participating locations, resulting in very few children being lost at the follow-up stages. Due to the follow-up time of 1 year, we were able to monitor the development of VA in contrast to only concentrating on the instant improvement of VA induced by correction of refraction error. Moreover, we measured VA at different distances, DVA and NVA, and differentiated NVA in uncrowded NVA and crowded NVA in contrast to previous studies (Stewart et al. 2005; Al-Bagdady et al. 2009) on the effects of bifocals that studied accommodation accuracy in children with bifocals. This resulted in new insights into the development of VA in children with DS with accommodation lags. A very important strength of our study is that we ruled out the effect of RTM, in the choice of our study design (random allocation in control group) and the choice of our analysis (adjusting for baseline), before any other explanation for the observed change was sought. It is important to rule out the effect of RTM as RTM may affect clinical trial data interpretation when the outcome measure has high variability (Pocock et al. 2016). The statistical phenomenon RTM occurs when repeated measures are made on the same subject. It happens because values are observed with random error (i.e. random measurement error and/or random fluctuations in a subject; Barnett et al. 2005). Thus, notwithstanding the large inter- and intrasubject variation in performance in children with DS, we were able to distinguish the real effect of bifocals because we could compare the observed change over time in the bifocal group to the randomly allocated unifocal group. This comparison was possible as the unifocal group represented the change over time due to RTM plus the change over time as a result of children getting older and more practised with the techniques, plus the change over time due to the treatment with full correction of refraction error including the effect of baseline NVA.

Limitations

The recommended multiple baseline measurements (Pocock et al. 2016) to reduce some of the variance in baseline measure were not feasible in the children with DS. While administering the tests for our study, we encountered the expected difficulties in children's co-operation reported by other authors (Courage et al. 1994, 1997; Woodhouse et al. 1996; McCullough et al. 2014; Doyle et al. 2016, 2017), and the described fluctuations in attention and concentration of the participants due to their cognitive delay. This resulted in missing data and relatively large variations within and between subjects. As a consequence of these missing data, we had a limited number of children in whom the required measurements could be collected. This was an unavoidable limitation of our study. We coped with this limitation by carefully selecting appropriate analytic tools (keeping in mind the effect of RTM), analysing short-term (T0–T1) and 1-year (T0–T3) changes separately in the limited numbers of children in whom we could collect these measurements. For these analyses, we checked statistical differences at baseline characteristics between these subgroups. Nevertheless, we could compare outcome measures in NVA for a considerable number (±50%) of children in treatment groups with no statistically significant differences at baseline characteristics. The noted large variations within the children were manageable by taking into account the biasing effect of RTM. By doing this, we could determine the additional effect of bifocals by analysing the difference between the observed changes in the bifocal group compared to the observed change in the unifocal group in an ANCOVA adjusted for baseline VA. Except for the change in crowded NVA, we found evidence that children with truly low and truly high baseline VAs may respond differently to the treatment.

