Beyond improving visual acuity in children with Down syndrome

The effects of bifocals

Christine de Weger - Zijlstra

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General Introduction

1.1 DOWN SYNDROME

In the Netherlands, Down syndrome (DS), also called trisomy 21, is the most common chromosomal anomaly among newborns [van Gameren-Oosterom et al. 2012]. Annually, about 275 children with DS are born. This is similar to the annual birth incidence of DS in the United States of 14.5 per 10 000 (Parker et al. 2010).

In children with DS, development is different in comparison with typically developing children [Borstlap et al. 2011, van Gameren-Oosterom et al. 2011]. They have a different growth curve and their body length is 3 standard deviations (SD) below the mean of the children in the general population. Their motor development is delayed and they reach developmental milestones later and with wider spread. Also, the order in which motor skills are acquired is different. Problems exist with postural control, postural reactions and fine motor skills.

Co-morbidity exists on numerous levels in children with DS, with relatively high prevalences compared to typically developing children [Borstlap et al. 2011]. Children with DS have sensory (visual and auditory) and cognitive limitations as well as physical and mental/developmental abnormalities. They often have diseases of the cardio-vascular and gastrointestinal tract.

In the United States, the median life expectancy of individuals with DS has risen significantly, from a 25 years in 1983 to a 49 years in 1997 [Yang et al. 2002]. In recent decades, a similarly substantial increase in life expectancy of children with DS has occurred in the Netherlands [Weijerman 2011].

1.1.1 Changing attitudes towards DS in society, medical care and scientific research

While the discovery of the extra chromosome 21 (Lejeune 1958) allowed for a reliable early diagnosis, it hardly affected the post 2nd world war trend of increasing institutionalization of children with DS and the lack of medical effort to reduce their developmental barriers. This lasted until about 1973 when in the Anglo-Saxon world a number of interrelated developments occurred [Rogers & Coleman 1992, George 2021]: more home education and less institutionalization (especially of young children); the availability of early systematic developmental stimulation programs; more adequate medical care for people with DS (resulting not only from an increase in medical knowledge, but also from a growing awareness that people with DS are

entitled to adequate medical care); the gradual integration of people with DS in education and work environments.

Although in the Netherlands, some of these developments, in particular early developmental stimulation and integration in education and work environments, did not arrive until the late 1980's [de Graaf & Borstlap 2009], the institutionalization of children with DS has become a rarity today. The movement continues to ensure that all people with DS are recognised as valuable and capable members of society, worthy of our understanding, acceptance and inclusion.

Preventive health care programmes for children with DS, regular screening sessions by Down Teams and medical guidelines [Borstlap 1998, 2011, van Gameren et al. 2021] introduced in the last decades have also considerably improved their overall well-being and quality of life.

The change in perspective from caring for 'the disabled' to supporting disabled individuals likewise means that more attention will be given to the individual's development in scientific research. Responding to the complexity of the problems that are often seen in children with DS - physiological limitations in addition to a combination of cognitive and perceptual limitations - can be a challenge, in particular because it is often unknown which disability is trailing at a particular stage of development of the child with DS.

Regarding the limited visual functions in children with DS, in the nineties, it was seen as a progress that children with DS were provided glasses as would be prescribed to typically developing children. However, nowadays awareness grows about differences in ocular disorders and visual functions between children with and without DS and consequently the possible need for a tailor-made intervention for the typical (combination of) ocular disorders of children with DS.

This thesis on the subtle interaction between perceptual and cognitive impairments fits within this context.

1.1.2 What kind of visual constraints may hamper the development of a child with DS?

To see sharply at far and near distances, the human eye has a constant (cornea and unaccommodated ocular lens) and variable component of refraction (accommodation: increasing curvature of the ocular lens to focus for closer viewing

distances). The constant and variable component of refraction can be independently affected and require correction. Children with DS usually have both problems as opposed to typically developing children who usually have neither of the two refractive problems or an error of the constant component only. Yet it is not a given that children with DS will get the complete correction for the constant refractive error and the extra correction for near vision. The question remained, what might be the effect of the systematic failure to see sharply at close distances on the development of the child with DS? And, what might be the effect when one cause of blurred near vision could be corrected?

1.2 VISUAL FUNCTIONS

1.2.1 Development of the visual system

In typically developing children visual acuity reaches adult-like values (0.0 LogMAR) around the age of 6 years [Pan et al. 2010, Lai et al. 2011, Jeon et al. 2010, Dobson et al. 2009].

For human vision, precise collaboration of diverse structures is required (see Fig. 1). From the eye to the cerebral cortex, the components mature in parallel, each influencing the development of the whole. Some developmental processes follow an innate plan that is programmed using molecular cues forming “hard-wired” neural circuits. The neuronal activity within the system itself that arises spontaneously or from visual stimulation controls the others [Adams 2004]. In children with congenital visual impairment, posterior tracts of the visual system are compromised when compared to those who are typically sighted. The degree of limitation of the neuro-anatomical development appears to be proportional with the degree of visual impairment [Bathelt et al. 2020]. Both nature and nurture sculps the anatomical configuration of the visual system. In a developing individual, visual experience adjusts the neural structures such that these best represent the world they are exposed to [Adams 2004 pp. 9]. Combined with the innate, “hard-wired” plan, this produces an efficient visual system because only elements that function appropriately are maintained: “use it or lose it.” Reliance on visual experience makes the system vulnerable: a fault during development may be detrimental. With anomalous visual experience, the system develops abnormally.

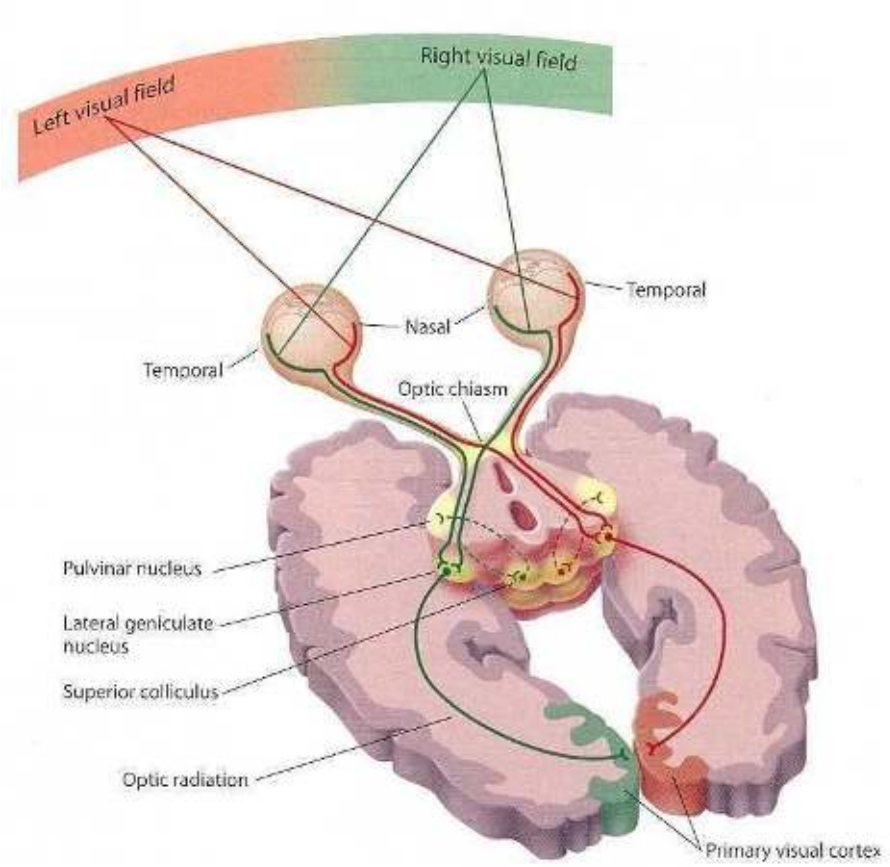

Figure 1. *Visual pathways*

The green lines represent the pathways which the light and electric signals originating from the right half of the visual field follow to the primary visual cortex in the left hemisphere of the brain. The red lines represent the pathways which the light and electric signals originating from the left half of the visual field follow to the primary visual cortex in the right hemisphere of the brain. It is in the brain, that the electric signals are first percepted as a conscious image.
Adapted and derived from https://www.slideshare.net/hanisahwarrior/neuroophthalmology-56822766

1.2.1.1 Cerebral visual impairment in children with DS

Cerebral visual impairment (CVI) is a verifiable visual dysfunction which cannot be attributed to disorders of the anterior visual pathways or any potentially co-occurring ocular impairment [Sakki et al. 2018]. In CVI, the brain does not correctly register or process visual information entering through the eyes [Guideline CVI 2019, Solebo

et al. 2017]. Another general definition of CVI is 'all visual dysfunctions caused by damage to, or malfunctioning of, the retro-chiasmatic visual pathways in the absence of damage to the anterior visual pathways or any major ocular disease' [Boot et al. 2010, Saidkasimova et al. 2007, Fazzi et al. 2007]. The diagnosis CVI is also used in cases where the extent of the impairment exceeds the extent that would be expected given the findings of ocular examination [Hoyt 2003, 2013]. Prematurity is a risk factor for CVI [Guideline CVI 2019].

In children with DS, CVI can be found because of the specific brain development in children with DS, which is different from that of typically developing children [Little et al. 2009, Woodhouse et al. 1996, Courage et al. 1994, Bosch 2016] (see paragraph 1.2.3.5). In a cohort of 607 patients with CVI, the most often found chromosomal aberration was trisomy 21 (in 21 patients) [Bosch et al. 2014].

Features of CVI which may also occur in children with DS (see paragraphs 1.2.2.1 and 1.2 3 to 1.2.3.4) are a reduced visual acuity that can vary over time, accommodative inaccuracy, crowding, oculomotor disorders including saccade delay, abnormal visual attention and abnormal behaviour in fixation, overlooking, abnormal vergence and tracking movements, visual field abnormalities, reduction of contrast sensitivity, reduced visual perception and recognition and papillar abnormalities including paleness, hypoplasia or a too large excavation as mentioned in the guideline CVI [Boot et al. 2010, Hoyt 2013, Guideline CVI 2019]. The presence of papillar abnormalities are mentioned as a commonly occurring feature of CVI, although these abnormalities are seen in anterior visual pathways. This finding might be attributable to axonal loss due to damage caused, through the phenomenon of retrograde transsynaptic degeneration, to the geniculostriate pathways [Jacobson et al. 1998, Fazzi et al. 2007].

1.2.2 Assessment of visual acuity in children with DS

In assessing visual acuity in children whose verbal development is delayed, like in DS, or who are simply too shy to talk to a stranger, the non-verbal visual acuity tests (matching or pointing out example visual objects (optotypes)) are useful. The results that these tests provide are far more reliable in characterizing visual function than those provided by a test based on detection [Teller 1986]. The attention span in children with DS is often short and highly variable depending on acquaintance, fatigue, emotional states, external circumstances or CVI. This may lead to a large

variation in test results. A test method that captures their attention but does not demand long and full concentration is most useful in children with DS.

Differences between visual acuity charts may include different spacing, which introduce systematic performance change because the smaller the spacing between the optotypes, the more difficult it is for the human visual system to decode the optotype, and even more so in children who have crowding (see paragraph 1.2.2.1).

Hence, we ensured by using the same visual acuity chart at subsequent assessments, that such interfering differences would not affect the outcomes.

1.2.2.1 Crowding

Crowding is generally defined as the deleterious influence of nearby contours on object recognition. It forms a bottleneck in perception or a separation difficulty [Levi 2008, Huurneman et al. 2012, Stuart & Burian 1962]. It can be seen as a developmental phenomenon, as crowding is found in typically developing children until the age of eight years [Jeon et al. 2010]. Children with DS may have binocular crowding possibly as a result of CVI [Bosch et al. 2014, CVI].

Schoolwork mostly consists of crowded visual tasks, such as looking at a row of numbers or letters in a word or crowded pictures, very often at near distances. Therefore, in children with DS who typically have accommodative (see paragraph 1.2.3.2) and crowding problems, it is of great importance to separately assess distant and near visual acuity and additionally differentiate between uncrowded and crowded near visual acuity, as done in this thesis work. Thus far, little is known about the development of crowded near vision in children with DS.

1.2.3 Differences in visual functioning in children with DS and typically developing children

During the last three decades, multiple authors reported on the many differences in visual functions, ocular disorders and brain structures between children with and children without DS [Creavin & Brown 2009, Morton 2011, Courage et al. 1994, Watt et al. 2015], revealing substantial differences in prevalences and severity of the ocular disorders in children with DS compared to typically developing children. Many of the abnormal findings on visual function examination in DS are features of CVI.

In this section, I will describe these differences and why they could limit DS children's development potentially.

1.2.3.1 Visual acuity and refractive disorders

Compared to age-matched typically developing children, distant visual acuity is reduced (difference ≥ 0.2 LogMAR*) in 80 to 100% of the children with DS even when refractive errors are corrected, mostly not exceeding 0.3 LogMAR [Courage et al. 1994, Woodhouse et al. 1996, Morton 2011, Zahidi et al. 2018]. Lack of concentration, motivation or persistence during acuity testing does not explain the deficit. Objective measurements of acuity by visual evoked potentials show that a real sensory deficit exists [John et al. 2004]. In children with DS, near visual acuity may even be more compromised compared to distant visual acuity as a consequence of accommodative deficit (see paragraph 1.2.3.2), whereas in typically developing children, no difference exists between distant and near visual acuity.

Refractive errors

In children with DS, refractive errors are common [Cregg et al. 2001, 2003, Haugen et al. 2001c, Creavin et al. 2009, Nandakumar & Leat 2009, Morton 2011, Watt et al. 2015], percentages vary from 40-90% depending on the definition of refractive error [Cregg et al. 2003] and there is absence of emmetropization (see Fig. 2).

At birth, there is no significant difference in the prevalence of any refractive error between those with and without DS. In typically developing children, the prevalence of refractive error decreases over time, which is called emmetropization. By contrast in children with DS, the trend is that with increasing age, prevalence of refractive errors rise. Their existing refractive errors may aggravate and even initial emmetropia (absence of refractive error) may develop in serious refractive errors within a short period [Cregg et al. 2003, Haugen et al. 2001b, Ljubic et al. 2011a]. For example, refractive error prevalence in children with DS rose from 7.1% in one-year-olds to 30% in 15-year-olds [Al-Bagdady et al. 2011]. The increase in variability of refractive error with age is supposed to occur because of a failure of emmetropization [Doyle et al. 1998, Al-Bagdady et al. 2011, Cregg et al. 2003, Haugen et al. 2001b, Woodhouse et al. 1997, Watt et al. 2015].