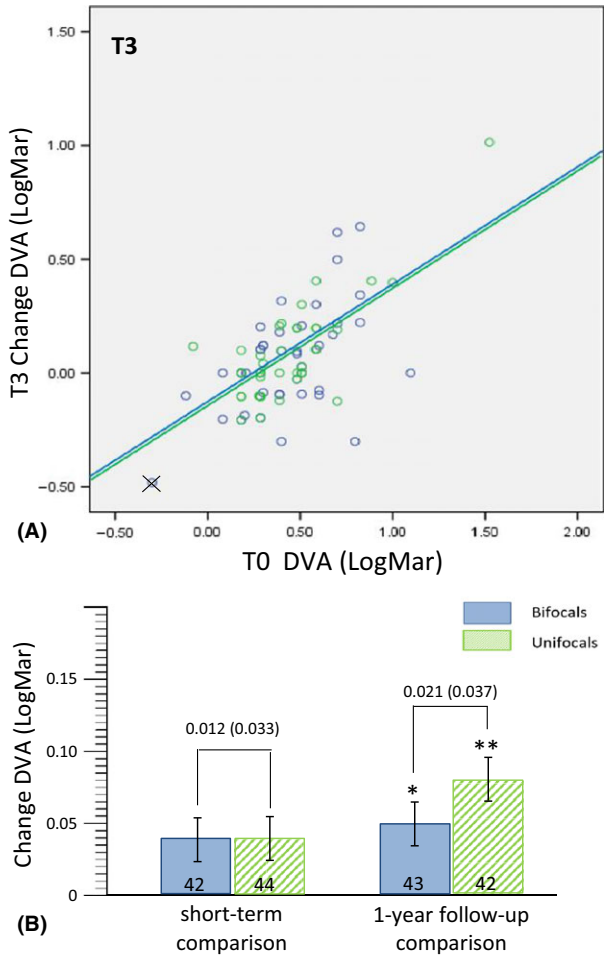

Fig. 5. (A) Scatterplot of the 1-year change (i.e. the within-subject difference between T0 and T3) as a function of baseline performance (T0) for DVA in the two treatment groups. Positive values indicate improvement. Solid lines are regression lines through the data. Regression line equation DVA, bifocals $Y = -0.124 + 0.517 \times x$, unifocals $Y = -0.146 + 0.517 \times x$. Note the change depended significantly on the baseline scores (partial correlation $R = -0.614$, $p < 0.001$): children with the higher thresholds at baseline showed the larger positive changes while children with the lower thresholds at baseline showed lower or even negative changes. This positive correlation represents differential treatment effects for the different baseline levels ($p = 0.03$), but also includes the effect of regression to the mean (RTM). B: Average short-term (T0–T3) and 1-year follow-up (T0–T3) changes in DVA in the two treatment groups. The number in each bar represents the number of children in that intervention group for whom the change could be calculated. Comparison of the changes between the two treatment groups, as quantified by the offset difference between the two parallel regression lines, is indicated at the top. DVA = distance visual acuity. Asterisks indicate significant differences analysed with ANCOVA using baseline as covariate: *Significance $p < 0.05$; **Significance $p < 0.01$; ***Significance $p < 0.001$. SEM = Standard error of the mean; [] = SEM. Whiskers indicate ±1 SEM.

As a consequence of combining routine VA check-up with the data collection for our RCT, some limitations, such as the lack of assessment of binocular DVA (which best represents VA in daily life) in all children at all visits, may have been introduced. In routine check-ups, DVA is first measured (preferably monocularly, and only when necessary binocularly) and thereafter the extra NVA tests for our study were applied. We chose to avoid additional assessments of DVA and preserve the children's energy for more detailed (uncrowded and crowded) assessments of NVA, our main outcome measure. However, this order may have resulted in limited co-operation in NVA assessments.

Further limitations included the deviations from the protocol, specifically the variation in applied VA charts, which may have created possible bias in comparisons with pre- and post-test VA as Kay picture chart may be easier resulting in relatively higher assessed VA than assessed with Lea symbols. In a few children, the charts were applied in a random order Kay picture pre-test and then Lea symbols post-test or contrariwise. But the number of children in which this occurred in NVA was limited (bifocals $n = 2$ and unifocals $n = 3$). We expect no bias in the final results towards more improvement in the bifocal group, because in the bifocal group one child had Kay pictures first and the other one had Lea symbols first; in the unifocal group, all three children had Kay pictures first. The variety in applied testing distance of NVA (mean 27 ± 10 cm, range 10–40 cm) showed no difference between the groups at any time-point. This deviation of the prescribed testing distance had to be applied as children with DS, who have relatively short arms, often use a closer working distance. We managed this variety by calculating the NVA by the ratio of distance and M-size of the acuity optotypes. Further, we chose S + 2.50 add which focuses the eyes at 40 cm with no accommodative effort. So, in effect, we were assessing NVA at the minimum limit of the effect of bifocal addition for those children assessed at 40 cm. Children who preferred to shorten the distance, inducing the need of accommodation, did so by their own choice. Additional deviations from the protocol include the postponed T1 visits, running out of the time frame maximally 8 weeks, and the omitted T2 assessments (bifocals $n = 2$, unifocals $n = 6$). These did not influence the results because these children were monitored in the same time intervals from the postponed or omitted visit on.