** footnote: LogMAR is a commonly used scale, expressed as the (decadic) logarithm of the minimum angle of resolution (MAR), which is the reciprocal of the acuity number (Snellen decimal). The LogMAR scale converts the geometric sequence of a traditional chart to a linear scale. It measures visual acuity loss: positive values indicate vision loss, while negative values denote normal or better visual acuity.*

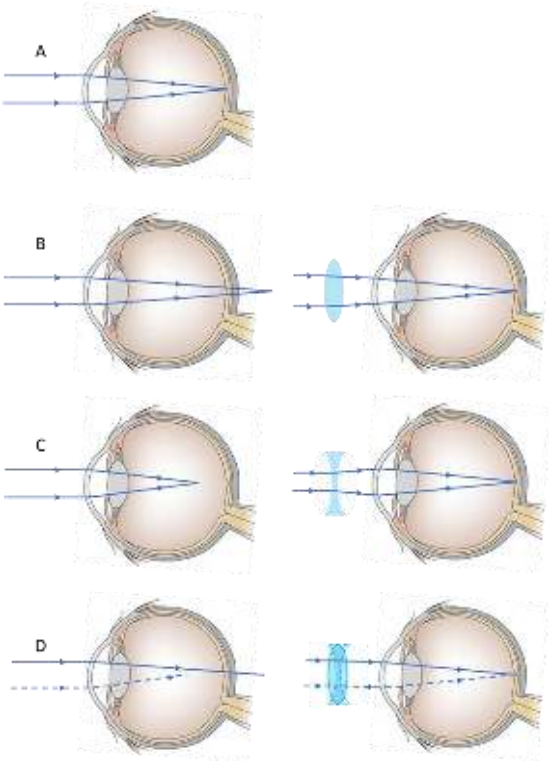

Figure 2. *Refractive errors and the suited corrective lenses*

The blue lines with arrows represent the rays of light.
*(**A**) Emmetropia, the eyeball and transparent structures have exactly the right sizes and refracting characteristics to produce a focused image on the retina. (**B**) Left: hyperopia, uncorrected, also called farsightedness. The eye ball is too small and/or the transparent structures have too low refractive power. Consequently the image is focused behind the retina. Right: hyperopia corrected with a convex (positive) lens which adds refractive power to achieve a focused image exactly on the retina. (**C**) Left: myopia, uncorrected, also called nearsightedness. The eye ball is too large and/or the transparent structures have too strong refractive power. Consequently the image is focused at some distance before the retina. Right: myopia corrected with a concave (negative) lens. (**D**) Left: astigmatism, uncorrected, also called cylinder. The refractive power of the eye is not the same in two mutually perpendicular directions, which results in a distorted image on the retina. The dashed lines indicate the two unequally focused parts of the image. Right: astigmatism corrected. The two unequally presented parts of the image (solid and dashed lines) are focused on the retina with a toric lens, which has two different refractive powers in two mutually perpendicular directions.*
Note: Presbyopia is a farsightedness for near viewing distances in adults from the age of 45-50 years. It occurs due to normal physiological age related changes in the adaptive power of the lens (decreased elasticity and increased hardness) and the power of the ciliary muscle of the eye.

Hyperopia. Before 2010, hyperopia often was defined as +2.5 dioptres or more, whereas nowadays, the definition of hyperopia in children with DS can be as low as ≥ +0.5 dioptres. The defocus from small hyperopic refractive errors (< +2.5 dioptres) reduces their acuity because of their inability to accommodate accurately. By contrast typically developing children can correct for these low hyperopic refractive errors by an appropriate accommodative response which explains why these refractive errors often go unnoticed in this group without consequences. Prevalences of hyperopia in children with DS up to 80% are reported in studies where hyperopia is defined as +0.50 dioptres or greater [Doyle et al. 1998]. Direct comparison with the general population is a complex matter as prevalences of types of refractive error vary with ethnicity and with age in the general population and in children with DS, but in a different way [Watt et al. 2015, Hashemi et al. 2018].

Myopia. In DS, the reported prevalence of myopia, 18-25% in myopia ≤ -0.5 dioptres [Doyle et al. 1998, John et al. 2004, Paudel et al. 2010, Watt et al. 2015] is lower than hyperopia. Myopia can develop to extreme levels.

Anisometropia. Reported prevalence of anisometropia 1.0 dioptre or more in children with DS of 9.4% [Ljubic et al. 2011a] up to 19.4 % [Paudel et al. 2010] is significantly higher than the prevalence of 5.8% [Deng & Gwiazda 2012] in the general population of children.

Astigmatism. The prevalence of astigmatism is high in DS, with a high rate of oblique astigmatism and a trend of increasing prevalence of (oblique) astigmatism with increasing age [Watt et al. 2015, Al-Bagdady et al. 2011, Woodhouse et al. 1997, Haugen et al. 2001c, Doyle et al. 1998, Ljubic et al. 2011b]. In a group of people with DS aged 1 to 34 years, Ljubic et al. [2011b] found a prevalence of astigmatism over 1.0 dioptre of 72%. The most prevalent form (52%) was oblique astigmatism. In the worldwide population, the reported prevalence of astigmatism (≥ 0.5 dioptre) in children is 15%, and the prevalence in Europe is 13% [Hashemi et al. 2018].

1.2.3.2 Accommodation

Perfect accommodation to a near fixation target should produce the refractive power required to maintain a clear image on the retina (see Fig. 3). The accommodative response shows a lead when the exerted accommodation exceeds the required refractive power, whereas the accommodative response shows a lag when the required refractive power is not obtained. Children with DS have no or only a poor

accommodative response, the accommodation often shows a lag in (50 to 90%) of the children with DS, which probably is a feature of CVI [Woodhouse et al1993, 1996, 2000; Cregg et al. 2001; Nandakumar et al. 2009,2010; Anderson et al. 2011; Doyle et al. 2016, 2017].

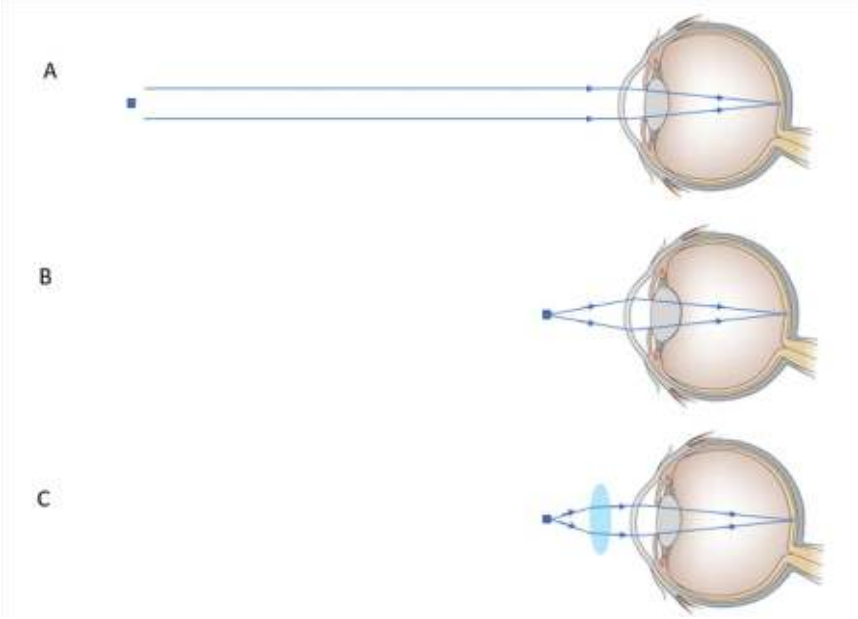

Figure 3. *Accommodation*

*The blue lines with arrows represent the rays of light. In (**A**), the of light emerge at a distance of at least several meters and approach the eye as an almost parallel beam. In an emmetrope eye the image will be focused on the retina when the muscle that controls the curvature of the lens (ciliary muscle) is relaxed. In (**B**), the rays of light emerge from a short distance and enter the eye as a diverging beam. The optic system has to adapt, increasing the refractive power by increasing the curvature of the lens, to produce a focused image on the retina. This changing of the curvature of the lens is called accommodation. In (**C**), a positive optical correcting lens (convex lens) is shown that can correct accommodative deficit.*

Accurate accommodation is essential for clear near vision. Reduced accommodative accuracy will cause significant difficulties for sustained close work.

From three months of age, the age at which the accommodative system becomes adult-like for typically developing infants, children with DS have significant lags of accommodation which do not improve with age, size of target and cognitive factors [Woodhouse et al. 1993, 2000, Stewart et al. 2005, Horwood & Ridell 2013]. The

precise aetiology and mechanism of the accommodative deficit in DS remains unidentified.

The accommodative amplitude in children with DS is not physically limited as it is in presbyopes [Cregg et al. 2001]. They potentially are able to accommodate with maximum amplitude, but the neural control of their accommodative system is insufficient to let them do so. There is a consistent degree of underaccommodation at all viewing distances. Underaccommodation occurs not only in hyperopic children, but in almost all children with DS regardless of the type and amount of refractive error. Doyle and colleagues [2016] were the first to report simultaneous binocular measurement of the near triad in DS, demonstrating that underaccommodation is linked to poor visual acuity (crowded letter or Kay picture recognition acuity [Kay 1983]). Children with worse visual acuity showed weaker accommodative responses. Moreover, they showed that participants with DS, notwithstanding underaccommodation, converge to near targets in the same manner as typically developing peers, regardless of the quality of their accommodative response. Pupil size response was also seen to be similar in children with and without DS. Hence, the concomitant accurate vergence responses indicate that underaccommodation by DS children is not so much a failure to visually engage near targets, but rather is a consequence of underlying neurological deficits.

In a subsequent study, Doyle and colleagues investigated the accommodative response to retinal blur in the absence of disparity. In that case, accommodative and vergence response in children with DS are weak, if any [Doyle et al. 2017]. An explanation of the high blur tolerance could be that the degraded visual acuity in DS, by reducing the ability to resolve high spatial frequency information, makes the eye insensitive to small amounts of retinal blur. Furthermore, Doyle showed that children with DS demonstrate significantly larger AC/A and smaller CA/C ratios compared to their typically developing peers [Doyle et al. 2017]. The high AC/A ratio is the result of low levels of accommodation and relatively normal vergence, rather than a result of accurate accommodation and excessive convergence, as seen in some forms of convergence excess esotropia in children without DS [Doyle et al. 2017]. The high AC/A ratio may induce esotropia, which is often seen in children with DS and is a unilateral amblyogenic factor.

Importantly, impaired accommodation and sustained blurred (near) vision in early life could be detrimental to general development and visual development. The blurred near vision in early life can result in a subtle bilateral amblyopia, particularly when

impaired accommodation occurs in combination with hyperopia, a common feature in children with DS [Doyle et al. 2016, Woodhouse et al. 1993, Cregg et al. 2001, Nandakumar & Leat 2009].

During screening of visual functions, professionals may possibly not recognize an accommodative deficit due to the low visual acuity and low contrast sensitivity in children with visual impairment. Children shorten the viewing distance to improve their visual acuity [Hamm et al. 2019]. Visually impaired children apply reduction of viewing distance even when their accommodation lags behind. If the viewing distance is reduced, the projected image on the retina is larger than from longer viewing distance, although it is not focused when the distance is closer than the near point of accommodation. Thus, we cannot conclude that accommodation is sufficient when visually impaired children shorten their viewing distance.

In children with DS, it is the exerted accommodative response that influences their visual acuity. Hence, we do not aim to measure their near point of accommodation or their accommodative amplitude, instead, we aim to assess and evaluate the accuracy of the exerted accommodative response to a near object. However, thus far, assessment of accommodative accuracy is not yet routinely performed during screening of visual functions in children with DS. Nott [1925] was the first to report on dynamic retinoscopy which provides a rapid objective measure of accommodative accuracy. In this research, we applied dynamic retinoscopy by moving the retinoscope closer to or further away from the child's eye until a neutral reflex was achieved during the child's fixation of a near point target [McClelland & Saunders 2003, Leat & Gargon 1996, Woodhouse et al. 1993]. We monitored the accommodative accuracy to detect possible change over time.

1.2.3.3 Strabismus

The reported prevalence of strabismus in children with DS is high, 19 to 34% [da Cunha & Moreira 1996, Haugen & Hovding 2001a, Yurdakul et al. 2006, Watt et al. 2015]; much higher than the 2-3% found in typically developing children [Hashemi et al. 2019]. Among children with DS who have strabismus, ~85% have esotropia [Haugen & Hovding 2001a], whereas exodeviations are observed infrequently.

In children with DS, acquired esotropia is predominant (~70% of the DS strabismics), whereas in typically developing children, infantile strabismus is more frequent [Yurdakul et al. 2006, da Cunha & Moreira 1996, Haugen & Hovding 2001a]. Acquired

esotropia is frequently found to be a result of imbalance between accommodation and convergence, and often occurs in hyperopia; both features often present in children with DS (see paragraph 1.2.3.2 and 1.2.3.1). Its onset occurs at the age of 3-6 years in children with DS and mostly around the age of 2 years in typically developing children.

In strabismus, one (the deviating) eye's image is suppressed in children under ~8 years, potentially reducing its cortical representation (amblyopia).

1.2.3.4 Nystagmus

Nystagmus, an involuntary binocular rhythmic oscillation of the eyes, is a frequently occurring impediment to visual acuity in children with DS. Compared to the prevalence of nystagmus in the general population, 0.24% [Sarvananthan et al. 2009], the prevalence in children with DS (9-30% [Morton 2011]) is high. In children with DS, nystagmus is mostly congenital. Nystagmus is also found frequently in CVI.

1.2.3.5 Development of the brain in children with DS and amblyopia

The brain sizes of typically developing foetuses and those with DS are relatively comparable until about 20 to 24 weeks of gestation, after which differences in foetal brain development emerge (e.g., differences in hypocampal cell proliferation [Guidi et al. 2018]). At birth, the brains of many infants with DS have less dentritic branching [Benavides-Piccione et al. 2004] and fewer synapses [Weitzdoerfer et al. 2001], both of which are likely to contribute to the reduced functional brain connectivity found in many newborns with DS [Imai et al. 2014]. Studies with younger children and young adults with DS indicate they have reduced brain volume relative to age-matched and sex-matched controls [Pinter et al. 2001]. The brain volume reductions were specifically found in the cerebellum as well as the frontal and temporal regions [Jernigan et al. 1993, Nadel 1999, Pinter et al. 2001].

Histologic reports describe differences in visual cortices of children with DS compared to typically developing children [Takashima et al. 1981, Scott et al. 1983, Ross et al. 1984, Becker et al. 1986, 1991, Coyle et al. 1986, Wisniewski 1990]. These differences include lesser brain weights, reduced hindbrain: reduced cerebrum ratio, decreased cortical sulcation (decreases in sulcal depth in bilateral Sylvian fissures and right central and parieto-occipital sulci), reduction in the number and density of neurons (specially in cortical layers II and VI), and less organized configuration of layers in the

visual cortex. Reduced synaptic formation, delayed myelination, progressive atrophy of the dentritic tree, and abnormalities in levels of neurotransmitters and in the ions surrounding the neural membranes are found. There also is evidence of cessation in growth of dendrites, dendritic atrophy after the first year of life, and poor maturation [Becker et al. 1991, Takashima et al. 1994]. As a result, cortical visual function is compromised [Little et al. 2009]. Impairment in their cortical visual function may be the result of the brain abnormalities, as described in histologic reports of differences in the brain development, or they may result from abnormal input during visual development [Little et al. 2009]. The magnitude of the cortical deficit is significant and should be considered along with poor quality of optical input [Little et al. 2009]. The study of Little et al. [2007] on the impact of optical factors on resolution acuity in children with DS revealed that grating resolution and interferometric thresholds (interferometric methods circumvent the optics of the eye and offer a grid image directly on the retina) are reduced. However, the discrepancy with typically developing children is greater for grating resolution acuity, suggesting that reduction of optical quality of visual input is a major contributor to poor visual performance in children with DS [Little et al. 2007].

As there is no evidence that the visual areas of the cortex (area 17 to 19) are spared from extensive neural deficits, it is highly probable that they contribute to the apparent amblyopia observed in many children with DS [Courage et al. 1994]. Compared to typically developing children, amblyopia can more frequently develop in children with DS as a result of reduction of optical quality due to uncorrected ocular disorders including uncorrected refractive errors, accommodative problems and strabismus [Joly & Frankó 2014]. Because of an undiagnosed amblyopia in children with DS, optical corrections may not have immediate effect on visual acuity. Additionally, central visual disturbances could further complicate an already compromised cognitive development.

In the general population through timely elimination of the underlying cause, amblyopia can be reduced in the course of time. The earlier such intervention on amblyopia is undertaken, the better the outcome when followed-up after cessation of the amblyopia treatment until the end of the critical age [de Weger et al. 2010]. In DS, amblyopia and its possible consequences should be reduced also. Therefore, in this thesis, we monitor and study the mutual influences of visual acuity (distant and near), refractive errors, accommodative responses, strabismus and cognitive development, as these combinations were not studied before in children with DS.

1.3 COGNITIVE DEVELOPMENT ASSESSED BY EXECUTIVE FUNCTIONS IN CHILDREN WITH DS

In this research in children with DS, we were looking for measures of the overall development in addition to visual/oculomotor measures, because we suspect that improving visual function may counteract developmental impairment. Executive function might provide an appropriate measurement space for this, because executive function is an umbrella term for a set of interrelated cognitive abilities. There is general agreement that there are four core executive functions (a) control of inhibition (inhibitory control, including self-control or behavioural inhibition) and (b) control of interference (selective attention and cognitive inhibition), (c) working memory, and (d) cognitive flexibility (also called set shifting, mental flexibility, or mental set shifting, which is closely linked to creativity) [Miyake et al. 2000, Diamond 2013]. From these, higher-order executive functions are built such as reasoning, problem solving, and planning [Collins & Koechlin 2012, Lunt et al. 2012]. Executive functions develop during life and are skills essential for mental and physical health, success in school and in life, and for cognitive, social, and psychological development [Biederman et al. 2004, Stevens et al. 2009, McDermott et al. 2012, Prager et al. 2016, Daunhauer et al. 2014, Will et al. 2017].

In recent decades, the number of studies examining executive functions of children with DS has increased alongside research examining typically developing children. The results of these studies support the hypothesis that an impairment of executive functions, relative to mental age, is a feature in children with DS.

Lee et al. [2011] distinguished cool and hot executive functions in her study in young children with DS, aged 4 to 10 years. Cool executive functions refer to memory and planning skills wherein emotions are not a significant factor. Hot executive functions refer to skills we use to regulate our behaviour through control and inhibition of emotions [Zelazo & Muller 2002]. In this young age group, executive function deficits in DS were more pronounced in the cool domain than in the hot domain [Lee et al. 2011]. An overview per executive function domain of their impairments compared to those in mental age-matched typically developing children is given in a review by Lukowski et al. [2019].

The assessment of executive functions can be task-based (the participant is asked to execute certain prescribed tasks) and/or informant-based (questionnaires are filled in by the participant and/or a proxy, i.e., a person in their primary social circle such as

parent or teacher). Task-based tests assess the level of performance of executive functions in ideal circumstances whereas informant reports provide a real-world assessment of the executive functions as performed in daily life [Hartman et al. 2007, Polanczyk & Jensen 2008]. Each of these assessing methods produces authentic information in different circumstances which are complementary [Daunhauer et al. 2017].

Levels of executive functions can be measured using a grading system, which showed that even young toddlers are already beginning to develop these skills [Hughes et al. 1998, 2005, Anderson 2002, Zelazo et al. 2003, Carlson 2005].

Several questionnaires filled in by a proxy to rate executive functions which are developed for children without DS can be used in children with DS, but a number of factors limit the available task-based testing options for the children with DS. First of all, the test has to be one that children with reduced visual acuity are able to perform. Furthermore, the test has to be such that it can be uniformly administered and, moreover it has to be suitable for a large (developmental)-age range because of the large range in developmental level of children with DS compared to their calendar age. In addition, the assessment should not take too much time because of their limited attention span, and it should not rely on their verbal abilities, as their verbal capacities are often impaired.

1.4 THE RESEARCH IN THIS THESIS: THE EFFECT OF BIFOCALS IN CHILDREN WITH DS

1.4.1 Study rationale

As explained above, many differences in ocular findings between children with and children without DS are described in the last decades [Watt et al. 2015], revealing the reduced visual acuity (distant and near) in children with DS [Morton 2011], the abundancy of refractive errors which increase with age, the absence of emmetropization and a consistent lag of accommodation which does not improve with age in children with DS [Watt et al. 2015] in contrast to the rapid improvement in accommodative accuracy in early infancy in typically developing children [Horwood & Ridell 2013]. Moreover the effort to accommodate may give rise to strabismus, which occurs far more often in children with DS: in 15-47% [Cregg et al. 2003, Haugen & Hovding 2001a, Morton 2011] than in the general population [Hashemi et al. 2019].

These ocular findings often found in DS and the frequently occurring nystagmus are features associated also to CVI.

Some authors have suggested a relationship between a constantly blurred retinal image and the lack of emmetropization [Haugen & Hovding 2001b, Cregg et al. 2001] resulting in the increasing range of refractive errors in children with DS [Haugen & Hovding 2001b]. Existing refractive errors may aggravate within a short period and even initial emmetropia may develop in serious refractive errors [Cregg et al. 2003, Haugen & Hovding 2001b]. Additionally, the blurred retinal image may be causal for their defective visual development (potentially damaging the visual cortical development resulting in bilateral amblyopia), presenting in visual acuities that do not reach normal levels [Cregg et al. 2001]. Generally their visual acuity is 0.3 LogMAR or poorer [Morton 2011].

Spectacle correction for the distance refractive error in the usual way which is the current intervention in children without DS does not appear to benefit the DS children's accommodative responses to near fixation targets. Hence, their near visual acuity hardly improves [Cregg et al. 2001]. This has important clinical and educational implications. Because young children mostly perform schoolwork at near, near vision should be sufficient, and given greater importance in clinical evaluation of vision in these children [Cregg et al. 2001].

1.4.1.1 Bifocals

The specific (combination of) ocular disorders in children with DS demand a specific approach, a tailor-made intervention. Bifocals could be such a tailor-made intervention as in the general population, correction of the refractive error with bifocals can optically correct poor accommodative accuracy. The application of bifocals is an intervention which focuses on a clear image on the retina for both distant and near vision. In presbyopes, near vision is immediately improved with bifocals because these adults have a well-developed visual acuity. This could be different in children with DS.

A few authors applied bifocal correction in small groups of children with DS [Stewart et al. 2005, Al-Bagdady et al. 2009, Nandakumar et al. 2009, 2010, 2011]. A retrospective study on the compliance in wearing bifocals showed better compliance with bifocals than with unifocals [Adyanthaya et al. 2014]. In the study of Nandakumar et al. [2009, 2010, 2011] children with DS, who were selected because they could

read and write, bifocal glasses were compared to the previously worn optical corrections (i.e., unifocals as prescribed in typically developing children). In that small scale study after 6 months, bifocals improved their near vision more and had a positive impact on their visual functioning: faster and improved performance on visual perceptual and some early literacy skills. Yet the effect on accommodative accuracy after stopping the bifocal treatment remained unclear. In the study of Al-Bagdady et al. [2009], some children had improved accommodative responses after stopping bifocals, but the study of Nandakumar & Leat [2010] did not repeat this result.

The recent publications that report better visuospatial memory than auditory memory in children with DS [Lanfranchi et al. 2004, Frenkel & Bourdin 2009] raised the question whether improved visual functions could possibly support their learning abilities. Additionally, recent studies in children without DS who have isolated visual impairment found that impaired visual acuity limits the acquisition of skills needed to respond appropriately to environmental demands, which are developed through the so called adaptive behaviour and executive functions [Sonksen & Dale 2002, Dale & Sonksen 2002, Heyl & Hintermair 2015, Bathelt et al. 2018, 2019, Keil et al. 2017, Tadic et al. 2009]. Moreover, children with additional neurological problems are at greater risk of poor education and well-being related outcomes compared to those with visual impairment alone [Chanfreau & Cebulla 2009]. Such children struggle more with abilities related to executive functions as well [Heyl & Hintermair 2015]. This raises the question whether such associations of visual functions with adaptive behaviour and executive functions also exist in children with DS.

Although Nandakumar & Leat [2009, 2010, 2011] showed the efficacy of bifocals to improve near vision in children with DS, their research was of limited scope as it did not cover the effectivity of bifocals in a large cohort that represents the population of children with DS.

Thus, the following questions are relevant for this thesis:

1. Does correction of near vision (bifocals) alter the quality of near vision in a large cohort that represents the population of children with DS?
    a. Is there a difference between a short-term and long-term change in near visual acuity when bifocals are used?

2. What is the short and long-term effect of bifocals on crowded near visual acuity (often needed in school tasks) in a large cohort that represents the population of children with DS?
3. What is the effect of bifocals on the lag of accommodation in children with DS?
4. What is the effect of bifocals on the manifestation of strabismus in children with DS?
    a. Is there a difference between a short-term and long-term effect on strabismus by the use of bifocals?
5. What is the effect of bifocals on the aggravation of refractive errors in children with DS?
6. Are there differences in adaptive behaviour, executive functions and visual acuity between typically developing children and children with Down syndrome?
7. Are impairments in visual functions in children with DS interrelated with their impairments in general development and executive functions?
8. Do bifocals alter the executive functions in children with DS?

To clarify these outstanding questions, we performed the studies described in this thesis as outlined below.

1.4.2 Thesis outline

To prevent avoidable visual impairment in children with DS, we conducted a randomized controlled trial to study the effects of bifocal glasses (addition 2.5 dioptres in straight-top longlines with the top placed at the pupillary centre) compared to unifocal glasses, both with full correction of distance refractive error assessed in cycloplegia. We included 119 children with DS, aged 2 to 16, in 15 locations, 14 hospitals and one institute for the visually impaired, geographically spread over the Netherlands. We could follow 104 of the children for one year in four subsequent visits, T0 baseline, T1 after ~6 weeks, T2 after ~6 months and T3 final assessments after one year. We studied the effects of the interventions on their visual functions, including visual acuity, both distant and near (uncrowded as well as crowded), accommodative accuracy, strabismus, refractive errors, and their cognitive development (by monitoring their executive functions) and explored associations

between these functions.
In chapter 2 [de Weger et al. 2019], we report the study design and the baseline measurements. We also quantified and compared the short-term and long-term effects of bifocals and unifocals on their near uncrowded, near crowded and distant visual acuity. Here we aim to answer the research questions 1, 1a and 2.
In chapter 3 [de Weger et al. 2020], any changes in their refractive errors, accommodative accuracy and ocular alignment and the presence of binocularity and stereopsis are studied to answer the research questions 3, 4, 4a and 5.
Because our intervention aimed to improve vision at near distances, and because near vision might even be more important for learning in children with DS than in typically developing children, we also studied their cognitive development. Therefore, in chapter 4 [de Weger et al. 2021a], we compare developmental level in adaptive behaviour (assessed with the Vineland-Screener questionnaire), executive functions (task-based (MEFS) and rating based (BRIEF-P and BRIEF)) and visual acuity at baseline measurements of our cohort to age-matched norm scores. Thus, we obtained the age-matched differences in developmental level between the children with DS and typically developing children. We also analysed possible associations at baseline between visual impairment and impairments in adaptive behaviour or executive functions to answer the research questions 6 and 7.
Chapter 5 [de Weger et al. 2021b] reports the one-year development in executive functions, assessed with the task-based MEFS test and with parent- and teacher-rated questionnaires BRIEF-P and BRIEF in each intervention group, bifocals and unifocals. Post-intervention, we explored possible associations between the impairments in executive functions and visual functions to answer the research question 8.
Chapter 6 gives an overview in the main findings in this thesis in a general summary and general discussion.
In the appendices, a summary in Dutch, the acknowledgements, curriculum vitae of the author and her list of publications and presentations, as well as the list of co-author affiliations can be found.

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2

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

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2 ABSTRACT

Purpose. Children with Down syndrome (DS) typically have reduced visual acuity (VA) and accommodative 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 refractive 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. Accommodative 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 accommodative lag compared to unifocals.

Keywords: *accommodative lag, child development, crowded near visual acuity, near addition in children, ocular accommodation, refractive error*

2.1 INTRODUCTION

Uncertainty exists about prescribing bifocals or unifocals in children with Down syndrome (DS) to correct distant 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. 2009aa, 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]. Accommodative 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 refractive errors. Additionally, refractive 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, 2009b, Al-Bagdady et al. 2011; Ljubic et al. 2011; Watt et al. 2015]. At birth, refractive errors are similar to those in typically developing children, but the refractive errors change and increase over time; the normal emmetropization mechanism does not occur. Children with DS who initially have no refractive error are at risk of developing refractive 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 in children with DS and that in some of those children, accommodative 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 DS 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 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 accommodative response.

2.2 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.

2.2.1 Participants

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 participants' parents or their legal guardians after explanation of the nature and possible consequences of the study.

Inclusion criteria were as follows:

- Diagnosed with DS, trisomy 21 as well as minority forms
- Accommodative lag >0.5D measured with 'modified Nott-method'
- Age range 2–18 years
- Able to understand the task instructions, and at age older than 5 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
- Must be able to perform a task sitting on a chair and working at a table
- With or without strabismus, and with or without nystagmus.

Exclusion criteria were as follows:

- Worn bifocals before
- Other eye diseases that seriously hamper vision like keratoconus, colobomas, cataract
- 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 cooperation 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 NCT02241356 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.

2.2.2 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 (see Fig. 1).

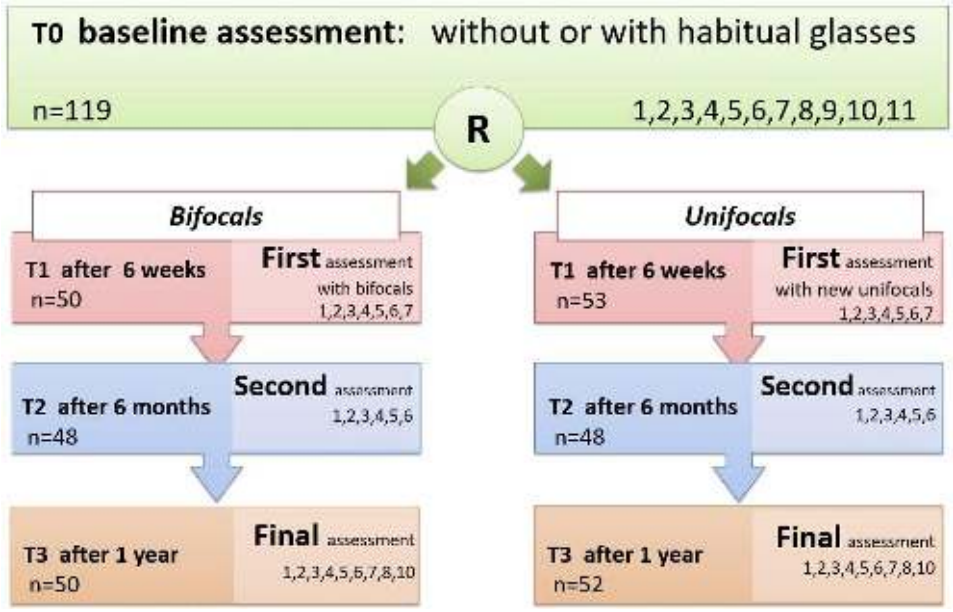

Figure 1. *Study design*

Time-line 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 refractive 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.

2.2.2.1 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.

2.2.2.2 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.

2.2.2.3 Intervention

Full correction of refractive 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 distance 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 refractive 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.