Covariates

We considered correcting for 'age', as this is usual in studies with children, but this was not applied in our analyses because none of the changes (DVA, uncrowded NVA, crowded NVA) were significantly correlated with calendar age ($-0.109 \leq R \leq -0.003$, $p \geq 0.449$). We also verified this using multiple linear regression analysis: after entering the variables 'age' and 'baseline measurement' together in the model, 'age' was not independently associated with VA with full correction of refraction error ($p > 0.088$ for all 'age' coefficients). This result could mean that calendar age does not represent the developmental level of the visual system in children with DS (as it does in

children without DS) because of the wide range of cognitive impairment levels in children with DS in combination with cerebral visual impairment (CVI). One could consider correcting for the children's developmental age, but this is easier said than done; to our knowledge, there is no unequivocal measure for developmental age in DS. We believe, however, that baseline VA already includes the developmental level of a child's visual system. As a result, our ANCOVAs with baseline as covariate may have implicitly corrected for developmental age.

As the regression lines obtained with these ANCOVAs pass through zero within the range of observed VAs (Figs 3A,B and 5A), and as further analyses indicated that both uncrowded NVA and DVA truly depend on baseline VA, it is possible that an individual child who already has a reasonably good VA (as inferred from repeated assessments) does not benefit from either intervention (bifocals or unifocals with full correction). The markedly fluctuating visual performance of children with DS makes it difficult to determine the precise VA cut-off points at which the interventions are no longer beneficial. However, our present analyses support the conclusion that likelihood of improvement in NVA will always be greater with bifocals than with unifocals. Further research is needed to evaluate the effects of the two treatments beyond their effects on VA.

Association of DS with CVI

The association of DS with CVI has been reported (Courage et al. 1994; Woodhouse et al. 1996; Little et al. 2009a) before; and Bosch (Bosch et al. 2014) recently confirmed the association of trisomy 21 with CVI in the study of chromosomal aberrations in CVI. All patients with chromosomal aberration in their cohort of children with CVI were intellectually disabled. CVI has been defined as damage to, or malfunctioning of, the retrochiasmatic visual pathways (optic radiations, occipital cortex, associative visual areas) in the absence of damage to the anterior visual pathways or any major disease (Dutton & Jacobsen 2001; Hoyt 2013). The frequent clinical ocular manifestations found in our study are also in line with findings in children with central nervous system abnormalities with CVI, found by Fazzi et al. (2007). They found that refraction errors occur in more than 75%: most frequently hypermetropia, isolated or associated with astigmatism, and less frequently myopia. In their study, reduced VA was prevalent and often associated with reduced contrast sensitivity (Fazzi et al. 2007). Other common findings found were as follows: strabismus (most frequently esotropia with angle variability); the absence of stereopsis; and nystagmus in 25% (Fazzi et al. 2007). Similarly, the other manifestations that we found, such as poor accommodation and crowding, have been reported in studies (Boot et al. 2010; Hoyt 2013) in children with CVI. Furthermore, the peculiar behavioural signs that we noted were also described (Hoyt 2013) in children with CVI: short visual attention span; markedly fluctuating visual performances; and the need for time, environmental stability, and repetition of items to obtain the best response.

Accommodation

Although previous authors (Al-Bagdady et al. 2009) have reported that the accommodation accuracy through the distance portion of the lens improves after wearing bifocals, we did not find any influence at all on accommodation accuracy through that part of the bifocal. In fact, we found no change in accommodation accuracy through the distance correction in either intervention group. These findings agree with the results of the Nandakumar study (2010), in which there was also no improvement in accommodation ability through the distance part of the lens. Part of the mechanism of accommodation is cortically organized (Braddick & Atkinson 2011), and recent findings indicate that it is impaired in children with DS like it is in CVI (Boot et al. 2010; Hoyt 2013). Similarly, Cregg concluded in 2001 that the accommodation system of the children with DS may have the physical capacity to respond to a given stimulus, but that the neural control of the system is defective. Thereafter, Doyle et al. (2017) found that in DS binocular disparity is the main driver of both accurate vergence and accommodation, and illustrated the diminished influence of retinal blur in DS. Taken together, these findings suggest that the better focussed image on the retina provided by the near part of bifocals for stimuli at short distances (compared to unifocals) might have no influence on the accommodation response because the cortical component of the accommodation response is defective.