2.2.2.4 Timeline

After inclusion, we followed the participants for 1 year, in four visits (see 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 accommodative 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. Anamnnesis and 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, accommodative accuracy
7. Minnesota Executive Function Scale (MEFS)
8. Objective refractive 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 and teachers)
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 accommodative 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 refractive 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.

2.2.2.5 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 cooperation or otherwise, were noted.

Accommodative accuracy (*6)*: To measure the accuracy of the accommodative 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 accommodative response could be calculated. We first started with the fixating object at a distance of 25 cm and in case there was no accommodative 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, accommodative accuracy was measured through the distance portion of the glasses.

Refractive error and ophthalmological examination (8,9): Measurement of objective refractive 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].

2.2.3 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 cooperation 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 ($R_{\text{pre, post}}$) in the GLM using: P rm = 100(1 – $R_{\text{pre, post}}$) [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 participants 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 refractive error

of the least ametropic eye for analysis of the refractive 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°.

2.3 RESULTS

2.3.1 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 accommodative lag (*n* = 9), insufficient cooperation 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.

2.3.2 Baseline measurements (T0)

The ocular findings (incidences, means and ranges) in our study population are listed in Table 2. The distribution and kind of refractive 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 significant differences in baseline (T0) measurements (Table 2).

Table 1. *Incidences of ocular findings*

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

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

Table 2. Baseline group averages (T0)

Baseline group averages (T0)

		Bifocals									Unifocals									p Value	Test statistic
		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		
T0	**T0**																						
	N=100								50										54				
	male								25	50	0								26	48	0	0.850 †	X^2[1]=0.036
	age (years)	7.68	3.21	8.00	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]=1.464
	wearing habitual glasses								35	nb	8								36	nb	13	0.295 †	X^2[4]=4.925
	no glasses								15	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	0.61	0.31	0.66	0.10	1.22	0.44	0.87	25		25	0.66	0.28	0.67	0.16	1.40	0.42	0.86	22		32	0.961 ‡	t(43)=-0.049
	DVA	0.43	0.27	0.40	-0.80	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
T0	**Accommodative 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
	Refractive error in cycloplegia: SER (in dioptres) of the least ametropic eye																						
	SER of the least ametropic eye	-1.88	3.08	-2.25	-11.25	6.50	-3.88	-0.09	50		0	-1.97	3.34	-1.75	-12.13	5.25	-3.40	-0.25	54		0	0.579 ‡	t(102)=0.522
	Hyperopia SER > S+0.5	3.14	1.35	2.75	1.25	6.50	2.00	4.16	38	76	0	2.67	1.41	2.60	0.63	5.25	1.31	3.88	40	74	0	0.141 ‡	t(76)=-1.479
	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	0.521 ‡	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																					0.750 †	X^2[2]=0.552
	with the rule								9		0								13		0		
	against the rule								3		0								3		0		
	oblique (106 163) 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	0.00	1.30	0.09	-5.00	3.88	0.00	1.25	54		0	0.981 ‡	t(102)=-0.087
	SER change in hyperopic new prescription	1.33	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	0.433 ‡	t(76)=0.680
	SER change in myopic new prescription	-1.46	0.90	-1.13	-3.25	-0.37	-2.19	-0.94	9		0	-1.37	1.96	-0.25	-5.00	0.00	-3.00	0.00	7		0	0.401 ‡	t(14)=-0.119

NVA = near visual acuity; DVA = distant visual acuity; SER = Spherical equivalent of the refractive error;
Std dev = standard deviation; Interq = interquartile; Min = minimum; Max = maximum; % = percent of children in that group.
† $\chi 2$ test.
‡ Student's t-test.

2.3.2.1 Refractive errors

Analysis of frequencies of refractive 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 S -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%).

2.3.2.2 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 refractive errors measured in cycloplegia. They were provided with new prescription for full correction of any refractive error.

2.3.2.3 Visual acuity

NVA. At baseline measurements, uncrowded NVA was assessed in 70% of the children in the bifocal group (in 31 children using LEA symbols chart and four using Kay picture test) and in 76% in the unifocal group (in 34 children using LEA symbols 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 symbols chart and three using Kay picture test) and 87% of the children in the unifocal group (in 40 children using LEA symbols chart and seven using Kay picture test). There was no significant difference in DVA scores between the two intervention groups (Table 2).

2.3.2.4 Accommodative response

The accommodative 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).

2.3.3 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 as the defined as the difference between the pre- and post-test of each participant.

Table 3. Group averages with newly prescribed glasses

Group averages with newly prescribed glasses

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
	Accommodative 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
	Accommodative 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
	Accommodative 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

NVA = near visual acuity; DVA = distant visual acuity; SER = Spherical equivalent of the refractive error;

Std dev = standard deviation; Interq = interquartile; Max = maximum; Min = minimum.

‡ Student's t-test

2.3.3.1 *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).

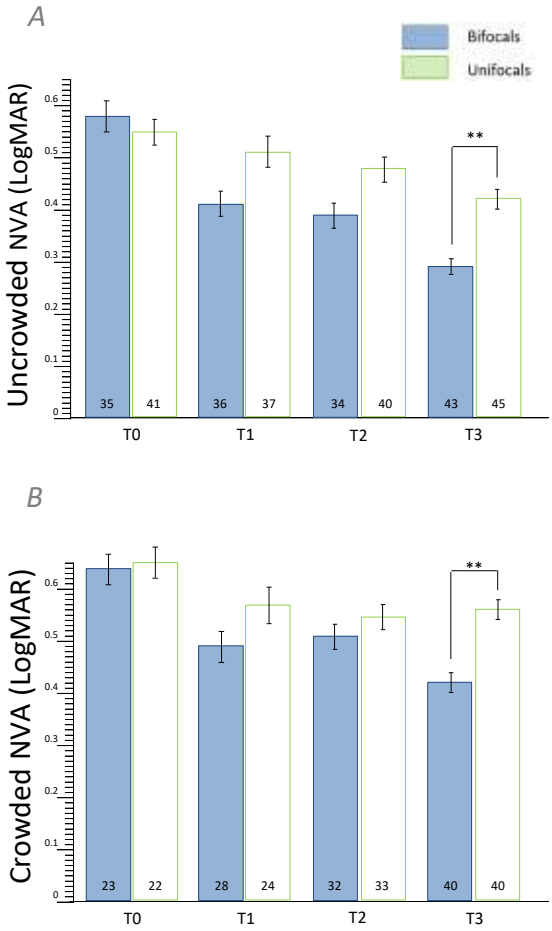

Figure 2. *Group averages of uncrowded en crowded NVA*

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.

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 participants, we have analysed the changes by comparing the measurements at the different time-points within participants 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 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 child's 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.

Table 4. Within-participant comparison of VA's (LogMAR)

Within subject comparison of VA's LogMAR)

Group averages of those children in whom changes could be calculated, i.e., the children in whom the same visual acuity measure could be obtained at two points in time. ***T1****: short term changes computed as the within-subject differences between T0-T1and* ***T3****: 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 90.18)	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

VA = visual acuity; NVA = near visual acuity; DVA = distant visual acuity. () = standard deviation; [] = standard error of the mean.

§ ANCOVA with baseline as covariate.

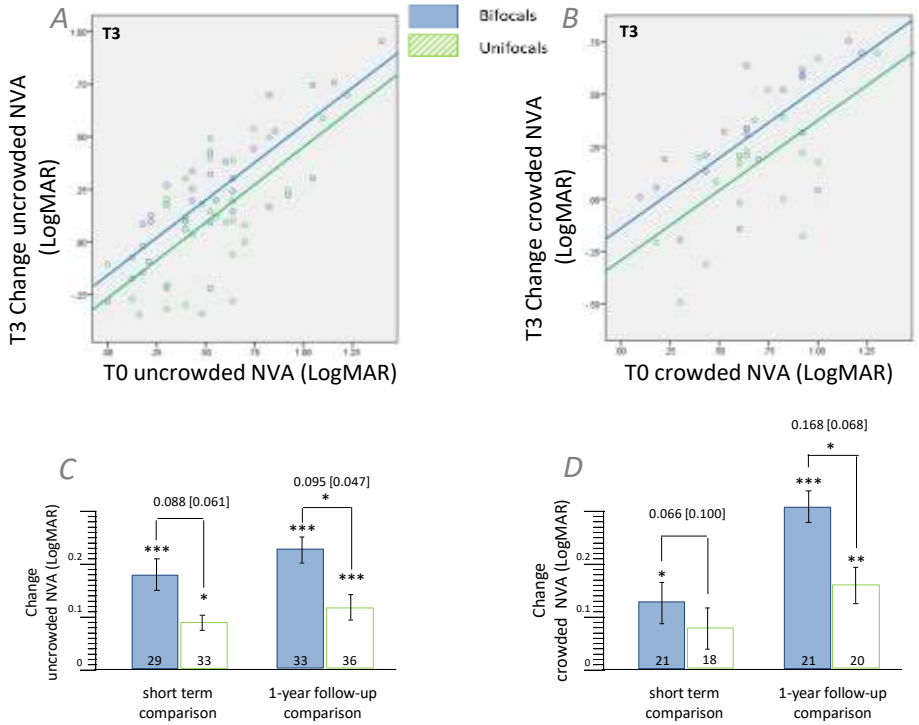

Figure 3. *Change in uncrowded and crowded NVA*

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*x, unifocals Y = -0.268+0.734*x; Regression line equations crowded NVA, bifocals Y = -0.135+0.673*x, unifocals Y = -0.303+0.673*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, are 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.*
Blue = bifocals; green = unifocals.

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

Uncrowded 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).

Crowded NVA. 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

Uncrowded 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 improvement in the bifocal group was larger.

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

2.3.3.2 Distant 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: $R_{\text{final, baseline}} = 0.588$). There was also evidence for a differential treatment effect ([Oldham 1962];

partial correlation coefficient, $R_{\text{change, average baseline and final DVA}} = 0.238$, $t(84) = 2.215$, $p = 0.030$). 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 accommodative lag of three dioptres at T0, and showed a plausible development in VA after receiving unifocals with full correction of refractive 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.

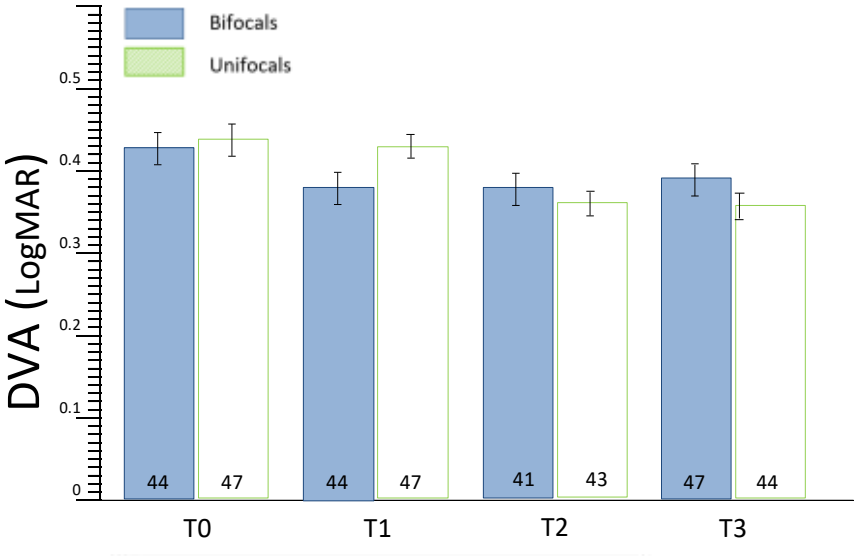

Figure 4. *Group averages of DVA*

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 = distant visual acuity; SEM = Standard error of the mean; Whiskers indicate ± 1 SEM.

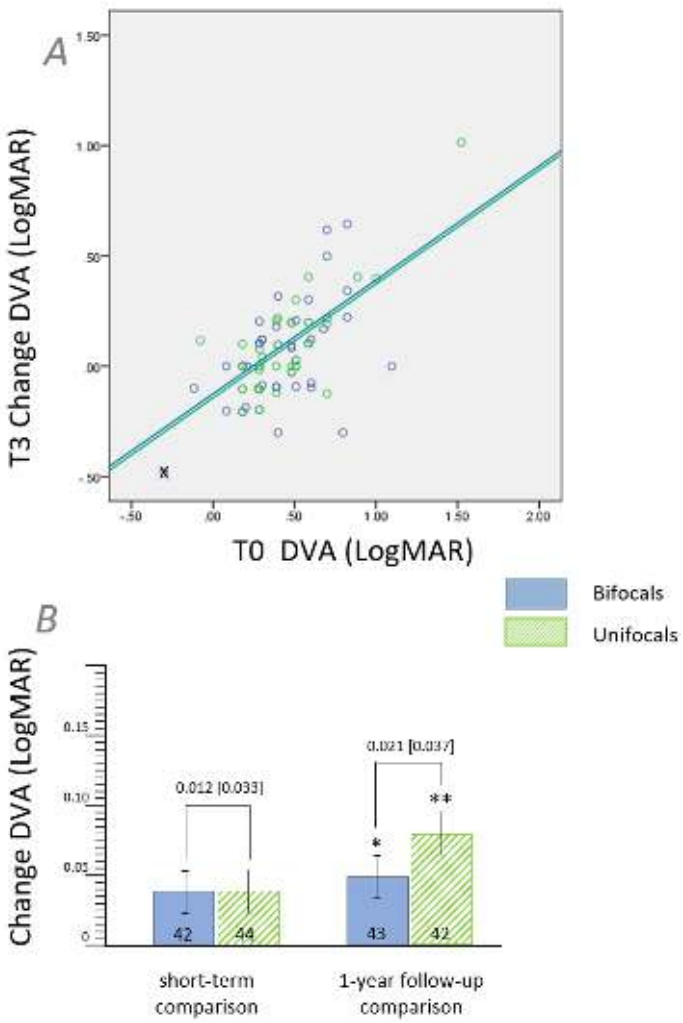

Figure 5. Change in DVA

(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*x, unifocals Y = -0.146+0.517 *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, are indicated at the top.
*DVA = distant 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.*

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).

2.3.3.3 Accommodative response

At T1, when the children wore their newly updated and full distance correction, all showed an accommodative lag through the distance correction or distance part of bifocals (Table 3). The average accommodative 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 accommodative 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).

2.4 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 refractive 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. Accommodative response showed no change in either intervention group, neither at the short-term nor after 1-year follow-up.

2.4.1 Strengths

Strengths of our study compared to previous studies [Stewart et al. 2005; 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 cooperation 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 refractive 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 accommodative accuracy in children with bifocals. This resulted in new insights into the development of VA in children with DS with accommodative 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 participant. It happens because values are observed with random error (i.e. random measurement error and/or random fluctuations in a participant [Barnett et al. 2005]). Thus, notwithstanding the large inter- and intra-subject 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 refractive error including the effect of baseline NVA.

2.4.2 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 cooperation 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 participants. 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.

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 cooperation 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.

2.4.3 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 refractive 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 (see Figs 3A,B and 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.

2.4.4 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 refractive errors occur in more than 75%: most frequently hyperopia, 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.

2.4.5 Accommodation

Although previous authors [Al-Bagdady et al. 2009] have reported that the accommodative accuracy through the distance portion of the lens improves after wearing bifocals, we did not find any influence at all on accommodative accuracy through that part of the bifocal. In fact, we found no change in accommodative 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 accommodative 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 accommodative 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 [Cregg et al. 2001]. 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 focused 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 accommodative response because the cortical component of the accommodative response is defective.

2.4.6 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 post-retinal 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 refractive errors in combination with accommodative 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 refractive errors.

2.4.7 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 in our study were provided with on average more than one dioptre additional correction for distant 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 accommodative lags at baseline representing one of the inclusion criteria (Table 2).

Despite the augmented correction, focusing 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 focused 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 refractive correction for near VA.

2.4.8 Performing plateau

Despite the optimal correction of refractive 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.

2.4.9 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 refractive error in children with DS with accommodative lags.

Notes

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3

Bifocals reduce strabismus in children with Down syndrome: evidence from a randomized controlled trial

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3 ABSTRACT

Purpose. Children with Down syndrome (DS) more often have strabismus, refractive errors, accommodative lags and reduced visual acuity (VA) than typically developing children. In this study, we compare the effects of bifocal glasses with those of unifocal glasses in children with DS. Changes in angle of strabismus, accommodation and refractive error were analysed in this paper.

Methods. In a multicentre randomized controlled trial, 119 children with DS, aged 2-16, were randomly allocated for bifocal or unifocal glasses (with full correction of refractive error in cycloplegia). The 15 centres, all in the Netherlands, followed the participants for 1 year. Changes in refractive error, accommodative accuracy, strabismus, binocularity and stereopsis were compared across 4 subsequent visits.

Results. Refractive errors and accommodative errors showed no significant change throughout the course of our study in either intervention group. The manifest angle of strabismus, however, reduced significantly in the bifocal group. This improvement was observed shortly after the children received their new correction (~6 weeks) (linear regression: $t = 3.652$, $p < 0.001$) and remained present in the final measurements after 1 year (linear regression: $t = 3.604$, $p < 0.001$). The percentage of children with positive binocularity and stereo tests showed no significant differences between the groups.

Conclusion. Bifocals with full correction of refractive error reduce the manifest angle of strabismus within a few weeks. No effects on accommodation, refractive error, stereopsis and binocularity occurred over the course of 1 year.

Keywords: *conventional strabismus treatment, esotropia, near addition in children, ocular accommodation, ocular alignment, refractive error*

3.1 INTRODUCTION

In children with Down syndrome (DS), strabismus, accommodative lag, refractive errors and poor visual acuity (VA) are more frequent and severe than in typically developing children. Prevalences mentioned in the literature for children with DS were 15–47%, 50–90%, 40-90% and 80-100%, respectively [de Weger et al. 2019].

The differences in visual development between children with and without DS have to be taken into account when prescribing glasses to children with DS. Major differences exist in accommodation, strabismus and refractive error. Firstly, in children with DS, accurate accommodation often does not develop in the first weeks of life as is the case with typically developing children [Woodhouse et al. 1993, 1996, 2000; Haugen et al. 2001b; Cregg et al. 2001; Al-Bagdady et al. 2009; Nandakumar & Leat 2009, 2010; Anderson et al. 2011; Doyle et al. 2016, 2017; Candy & Bharadwaj 2007; Horwood et al. 2015].

Secondly, in children with DS, the prevalence of strabismus, usually in the form of acquired esotropia, is higher than in typically developing children. The onset of esotropia is between age 3 and age 6, mostly at age 4, whereas in typically developing children, the onset of acquired esotropia is more often earlier in life, around the age of 2 [da Cunha & Moreira 1996; Haugen & Hovding 2001a; Von Noorden & Campos 2002; Yurdakul et al. 2006; Morton 2011, Watt et al. 2015]. In the majority of children with DS, the potential for binocularity could have developed in their early years before the onset of manifest strabismus. However, due to the risk of ocular comorbidities in children with DS, there are many other factors that could have prevented normal visual development and binocularity including uncorrected significant refractive error, anisometropic amblyopia, ocular pathology including congenital cataract, all of which are likely to be present from birth.

Thirdly, in children with DS, the emmetropization process in their first years of life is not the same as in typically developing children. In particular, their refractive errors do not diminish, leaving them, for instance, with hyperopia and oblique astigmatism [Cregg et al. 2003; Haugen et al. 2001b; Ehrlich et al. 1997; Atkinson et al. 2000].

Recent evidence shows that in children who lack the ability to accommodate accurately, bifocals help to improve near visual acuity (NVA) as they produce focused images on the retina for both distant and near vision without requiring accommodation [Nandakumar & Leat 2010; de Weger et al. 2019].

A recent study by Doyle et al. [2017] demonstrated that retinal disparity is the main driver to both the accommodative and vergence systems in DS and furthermore illustrated the diminished influence of retinal blur cues to accommodation and vergence in DS, both indicative of a sensory deficit of the accommodative system [Doyle et al. 2017]. This supports the earlier finding that the accommodative system of children with DS may have the physical capacity to respond to a given stimulus, but the neural control of the system is defective [Cregg et al. 2001; Doyle et al. 2016], resulting in a consistent lag of accommodation and a defocused (optically) retinal image at near in most children with DS. Consequently, for near vision without near addition, they attempt to compensate for the accommodative lag by increasing the accommodative effort. The increased effort is accompanied by convergence excess.

Thus, it seems likely that the accommodative lag is a contributing factor in the incidence of esotropia. If alignment and refractive error problems are detected early, latent deviations might be managed before adverse sequelae develop [Watt et al. 2015].

Bifocals diminish the need for accommodation and thereby prevent excessive convergence. Therefore, bifocals could reduce or prevent a manifest angle of strabismus in children with DS. However, thus far there is not enough evidence to support this effect of bifocals. Until now, the only published study on the effect of bifocals on ocular alignment in children with DS is the one by Haugen & Hovding [2001a], who mentioned relief of strabismus with bifocals in four out of five children with DS. Three other studies on strabismus therapy in DS concentrated on surgical methods [Yahalom et al. 2010; Perez et al. 2013; Motley et al. 2012]. In relation to surgical methods, the effect of bifocals on strabismus could be relevant because in this vulnerable group, non-surgical therapy would be preferred.

To analyse the effect of bifocals on the manifest angle of strabismus in a large group of children with DS, we included the assessments of ocular alignment and strabismus in our multicentre randomized controlled trial [de Weger et al. 2019].

In the present study, we analysed the effects of bifocals on the angle of strabismus, binocularity, stereopsis, refractive errors and accommodative lags.

3.2 METHODS AND PATIENTS

3.2.1 Study design

We conducted a multicentre randomized controlled trial to compare the effects of bifocals with the effects of unifocals in 119 children with DS, aged 2-16, with accommodative lags. The children from participating institutes were randomly allocated to the two intervention groups: bifocals and unifocals. Randomization, a permuted block randomization schedule, stratified by gender, age and language development (parents report: speaking in 1-3 word sentences and speaking in 4 word or longer sentences). This schedule was used to randomly assign a child with equal probability to one of the two treatment groups. The intervention group to which the child was assigned was always known to the participant, the orthoptist and the investigator, because bifocal glasses are a visually prominent marker.

In both groups, we applied full correction of refractive error measured using cycloplegia. The bifocal segment top of the applied longline (flat-top or D-segment) bifocals with addition S +2.5, used in the bifocal group, was placed at the pupillary centre, as used in previous studies in which good results were achieved in improving near vision and compliance in wearing these glasses [Stewart et al. 2005; Al-Bagdady et al. 2009]. The children were seen on four occasions, T0 (baseline), T1 ~6 weeks, T2 6 months and T3 1 year after inclusion. For further details, see de Weger et al. [2019] and Fig. 1.

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).

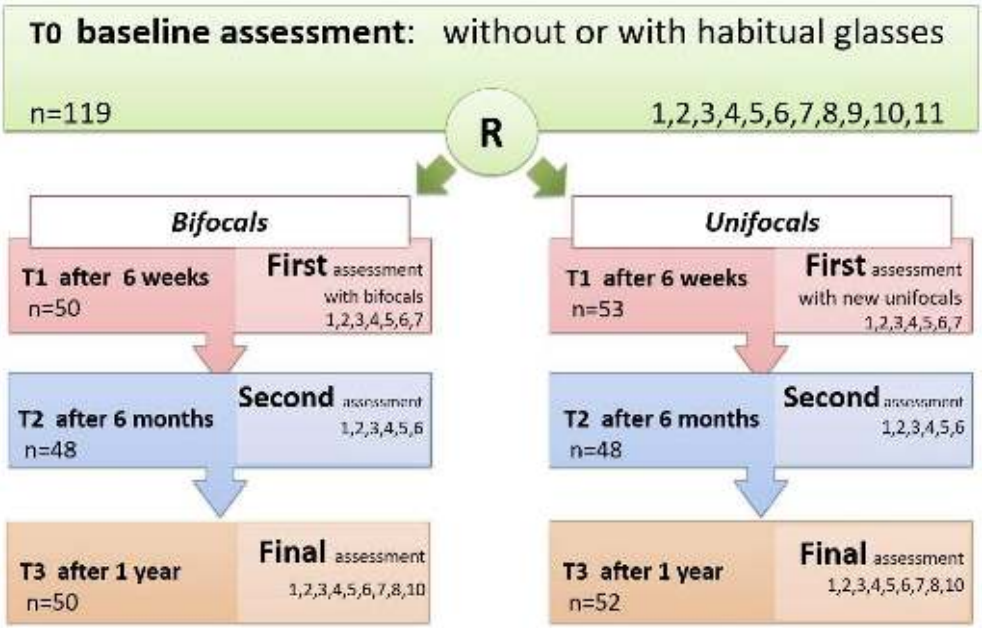

Figure 1. *Study design*

Time-line 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 refractive 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.

3.2.2 Measurement procedures

Compliance in using the bifocals in an appropriate way was assessed in a qualitative manner, by observation and parent report at the start of T1, T2 and T3, and was reaffirmed by the orthoptists during assessment.

In case of (nearly) straight eye position (evaluated with corneal light reflex at the beginning of the assessment), binocularity and stereopsis were assessed. Binocularity was assessed by positive base out 15 dioptre prism test. Stereopsis was tested with Lang Stereotest (no dissociation glasses needed) (Lang-Stereotest AG, Küsnacht, Switzerland), Titmus Fly (with polarization dissociation glasses) (Stereo Optical Co., Inc., Chicago, IL) or TNO test (red/green dissociation glasses) (Lameris Ootech,

Nieuwegein, The Netherlands), chosen by the orthoptist according to the developmental stage of the child.

After that, both manifest and latent strabismus were assessed with the cover test at 30 cm and 5 m. At the first (T0), second (T1) and fourth (T3) visit, the manifest or latent angle was measured using the prism cover test at 30 cm and 5 m. If the prism cover test was not feasible because of lack of cooperation, the Hirschberg corneal reflex test ([Hasebe et al. 1998] at 30 cm and 2.5 m was applied to measure the manifest angle.

Accommodative accuracy was measured at all four visits with dynamic retinoscopy, the 'modified Nott method' [Woodhouse et al. 1993; Leat & Gargon 1996; McClelland & Saunders 2003] through unifocals or in the case of bifocals through the distance portion. First, the accommodative accuracy was assessed at a distance of 25 cm (4 dioptres of accommodation). If no accommodative lag was found, the measurement was repeated at 16.7 cm (6 dioptres of accommodation). In previous studies, these distances were found to be useful to elicit accommodative lags [Woodhouse et al. 1996; Al-Bagdady et al. 2009; Stewart et al. 2007; Nandakumar & Leat 2009].

Refractive errors were assessed at the end of the first (T0) and fourth (T3) visit. A combination of streak retinoscopy and autorefraction was applied [Wübbolt et al. 2006; Marsack et al. 2017]. Measurements were taken under cycloplegia (cyclopentolate 0.5% in young children (> 3 months < 6 years) and 1.0% from the age of 6 years, as in guidelines for usual care) or if cycloplegia was not possible because of contraindications, under mydriasis (tropicamide 0.5%).

3.2.3 Statistical analysis

Statistical analysis was performed using the statistical package for the social sciences (SPSS version 23, IBM Inc., Chicago, IL). Ancova (general linear model, GLM) with baseline performance as the covariate was used to analyse the differences between the two intervention groups. Correction for baseline measurement was applied, because changes were significantly correlated with baseline measurements. Multiple linear regression analysis was applied to analyse the influence of explanatory variables and their interaction.

The difference between the pre- and post-test was determined as the observed change over time: T1-T0 is the short-term change and T3-T0 is the 1-year change (negative values indicate improvement). For analyses of the manifest angle of

strabismus, we used the angles measured with prism test. If these were not available, we used the assessments with Hirschberg corneal reflex test and recalculated the values to prism dioptres. If Hirschberg corneal reflex test data were also not available, we used manifest angles assessed with the cover test, which were converted to prism dioptres as well. For analyses, the refractive errors were expressed in spherical equivalent of the least ametropic eye (SER). For analyses of age dependency of the intervention effect on manifest strabismus, the participants were stratified into age groups, under 6 years and over 6 years, because strabismus is most common onset at the age of 4 (between 3 and 6 years of age).

Influences of the phenomenon of regression to the mean (RTM) and differential treatment effect were analysed as in de Weger et al. [2019].

3.3 RESULTS

The population of children with DS that was included in this study proved comparable to DS populations described in the literature as far as ophthalmological findings are concerned (reviews of Watt et al. [2015]and Afifi et al. [2013]). Randomization resulted in two intervention groups with no statistical baseline difference in mean age, gender prevalence, strabismus, nystagmus, compliance in wearing glasses, absence of prescription glasses, attendance of mainstream school education, refractive errors (hyperopia, myopia, astigmatism, axis), SER, uncrowded NVA, crowded NVA, DVA, and accommodative lag [de Weger et al. 2019].

3.3.1 Compliance

Nearly all children learned to use their bifocals in the appropriate way. After a few weeks of using their newly prescribed bifocals, parents and orthoptists of only six children reported incorrect use; after 6 months, four children did not use their bifocals correctly; and after 1 year, only one child did not always use the bifocal adequately. All children whom were issued bifocals continued to participate in the study.

3.3.2 Refractive errors

The refractive errors were not significantly different between the two intervention groups when measured a second time after 1 year (ancova, F(79) = 1.319, p = 0.254) (see Fig. 2A, Table 1).

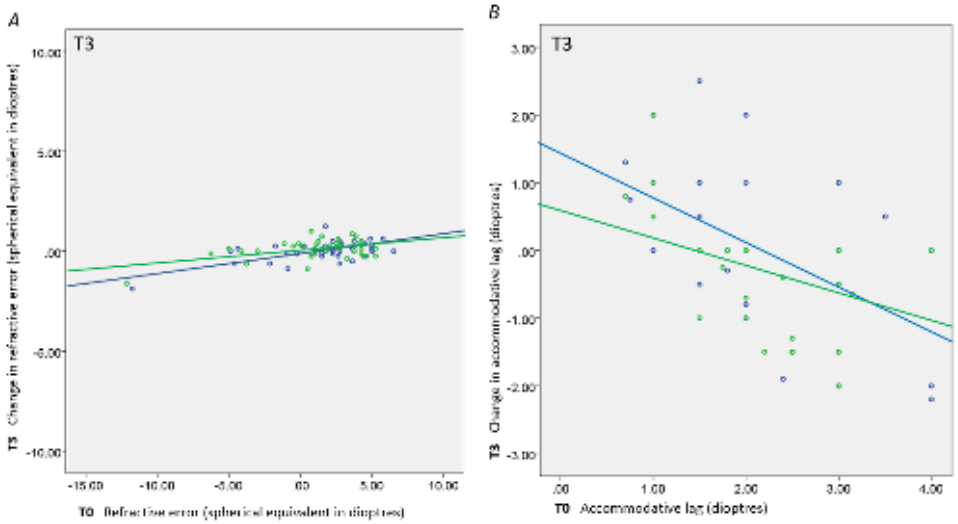

Figure 2. Change in refractive error and accommodative lag

A and B: *Scatterplots of the one-year change (i.e., the within-subject difference between T0 and T3) as a function of baseline (T0) for refractive errors (i.e., spherical equivalent of least ametropic eye) (**A**) and accommodative lags measured through unifocals or the distance part of the bifocals (**B**) by dynamic retinoscopy 'modified Nott method' in the two treatment groups. **A**: Positive refractive errors indicate hyperopia, negative errors indicate myopias. **B**: Positive changes in accommodative lag (y-axis) correspond with increased lags, negative with decreased (improved) lags. Solid lines are regression lines through the data.*

***A**: Regression line equations, bifocals Y = 0.12+0.09*x, unifocals Y = 0.02+0.06*x;*

***B**: Regression line equations, bifocals Y = 1.39-0.65*x, unifocals Y = 0.63-0.42*x.*

Blue = bifocals; Green = unifocals.