Amblyopia

In the 1990s, the differences in brain development in children with DS have been described (Takashima et al. 1981; Becker et al. 1986). This difference in development of the visual cortex was then interpreted as partly reflecting amblyopic types of cortical defects. The brain of both children with DS and children with amblyopia have abnormal organization of layers in the visual cortex along with decreased dendritic intersections and spines (Takashima et al. 1981; Becker et al. 1986), which could explain some of the postretinal reduction in vision. Although the reduced VA may also reflect symptoms of CVI, as we now know, amblyopia may not be excluded in our study, because of the possibility of coexisting (refraction) amblyopia due to blurred vision as a consequence of uncorrected refraction errors in combination with accommodation lags. That is why the visual loss in children with DS should be specifically evaluated and, if amblyopia is found to be the possibly cause, treated with spectacles correcting refraction errors.

Full correction of the ametropia

Full correction of the ametropia, as suggested in CVI by Hoyt (2013), should also be considered in children with DS as there is growing evidence (in the general population of children) that a period of only wearing glasses can significantly improve VA, without the need of any other modes of (amblyopia) treatment (Maconachie & Gottlob 2015). The observed changes in VAs in the unifocal group, although partly due to RTM, could also reflect an improvement in NVA due to full correction of the ametropia in the hyperopes. The majority of the participants were hyperopes, who, till that time, did not receive full correction of the hyperopia and were provided with on average more than one dioptre additional correction for distance

vision (Table 2). This adjustment for DVA with full correction facilitated NVA in the unifocal group as well, because full correction also augmented the correction at near. This augmented correction for near provided more correction of the abnormal accommodation for our participants, as, in our study, all participants had accommodation lags at baseline representing one of the inclusion criteria (Table 2).

Despite the augmented correction, focussing at near was still more difficult with unifocal glasses than with bifocals. We found significantly better average scores in the bifocal group for both uncrowded and crowded NVA tests after one year. The reason for the significant difference after 1 year may be the smaller amount of accommodation required for NVA tests with bifocal glasses compared with unifocals. Bifocals facilitate the children more and give them the opportunity to improve and develop their NVA more easily by practicing with a focussed image on their retina more often. The statistically significant difference between the two interventions in crowded NVA, which was not present when the children just started wearing their new glasses, implicates the need for time to achieve a larger improvement of crowded NVA. This need for time to achieve improvement of crowded NVA might be explained as pre-existing amblyopia, which was treated with a period of only wearing optimal refraction correction for near VA.

Performing plateau

Despite the optimal correction of refraction error in the bifocal group and the improved VA in our study, none of the mean visual acuities (uncrowded NVA, crowded NVA nor DVA) exceeded 0.3 LogMar at T3 (Table 4), which is considerably poorer than that of typically developing children. This may suggest that 0.3 LogMar is the performing plateau for mean VA in children with DS as a consequence of the differences in brain development (resulting in CVI) compared to children without DS. To provide these children with the best optical correction possible is important, but we still need to acknowledge that they still have a disadvantage in learning due to poorer vision than typical developing children (Zahidi et al. 2018). Further research with bifocals with full corrections of the ametropia and longer follow-up times may possibly reveal a higher maximum VA plateau in DS.

Conclusion

After one year of wearing the newly prescribed glasses, bifocals with full correction of the ametropia led to larger improvement in NVA compared with unifocals. Both interventions depend on baseline visual acuity; children with poorest baseline visual acuity benefit most. The larger improvement in NVA was not at the expense of DVA; after 1 year, DVA improved equally with both interventions. Observing the long-term effect, we suggest prescribing bifocals with full correction of refraction error in children with DS with accommodation lags.

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