Table 1. *Refractive errors*

Group averages of refractive errors measured in cycloplegia and expressed in spherical equivalents of the least ametropic eye (SER) assessed at T0 (baseline assessment) and at T3 (final assessment after 1 year).

Spherical Equivalent of the refractive error

		Bifocals					Unifocals						
		mean	std dev	range min	range max	n	mean	std dev	range min	range max	n	p Value	Test statistic
T0	SER of the least ametropic eye	1.68	3.29	-11.75	6.50	50	1.32	3.14	-12.13	5.25	54	0.579 ‡	t(102)=0.556
	Hyperopia	3.14	1.35			38	2.67	1.42			40	0.141 ‡	t(76)=1.487
	Emmetropia	-0.04	0.26			3	0.00	0.33			7	0.847 ‡	t(8)=-0.199
	Myopia	-3.93	3.33			9	-5.06	3.50			7	0.524 ‡	t(14)=0.654
T3	SER of the least ametropic eye	1.74	3.84	-13.63	6.50	40	1.27	3.70	-13.75	5.38	42	0.253 §	F(79)=1.325
	Hyperopia	3.49	1.46			30	2.92	1.47			31	0.772 §	F(58)=0.085
	Emmetropia	0.06	0.62			2	0.00	0.37			4	0.899 §	F(3)=-0.019
	Myopia	4.39	4.05			8	-5.32	4.10			7	0.163 §	F(12)=2.212

Hyperopia: SER > S +0.5. Emmetropia: S -0.5 ≤ SER ≤ S +0.5. Myopia: SER < S -0.5.
Max = maximum; Min = minimum; Std dev = standard deviation.
‡ Student's t-test
§ ANCOVA with baseline as covariate

3.3.3 Accommodative lag

The accommodative lag assessed at 25 cm showed no significant change over time in either intervention group. Neither were any differences found between the two intervention groups at T1, when the children started wearing their newly prescribed glasses, nor at later time-points T2 and T3 (see Fig. 2, Table 2). At T1, the mean change in accommodative lag was -0.23 ± 1.09 in the bifocal group and -0.32 ± 1.06 in the unifocal group (ancova, $F(74) = 0.030$, p = 0.862). At T2, the mean change in accommodative lag was -0.34 ± 0.93 in the bifocal group and -0.20 ± 0.76 in the unifocal group (ancova, $F(67) = 0.048$, p = 0.828). After 1 year, at T3, the mean change in accommodative lag was -0.01 ± 1.20 in the bifocal group and -0.36 ± 0.83 in the unifocal group (ancova, $F(67) = 1.325$, p=0.254).

Note that the observed changes in accommodative accuracy showed a significant correlation with the baseline values (correlation bifocals: $R = -0.506$, p = 0.002; unifocals: $R = -0.410$, p = 0.013). In both groups, large accommodative lags at baseline tended to decrease while small accommodative lags at baseline tended to increase (see Fig. 2B). Further analysis indicated, however, that this significant negative correlation was due to a large percentage of RTM (61%; $R_{(pre, post)} = 0.386$, p = 0.001, P rm = 1-0.386). Regression to the mean (RTM) is a statistical phenomenon

which is always present in repeated measures, most notably in measures that have considerable uncertainty [Oldham 1962; Barnett et al. 2005; Trochim 2006].

Table 2. *Accommodative lag*

Accommodative lag in dioptres measured at 25 cm assessed by dynamic retinoscopy 'modified Nott method' at T0 through habitual correction and at T1, T2 and T3 through the distance segment of bifocals or through unifocals.

Accommodative lag

		Bifocals					Unifocals						
		mean	std dev	range min	range max	n	mean	std dev	range min	range max	n	p Value	Test statistic
T0	Accommodative lag (dioptres)	2.17	0.91	0.7	4.0	44	2.25	0.88	0.3	4.0	50	0.673 ‡	t[92]=-0.423
T1	Accommodative lag (dioptres)	1.74	0.99	0.5	4.0	39	2.00	1.05	0.5	4.0	40	0.313 ‡	t[79]=-1.015
T2	Accommodative lag (dioptres)	1.79	0.88	0.0	4.0	33	1.94	0.95	0.3	4.0	40	0.499 ‡	t[71]=-0.680
T3	Accommodative lag (dioptres)	2.1	1.1	0.5	4.0	35	1.99	0.88	0.5	4.0	37	0.570 ‡	t[70]=-0.570

Max = maximum; Min = minimum; Std dev = standard deviation.

‡ Student's t-test

3.3.4 Manifest angle of strabismus

The scatterplots in Fig. 3 illustrate that bifocals had more effect than unifocals in reducing the manifest angles of strabismus. In these plots, full correction of ocular alignment towards straight eye position would result in regression lines with a negative slope of −1 passing through the origin (dotted black lines). Hence, the beneficial effect of bifocals over unifocals is evident from the fact that the slopes of the regression lines were steeper and closer to −1 for the bifocal group (blue) compared with the unifocal group (green). Note that this difference was already present at T1, shortly after the children started wearing their newly prescribed glasses (treatment × baseline interaction: $t = 5.913$, $p < 0.001$) (Tables 3 and and 4). Further changes between T1 and T3 were not significant ($t = 0.857$, $p = 0.394$); the initial improvements remained until the final measurements after 1 year ($t = 6.813$, $p < 0.001$). For this analysis, we excluded the two participants with the largest manifest angles of strabismus (45 prism dioptres), one in the bifocal group and one in the unifocal group (crosses). The slope values of the regression lines in the bifocal group were strongly biased by the one child having a 45 prism dioptres manifest angle of strabismus. However, with all participants included, the treatment difference was still statistically significant (treatment × baseline interaction at T1: $t = 3.652$, $p < 0.001$ and T2: $t = 3.604$, $p < 0.001$).

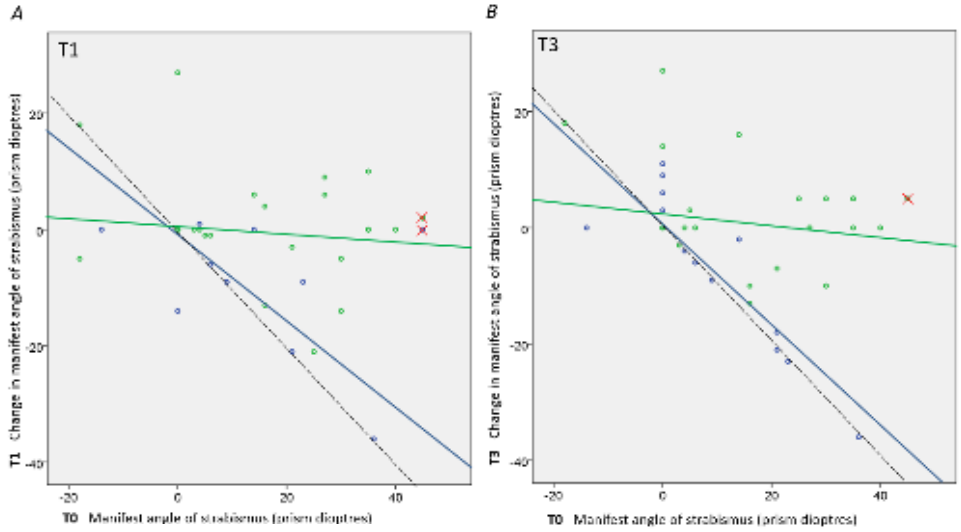

Figure 3. *Change in manifest angle of strabismus*

***A and B**: Scatterplots of change as a function of baseline (T0) manifest angle of strabismus. (**A**) short-term change (i.e., the within-subject difference between T0 and T1); (**B**) 1-year change (i.e., the within-subject difference between T0 and T3) . Positive values in manifest angle of strabismus (x-axis) indicate esotropias, negative values indicate exotropias. Negative changes in manifest angle of strabismus (y-axis) indicate decreased (improved) esotropias or increased exotropias, depending on the manifest angle of strabismus at baseline. Solid lines are regression lines through the data excluding the two large esotropias (crosses; one in bifocal and one in unifocal group). Dotted black lines indicate the change in manifest angle of strabismus that is required for perfect correction to 'straight eyes'. **A:** Regression line equations, bifocals Y = 0.54-0.76*x, unifocals Y = 0.91-0.09*x; **B:** Regression line equations, bifocals Y = 0.30-0.88*x, unifocals Y = 2.23-0.12*x. At T1 (i.e., shortly after the children started with their newly prescribed glasses), the slopes of the regression lines of bifocals and unifocals are significantly different (A: t = 5.913, p < 0.001; B: t = 6.813, p < 0.001) representing a significantly different treatment effect of the two interventions. Blue = bifocals; Green = unifocals.*

Angle of manifest strabismus

A **All participants**

		Bifocals						Unifocals							
		n	mean	std dev	median	interq 25	interq 75	n	mean	std dev	median	interq 25	interq 75	p Value	Test statistic
T0	Absolute Angle of manifest strabismus (prism dioptres)	50	4.04	9.61	0.00	0	0	54	8.33	13.26	0.00	0	17	0.071 ¶	1125.5
T1	Absolute Angle of manifest strabismus (prism dioptres)	50	2.12	7.30	0.00	0	0	53	8.36	14.09	0.00	0	17	0.002 ¶	972.000
T3	Absolute Angle of manifest strabismus (prism dioptres)	50	2.16	7.64	0.00	0	0	52	8.77	14.48	0.00	0	14	0.010 ¶	1000.500

B **Children aged under 6 years**

		Bifocals						Unifocals							
		n	mean	std dev	median	interq 25	interq 75	n	mean	std dev	median	interq 75	interq 75	p Value	Test statistic
T0	Absolute Angle of manifest strabismus (prism dioptres)	15	1.67	5.45	0.00	0	0	15	4.87	7.18	0.00	0	14	0.122 ¶	83.500
T1	Absolute Angle of manifest strabismus (prism dioptres)	15	0.33	1.29	0.00	0	0	15	5.20	9.13	0.00	0	5	0.033 ¶	74.500
T3	Absolute Angle of manifest strabismus (prism dioptres)	15	0.40	1.55	0.00	0	0	14	6.14	10.3	0.00	0	8	0.023 ¶	66.000

C **Children aged over 6 years**

		Bifocals						Unifocals							
		n	mean	std dev	median	interq 25	interq 75	n	mean	std dev	median	interq 25	interq 75	p Value	Test statistic
T0	Absolute Angle of manifest strabismus (prism dioptres)	35	5.06	10.83	0.00	0	6	39	9.67	14.82	0.00	0	25	0.237 ¶	593.000
T1	Absolute Angle of manifest strabismus (prism dioptres)	35	2.89	8.60	0.00	0	0	38	9.61	15.55	0.00	0	19	0.022 ¶	504.500
T3	Absolute Angle of manifest strabismus (prism dioptres)	35	2.91	9.01	0.00	0	0	38	9.74	15.75	0.00	0	22	0.094 ¶	546.000

Group averages of the absolute manifest angle of strabismus in prism dioptres at T0 (baseline assessment), T1 (when the children started using their new glasses), T3 (final assessment after 1 year). All participants ***(A)*** *were stratified into age groups depending on age 6* ***(B and C)*** *because strabismus is commonly onset prior to the age of 6. Note the reduction of the size of strabismus angle when using bifocals: A, B and C (ANCOVA, all p < 0.001); in the unifocal group no changes were found (ANCOVA, all p > 0.087).*

Interq = Interquartile; Std dev = standard deviation Mann-Whitney U-test.

Table 4.

A **All Participants**

	Bifocals									Unifocals										p Value	test statistic
	n	Exotropia medium	Orthotropic	esotropia	micro	small	medium	large	very large	n	Exotropia medium	Orthotropic	esotropia	micro	small	medium	large	very large			
T0	**50**	1 (2)	39 (78)	10 (20)	2	2	4	2	0	**54**	2 (4)	34 (63)	18 (33)	4	0	7	7	0		0.245 †	$X^2(2)=2.812$
T1	**50**	2 (4)	44 (88)	4 (8)	1	0	2	1	0	**53**	1 (2)	33 (62)	19 (36)	6	0	6	7	0		0.003 †	$X^2(2)=11.610$
T3	**50**	1 (2)	42 (84)	7 (14)	3	3	0	1	0	**52**	0 (0)	33 (63)	19 (36)	4	1	6	8	0		0.023 †	$X^2(2)=7.582$

B **Children aged under 6 years**

	Bifocals									Unifocals										p Value	test statistic
	n	Exotropia	Orthotropic	esotropia	micro	small	medium	large	very large	n	Exotropia medium	Orthotropic	esotropia	micro	small	medium	large	very large			
T0	**15**	0 (0)	13 (87)	2 (13)	1	0	1	0	0	**15**	1 (7)	9 (60)	5 (34)	2	0	3	0	0		0.222 †	$X^2(2)=3.013$
T1	**15**	0 (0)	14 (93)	1 (7)	1	0	0	0	0	**15**	0 (0)	9 (60)	6 (40)	3	0	3	0	0		0.040 #	$X^2(1)=4.658$
T3	**15**	0 (0)	14 (93)	1 (7)	1	0	0	0	0	**14**	0(0)	8 (53)	6 (40)	3	0	2	1	0		0.031 #	$X^2(1)=5.179$

C **Children aged over 6 years**

	Bifocals									Unifocals										p Value	test statistic
	n	Exotropia medium	Orthotropic	esotropia	micro	small	medium	large	very large	n	Exotropia medium	Orthotropic	esotropia	micro	small	medium	large	very large			
T0	**35**	1 (3)	26 (74)	8 (23)	1	2	3	2	0	**39**	1 (3)	25 (64)	13 (33)	2	0	3	7	0		0.608 †	$X^2(2)=0.997$
T1	**35**	2(6)	30 (86)	3 (9)	0	0	2	1	0	**38**	1 (3)	24 (62)	13 (34)	3	0	3	7	0		0.028 †	$X^2(2)=7.139$
T3	**35**	1 (3)	28 (80)	6 (17)	2	3	0	1	0	**38**	0 (0)	25 (64)	13 (34)	1	1	4	7	0		0.163 †	$X^2(1)=3.632$

Ocular Alignment continued

The number of children in the categories of ocular alignment: exotropia, orthotropia and esotropia, subdivided in size, micro, small, medium, large and very large, assessed at:
T0 (baseline assessment),
T1 (when the children started using their new glasses),
T3 (final assessment after 1 year).
All participants were stratified into age groups depending on age 6 because strabismus is commonly onset prior to the age of 6.
Note the reduction in proportion of esotropia, and prevention of the onset of esotropia when starting with bifocals: (McNemar, p=0.030); in the unifocal group no reduction was found: (McNemar, p=0.368).
Micro = manifest strabismus angle of 1-6 prism dioptres;
Small = manifest strabismus angle of 7-13 prism dioptres;
Medium = manifest strabismus angle of 14-28 prism dioptres;
Large = manifest strabismus angle of 29-57 prism dioptres;
Very large = manifest strabismus angle of > 58 prism dioptres.
n = number of children assessed; a value between brackets () indicates the percentage.
† $\chi 2$ test
 # Fischer's Exact test

Besides baseline angle of manifest strabismus, other factors could have influenced the observed change in the angle of manifest strabismus during the development of the child. We therefore checked, in a multivariate linear regression, for other variables influencing the change of the manifest angle of strabismus (age, accommodative lag, refractive error, nystagmus, distant visual acuity, uncrowded near visual acuity and crowded near visual acuity). No other variables with significant influence on the strabismus angle (all $p > 0.155$) were found.

When stratifying the participants into age groups under 6 years and over 6 years, we found no age group effect (treatment x age group at T3: $t = -0.007$, $p = 0.994$) on the manifest angle of strabismus after 1 year (Tables 3 and 4).

3.3.5 Binocularity and stereopsis

There were no differences in relative frequencies of positive tests between the groups at any time-point (all $p > 0.212$) (Tables 1 and and 2). However, measures of stereopsis could not be collected in all children, and the choice of test applied varied according to the developmental stage of the child. By combining the results of assessments with different stereo tests in those children in whom we could assess stereopsis, we only could compare the presence of stereopsis, without being able to grade the stereopsis (Table 5). This analysis showed that the relative frequencies of positive stereo tests were not significantly different between the two intervention groups, neither at T1, nor at T2 or T3 (all $p > 0.444$).

Table 5. *Binocular functions*

Number of children with positive test results and children who did not need to be assessed, mainly because of ocular alignment which is incompatible with binocularity or could not be assessed because of poor cooperation. Value between brackets () indicates percentage.

		Bifocals			Unifocals			
		present at that point in time	positive test result	not assessed	present at that point in time	positive test result	not assessed	P Value
T0	Stereopsis	50	26 (52)	9 (18)	53	28 (52)	14 (26)	0.530 †
	Binocularity with 15 dioptre prism test		42 (84)	4 (8)		35 (65)	11 (20)	0.171 †
T1	Stereopsis	50	35 (70)	6 (12)	53	27 (50)	16 (30)	0.372 †
	Binocularity with 15 dioptre prism test		36 (72)	8 (16)		30 (56)	19 (35)	1.000 †
T2	Stereopsis	48	32 (64)	10 (20)	48	31 (57)	15 (28)	0.955 †
	Binocularity with 15 dioptre prism test		38 (76)	8 (16)		30 (56)	16 (30)	0.149 †
T3	Stereopsis	50	33 (66)	8 (16)	52	31 (50)	15 (28)	0.919 †
	Binocularity with 15 dioptre prism test		40 (80)	4 (8)		30 (56)	12 (22)	0.296 †

† $\chi 2$ test

3.4 DISCUSSION

Our results indicate a significant improvement in ocular alignment with bifocals. We found a significant difference in reduction of manifest angle of strabismus between bifocals and unifocals: in the bifocal group, more children with orthotropia were found and in those in whom manifest strabismus remained, the ocular alignment was cosmetically better because of smaller manifest angles of strabismus; by contrast, in the unifocal group, the manifest angle of strabismus did not change. The improvement in the bifocal group was visible shortly after starting the use of bifocals and persisted up to the following year.

3.4.1 Time frame of changes

We observed a clear difference regarding the time frame in which the effects of bifocals occurred. Our present study did not reveal a change in mean refractive errors in either intervention group over the course of 1 year; apparently this time frame was too short [Esposito Veneruso et al. 2018]. Yet, NVA did improve significantly after one year in the bifocal group, as we reported in our previous study [de Weger et al. 2019]. This agrees with the finding of Atkinson & Braddick [1983] who described the time frame (several years) needed for visual acuity to develop. In contrast, the

manifest angle of strabismus showed an almost immediate effect in the bifocal group shortly (~6 weeks) after the start with the new corrections that persisted up to the final measurements after one year. During these months, this improved ocular alignment could have supported the development of better near vision. And, vice versa, the improved visual acuity could have supported the relief of strabismus, in line with the finding of Binder et al. [2016]. He observed that some patients presenting with CVI and strabismus experience reduction of strabismus concurrently with improvement in their visual acuity, even to the point of spontaneous resolution of strabismus.

3.4.2 Age

Although strabismus is most common onset at the age of 4 (between 3 and 6 years of age), and more improvement of ocular alignment might have been expected in these young children, we found no difference in effect of the bifocals when comparing age groups under 6 years and over 6 years. This implies that we did not find an age limit for treatment of strabismus with bifocals.

3.4.3 Refractive error, accommodation and convergence

At baseline, strabismus occurred with all forms and magnitudes of refractive errors, as previously described by Cregg et al. [2003]. After one year, we found better ocular alignment in the bifocal group independent of the children's baseline refractive error. This finding agrees with the findings of Doyle et al. [2016, 2017]: (i) the vergence response to disparity is relatively intact and independent of accommodative and pupillary response, that is when eliminating the need for accommodative response, the vergence response is accurate; and (ii), when children with DS change their viewing distance to a nearer target, they are not able to scale their accommodative response accurately. In our study, wearing bifocals with full correction of any refractive error, which diminishes the need to exert accommodation for both distant and for near vision, led to better alignment compared to wearing unifocals. Unifocals only diminish the need to exert accommodation for distant vision, while the problem of not being able to scale the accommodation for near distances persists.

Therefore, if accommodation is not demanded while wearing bifocals, children with accommodative lags (like in DS or CVI [Boot et al. 2010; Hoyt 2013; Fazzi et al. 2007]) will not be troubled by the associated (excessive) convergence response when changing viewing distance.

3.4.4 Conventional strabismus treatment

We believe that the results of our study, which are in line with Haugen & Hovding [2001a], underline the usefulness of the non-surgical intervention in DS in convergent strabismus. The more so because the improvement of ocular alignment with bifocals is an additional benefit to the improved near visual acuity with bifocals. A non-surgical intervention is preferred because children with DS often have comorbidity such as congenital heart defects, and an intervention without anaesthesia is therefore preferred.

3.4.5 Strengths and limitations

The overall strength of our RCT compared to all previous studies is described in our previous publication [de Weger et al. 2019]. An important strength relevant for this paper, is the representativeness of the distribution of angles of strabismus for ocular alignment in DS.

However, the scarcity of large esotropias (> 40 prism dioptres) or exotropias in a representative population of children with DS led to a very small number of children with exotropia or large esotropia in our study population. As a consequence, our findings regarding the effect of bifocals and unifocals on strabismus may not be generalized to children with exotropias or esotropias with an angle over 40 prism dioptres.

Unfortunately, the manifest angle of strabismus could not be assessed in a uniform way for all participants because of the expected cooperation problems [Courage et al. 1994, 1997; Woodhouse et al. 1996; McCullough et al. 2014; Doyle et al. 2016, 2017]. Our approach to deal with this limitation was to combine data from testing methods, as did Yurdakul et al. [2006], Yahalom et al. [2010] and Perez et al. [2013], and limit the analyses to measurements at short distances.

In the analysis of the quality of binocularity and stereopsis, we encountered substantial variability in cooperation and communication in children with DS, as did Yahalom et al. [2010] and Haugen & Hovding [2001a]. More research is needed to study the development of binocularity and stereopsis after longer follow-up times in children who ideally start using bifocals at a young age, such as the age of 2.

3.4.6 Conclusion

Bifocals with full correction of refractive errors help relieve the manifest angle of strabismus in children with DS with accommodative lags within a few weeks, whereas unifocals have no effect, not even after a year. In the bifocal group, the angle of strabismus was reduced or orthotropia was achieved. Once the need for an accommodative effort is eliminated with bifocals, ocular alignment can improve. The improvement in ocular alignment indicates that bifocals could be an important solution for children with DS and strabismus, which is preferable to surgical interventions in view of the large number of contraindications for anaesthesia.

Notes

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4

Differences between children with Down syndrome and typically developing children in adaptive behaviour, executive functions and visual acuity

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4 ABSTRACT

Purpose. In children with Down syndrome (DS) development of visual, motor and cognitive functions is atypical. It is unknown whether the visual impairments in children with DS aggravate their lag in cognitive development.

Methods. Visual impairment and developmental lags in adaptive behaviour and executive functions were assessed in 104 children with DS, 2–16 years, by comparing their adaptive behaviour, executive functions and visual acuity (distant and near) scores against published age-matched norm scores of typically developing children. Associations between these lags were explored.

Results. Mean (± SEM) differences to age-matched norms indicated reduced performance in DS: Vineland Screener questionnaire, -63 ± 3.8 months; task-based Minnesota Executive Function Scale (MEFS), -46.09 ± 2.07 points; BRIEF-P questionnaire, 25.29 ± 4.66 points; BRIEF parents' and teachers' questionnaire, 17.89 ± 3.92 points and 40.10 ± 3.81 points; distant and near visual acuity, 0.51 ± 0.03 LogMAR and 0.63 ± 0.03 LogMAR (near -0.11 ± 0.04 LogMAR poorer than distant). Adaptive behaviour (Vineland-S) correlated with the severity of visual impairment (r = -0.396).

Conclusion. Children with DS are severely impaired in adaptive behaviour, executive functions and visual acuities (near visual acuity more severely impaired than distant visual acuity). Larger impairment in adaptive behaviour is found in children with larger visual impairment. This supports the idea that visual acuity plays a role in adaptive development.

***Subject terms**: Health care, Cognitive control, Pediatrics research, Neuroscience, Neuronal development*

4.1 INTRODUCTION

Approximately 14.6 in 10,000 children are born with Down syndrome (DS), the most common genetic anomaly[1,2]. They have neurological deficits as well as visual impairments. Both of these may challenge the development of functions that rely on executive control. However, it is unknown whether a relation exists between the visual impairments in children with DS and their lag in cognitive development. Possibly, visual impairments aggravate cognitive development. To study this relation, developmental lags in children with DS need to be specified and quantified. Once we know what may be expected with regard to the development of a child with DS, research on evidence-based interventions for this group could be initiated.

In children with DS, motor, cognitive, practical and social skills develop slower and to a lower level compared with typically developing children[3]. Shortly after birth, there is growth and maturation, but it is slow. In the next several months, the development of neuronal morphology of the visual cortex (where visual information is processed), cerebellar and brain stem size, brain weight, skull size, and visual acuity slows down further[4]. Ocular disorders also limit their visual acuity and visual functioning. These disorders include: frequently occurring and severe refractive errors, nystagmus and accommodative lags (inability to accurately change the shape of the eye lens to focus the image of near objects on the retina)[5,6].

In children with isolated visual impairment, visual acuity limits the acquisition of skills needed to respond appropriately to environmental demands across a range of contexts, so-called adaptive behaviour and executive functions[7-12]. Severe early-onset visual impairment is considered a major neurodevelopmental disorder. It impacts multiple developmental processes, such as vulnerabilities in motor, cognitive, language, social and attentional domains—all aspects of adaptive behaviour[12]. Studies by Sonckson and Dale[7], Dale and Sonckson[8] and Tadic et al.[13] showed cumulative debilitating consequences on cognitive, language and social skills. Even children with mild to moderate visual impairment show reduced adaptive behaviour. They have more difficulties with skills that affect development and learning than well sighted, typically developing children[11].

Table 1. *Normative studies used*

Published studies on typically developing children from which we extracted normative data. For each test, the table lists the source of the normative data (i.e., the published study),the number of included children and their age range.

Normative studies	Source	n=	Age range (years)
Vineland-S	Sparrow et al., 1993 [15,16]	979	0-6
MEFS	Carlson, 2019 [37]	32,800	2-17
BRIEF-P	Gioia et al., 2003 [17,18]	1747	2-5
BRIEF parents' version	Huizinga et al., 2009 [20,21]	3,333	5-17
BRIEF teachers' version	Huizinga et al., 2009 [20,21]	941	5-11
Visual acuity (total n=2985)	Salomao et al., 1995 [38]	646	0-2.5
	Pan et al., 2010 [39]	1722	2.5-6
	Lai et al., 2011 [40]	212	3-6
	Huurneman et al., 2012 [36]	75	4-8
	Jeon et al., 2010 [41]	78	5-11
	Dobson et al., 2009 [42]	252	5-12

Executive functions are neurocognitive skills that serve as the foundation for early learning. These functions include working memory, control over impulsive thoughts and behaviours, ability to think flexibly and break habits that can get in the way of learning[14]. Differences in parent-rated executive functions were found between school-aged children with all degrees of visual impairment and age-matched typically sighted, typically developing children[10]. Children with severe to profound visual impairment had the greatest difficulties. With teacher-ratings, Heyl and Hintermair[9] found that visually impaired students also performed poorer at school than typically developing children. Compared to children in mainstream schools, visual impaired children at special schools had even more problems in all domains of executive functions. Almost all domains of behavioural problems and the executive function domains correlated. Although their study may have included some children with DS at special schools, the relation between visual acuity and adaptive behaviour or development of executive functions has not yet been studied in a large cohort of children with DS.

In addition to the learning difficulties associated with the typical malformation of central brain structures in DS, visual impairment could also have an impact on the acquisition of skills needed to respond appropriately to environmental demands. Children with DS attend regular schools where they have to find their way between typically developing children, or they attend special schools where children with other

demands surround them. Insight in the development of adaptive behaviour and executive functions of children with DS in combination with their limited visual acuity may contribute to better tailored therapeutic care and guidance at school.

The current study, therefore, compares adaptive behaviour, executive functions and visual acuity in children with DS with published norm scores of typically developing children and analyses possible associations between these different abilities. Adaptive behaviour and executive functions in everyday life were assessed using parents' questionnaires, Vineland-Screener (Vineland-S)[15,16], BRIEF-P[17–19] and BRIEF[20–22] questionnaires commonly used in DS in clinical practice. The assessment of executive functions was complemented with the teachers' questionnaire of BRIEF and a task-based test, the Minnesota Executive Function Scale (MEFS)[23,24]. Visual acuities were assessed with symbol discrimination on visual acuity charts, LEA symbols[25] or Kay pictures[26].

4.2 METHODS

The assessments presented here were part of a randomized controlled trial (RCT) on the effects of wearing bifocal eye glasses in children with DS[27]. The project was conducted in accordance with the tenets of the Declaration of Helsinki. It was reviewed and approved by the Dutch Medical Ethics Committee of the Isala Hospitals (NL48288.75.14/METC: 14.0333) and registered in ClinicalTrials.gov (NCT02241356). For the current cross-sectional study, we used the baseline measurements of this RCT, i.e., before children were randomized in one of the two treatment groups (bifocal or unifocal glasses). The data were collected at 15 participating locations in the Netherlands, 14 hospitals and 1 institution for the visually impaired. Locations were geographically spread across the country, serving both rural and urban populations of diverse social economic status.

Normative data were obtained from studies on typically developing children (see Table 1).

4.2.1 Participants

Written informed consent was obtained from both parents of each child, or from one parent in case of single parenthood. Inclusion criteria included (1) diagnosis of Down syndrome, (2) age range from 2 to 18 years, (3) ability to respond (verbally or non-verbally) to visual acuity tests if they were older than 5 years. Age two, the age at

which most children could sit and look downwards to their toys in their hands, was chosen as youngest age for inclusion. A total of 104 children with DS between 2 and 16 years (23 and 205 months) old were included. The children were recruited from participating locations in cooperation with the Dutch DS foundation and many organizations of medical and allied health professionals who are involved in the medical guidance of children with DS. Participants' characteristics are listed in Table 2. More details about participants and study design of the RCT are given in our previous papers[27,28].

Table 2. *Cohort characteristics*

Data are given either as numbers (n =) and percentages (%) or as mean with standard deviation.

Cohort characteristics	n=	%	mean	standard deviation
Number of children with DS	104			
Boys	51	49		
Children attending school	91	88		
Children not using glasses	28	27		
Nystagmus	17	16		
Manifest strabismus	31	30		
Age (months)			105.3	42.7
Accommodative lag (dioptres)			2.21	0.89
Distant visual acuity (LogMAR)			0.43	0.26
Uncrowded near visual acuity (LogMAR)			0.56	0.32
Crowded near visual acuity (LogMAR)			0.64	0.29

4.2.2 Assessment procedures

Procedures for assessments of visual functions and executive functions were protocoled. The local investigators, orthoptists from the participating locations, were trained to perform unfamiliar orthoptic tests, to administer the MEFS as prescribed by Reflection Sciences, LLC, and to use the digital research data manager ResearchManager[29].

First, informed consent and the medical history was obtained from the parent(s). Next, a baseline orthoptic assessment was performed, followed by an assessment of executive functions with the MEFS. Children wore their habitual glasses during these assessments. If the child had no glasses prescribed, assessments were performed without glasses. At the end of the first visit, the BRIEF-P or BRIEF (parents' and teachers' versions) and Vineland-S questionnaires were handed out.

If a 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 (Code of conduct in the Netherlands 2002, NVK Code of conduct in the Netherlands 2001). Reasons for missing data, as a result of a lack of cooperation or otherwise, were noted.

4.2.2.1 Adaptive behaviour, Vineland-S questionnaire

Parents were asked to fill out the questionnaire Vineland-Screener (Vineland-S[15,16], either on paper or online. This questionnaire with 72 items covering the four domains of adaptive behaviour—communication, socialization, daily living skills, and motor skills—was used to estimate the adaptive behavioural age of the child. In typically developing children, the adaptive behavioural age (assessed by their adaptive behaviour in the Vineland-S) equals their calendar age. In our study, we refer to this adaptive behavioural age estimated with Vineland-S questionnaire as 'Vineland adaptive behavioural age'. Control data were obtained from Sparrow et al.[15] (n = 979, age range 0-6 years).

4.2.2.2 Executive functions

Executive functions were measured in a task-based test (Minnesota Executive Function Scale, MEFS) and complementary information[30] was obtained with ratings of contextual executive function performance by the children's parents and teachers (BRIEF-P and BRIEF questionnaires).

Task-based test of executive functions, MEFS

The MEFS is a standardized game-like test to measure executive function and learning readiness in children[24]. It captures the gradual development of executive functions across the entire preschool and subsequent elementary school period. The MEFS measures a combination of attention span, the ability to retain information, behavioural management and flexible thinking. It has been tested in more than 32,800 typically developing children, aged 24–215 months, in the United States and is valid and reliable (Intraclass Correlation: 0.94) across a wide range of executive functions[23,24,31]). The MEFS is an engaging computer card-sorting game that is administered one-on-one with a child. In this rule-switch task, examiners asked the participants to match a card to a target[14,32,33]. First, in teaching trials, the examiner directed the child to match the cards on one dimension (colour; e.g., "green ones go

here", or shape: e.g., "lions go here"). After this, the MEFS test includes 7 levels of increasing difficulty, determined by the rules and the images to sort. The 7 levels (corresponding to test scores 10, 20, 30, 40, 50, 60, ≥ 70) are subdivided in decimals to indicate scores of subsets. This test did not presume the verbal ability of the child and the cards are large enough to be distinguished easily by participants with reduced (near) vision with a visual acuity of 1.0 LogMAR. The test was administered on an iPad Air (iPad Air 2, 16 GB–Screen with and height, 197 × 147 mm; resolution 1536 × 2560 pixels; pixel pitch 0.077 mm^2). Children with DS tend to love games on tablets, so we typically obtained good cooperation of the children with the MEFS.

Rating-based assessment of executive functions, BRIEF and BRIEF-P questionnaires

To obtain informant report, we asked the parents to fill out one of two questionnaires. Depending on the calendar age of the child, this was either the BRIEF-P (Behavioural Rating Inventory of Executive Function for preschool age, designed for the age range 2–5 years)[17–19] or the BRIEF (Behavioural Rating Inventory of Executive Function, designed for the age range 5 to 17 years)[20–22]. We also asked the parents to have the teacher fill out the teachers' questionnaire of the BRIEF (age range 5 to 11 years). The BRIEF and BRIEF-P questionnaires are designed to provide an ecologically valid real-world assessment of executive functions.

In our study, we adjusted the age limits of the BRIEF-P and BRIEF questionnaires to better match the administered questionnaire to the adaptive developmental age of children with DS. The BRIEF-P was intended for participants under the age of 8, whereas the BRIEF was intended for participants older than 8 (see Table 3a). The age limit of 8 years was based on the study of van Gameren et al.[34] and personal communication with M. Huizinga, author of the Dutch BRIEF questionnaire[21,22]. Van Gameren et al.[34] found a developmental age in children with DS of half their calendar age but with a wide confidence interval.

The BRIEF-P questionnaires collected ratings on 5 executive functions-scales: inhibition, shift (being flexible in switching allocation of attention), emotional control, working memory, and plan/organize. The BRIEF questionnaires, parents' and teachers' versions, collected ratings on 8 executive functions-scales: inhibition, shift (being flexible in the allocation of attention), emotional control, initiate, working memory, plan/organize, organizing of materials, and monitor. For each of the 63 (BRIEF-P) or 86 (BRIEF) statements, parents indicated whether the particular behaviour described in the item had Never, Sometimes, or Often been a problem for their child within the last six months. Teachers did so for 75 (BRIEF) statements. For

each of these questionnaire types, we only considered the raw aggregated score across domains, the raw Global Executive Composite (rGEC). Higher scores represent greater levels of executive function impairment.

4.2.2.3 Visual functions

Visual acuities—both at distant and at near—were assessed with their habitual glasses or without glasses if the child did not use glasses. We applied non-verbal or verbal methods (matching or naming LEA symbols[25] or Kay pictures[26] on visual acuity charts) according to the capacity of the child. Distant visual acuity was typically tested at 5 m with LEA symbols linearly arranged cards or Kay Pictures. Uncrowded and crowded near visual acuity was assessed binocularly at 40 cm with LEA symbols with absolute spacing[35,36]. Near vision was measured without bifocals, as only baseline measurements were included in this study. In case 40 cm was not feasible because the child insisted to keep the card at a closer distance (n = 13), the actual distance (range 10 to 40 cm) was noted and visual acuity scores were corrected accordingly (although a shorter distance gives less accurate near VA estimates)[36].

4.2.3 Data analysis

Statistical analysis was performed using the statistical package for the social sciences (SPSS version 23, IBM Inc., Chicago, IL).

Only questionnaires in which the number of filled in items passed the limits listed in the respective manuals[16,18,21] were included. We analysed the BRIEF-P, BRIEF parents' version, and BRIEF teachers' versions separate from each other.

Because of the expected discrepancy between calendar age and the adaptive behavioural age for children with DS, the BRIEF-P and BRIEF questionnaire data were not transformed into age-adjusted scores. Instead, we used the raw scores (raw Global executive composite score, rGEC) for all our analyses. In this way, relations between age and total difficulties could be evaluated. Subdomains of the Vineland-S or BRIEF-P and BRIEF questionnaires were not analysed separately because the study focus was on a general developmental assessment. We also used the raw MEFS score, the Total Score, as opposed to its norm-referenced score.

Continuous data are summarized by mean, standard deviation (SD) and range—nominal data by frequencies and proportions. Student's *t*-test and Chi-square test were applied to analyse group differences, respectively.

The scores of the Vineland-S, MEFS as well as the BRIEF-P, BRIEF and visual acuity data were all analysed as a function of calendar age. Pearson correlations or Spearman correlations were computed, and data were compared to norm scores (see Table 1). We used normative data of the Vineland-S[15,16], n = 979, age range 0–6 years, MEFS[37], n = 32,800, age range 24 months–18 years, BRIEF-P[17,18], n = 1747, age range 2–5 years, BRIEF parents' version[20,21], n = 3333, age range 5-17 years and BRIEF teachers' version[21], n = 941, age range 5–11 years. The normative data on visual acuity include several studies, total n = 2985, age range 0–12 years: Salomao et al.[38], n = 646, 0–36 months; Pan et al.[39,] n = 1722, 30 months–6 years; Lai et al.[40,] n = 212, 3-6 years; Huurneman et al.[35,] n = 75, 4–8 years; Jeon et al.[41], n = 78, 5–11 years; Dobson et al.[42], n = 252, 5–12 years. For display purposes, a Loess line fitted to the scores of the children with DS was plotted in Figs. 1, 2, 3 and 4.

To compare the data of children with DS to norm scores, we first calculated the difference between the score of the child with DS and the corresponding norm score for that child's calendar age (i.e., the developmental lag). Thereafter, we analysed the difference scores in a One-sample *t*-test, to test if the mean of the difference scores differed from zero. In a similar way, we also compared the MEFS scores of the children with DS to norm scores corresponding to their Vineland adaptive behavioural age. For this analysis, we first calculated the difference between the score of the child with DS and the norm score matching the child's adaptive behavioural age. Thereafter, we tested the difference scores in a One-sample *t*-test.

The relation between the developmental lag and calendar age was analysed by linear regression. In the text, B is the estimate of the slope that represents the average change in the dependent variable for a unit change in the independent variable (age).

Visual acuity is typically assessed with uncrowded linearly arranged vision charts at distance. In our cohort, distant visual acuity was assessed with uncrowded linearly arranged optotypes as well. Near visual acuity was assessed in two ways, with uncrowded vision charts and with crowded vision charts. In our analyses, we used the uncrowded distant and near visual acuity assessments (assessed with uncrowded linearly arranged distant and near vision charts). Because uncrowded distant visual acuity equals uncrowded near visual acuity in typically developing children[36], we used norm scores for distant visual acuity in analyses of near visual acuity as well.

To study the association of developmental lags (difference in scores between children with DS and age matched norm scores) in adaptive behaviour and executive functions

with visual impairments, we used the difference in distant visual acuity (expressed in LogMAR) between children with DS and age-matched norm scores. In multivariate linear regressions of the lags in scores of Vineland adaptive behaviour and the different executive functions assessments, the association with visual impairment was analysed in covariance with age, gender and school attendance. These covariates were chosen according to findings of Papadopoulos et al.[42] and Metsiou et al.[43]. Information about school attendance was obtained from the parents and was irrespective of duration or type of school. Thereafter, the influence of nystagmus and strabismus was analysed by entering these measures as covariates in the multivariate linear regression.

4.3 RESULTS

Figures 1, 2, and 3 show results from the Vineland-S, the MEFS, the BRIEF-P, and the BRIEF parents' and teachers' versions. For completeness, each figure plots the data of boys and girls separately (boys in blue, girls in red), but in our univariate analyses we have pooled the data across gender because there were no significant differences between boys and girls in our cohort.

4.3.1 Vineland screener questionnaire

The Vineland Screener questionnaires were returned sufficiently filled out by 83 (80%) of the parents. The Vineland adaptive behaviour (expressed in an age in months) of our participants increased systematically with their calendar age, resulting in a strong positive correlation between the two variables ($r = 0.722$, $p < 0.001$; Spearman rank correlation, $r = 0.718$, $p < 0.001$) (see Fig. 1). Note, however, that this measure of adaptive behaviour in children with DS fell below the norm score of typically developing children (identity line, derived from n = 979 children)[15,16]. The average difference between Vineland adaptive behaviour and calendar age in children with DS was -63 ± 35 months (*t*-test, $t(82) = -16.519$, $p < 0.001$). The magnitude of this developmental lag also correlated with calendar age. With increasing calendar age, the Vineland adaptive behaviour in DS was rated further behind normal ($r = 0.965$, $p < 0.001$, $B = -0.78 \pm SEM\ 0.02$, $R^2 = 0.931$). As inferred from the slope, B, of the regression line, the development is about 80% slower in children with DS compared to the typically developing peers.

To detect possible bias, we compared the mean calendar age in the group of children with a filled in Vineland questionnaire and those without (n = 83 and n = 21, respectively, p = 0.579). We found no differences.

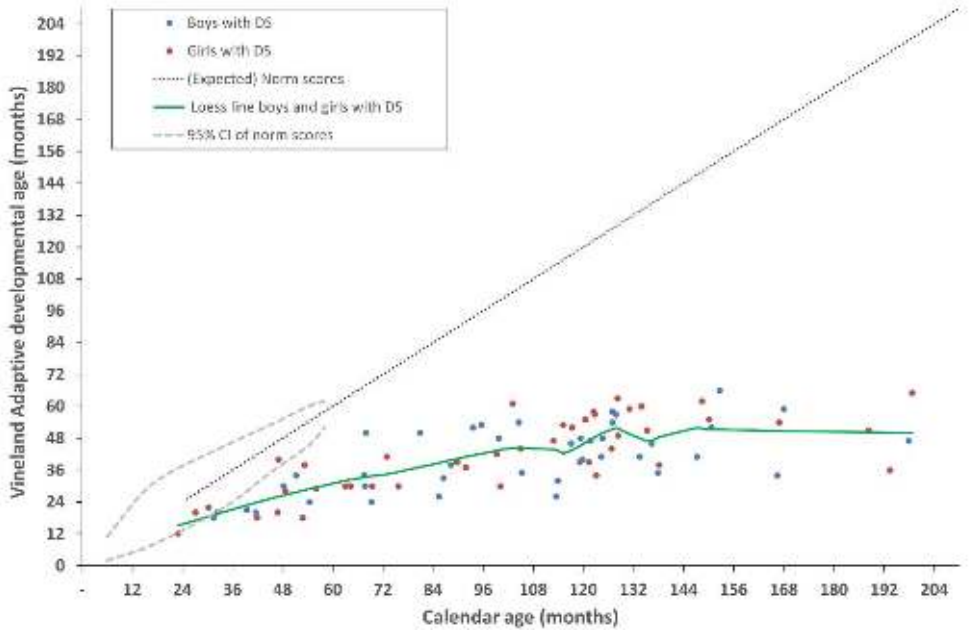


Figure 1. *Vineland Adaptive behaviour*

Adaptive developmental age as estimated by their adaptive behaviour in the Vineland-S, as a function of calendar age in 83 children with DS. Note that all scores fell below the norm (identity line; n = 979, age range 1–72 months; Sparrow et al.[15,16]). According to the measurement focus of the Vineland-S, the norm scores of typically developing children equal their calendar age. Blue bullets: Measured boys with DS (n = 40). Red bullets: Measured girls with DS (n = 43). Solid green line: Loess line fitted to the data of the children with DS pooled across boys and girls. Dotted purple line: (Expected) norm scores (mean) of typically developing children pooled across boys and girls. Grey dashed lines: upper and lower bound of the 95% confidence interval of norm scores of typically developing children.

4.3.2 Minnesota executive function scale

The MEFS was successfully administered in 86 (83%) participants in the age range from 28 to 205 months. In Fig. 2, we first analysed the MEFS data as a function of calendar age and compared the scores of our participants (n = 86) to the normative data of typically developing children (n = 32,800[37]).

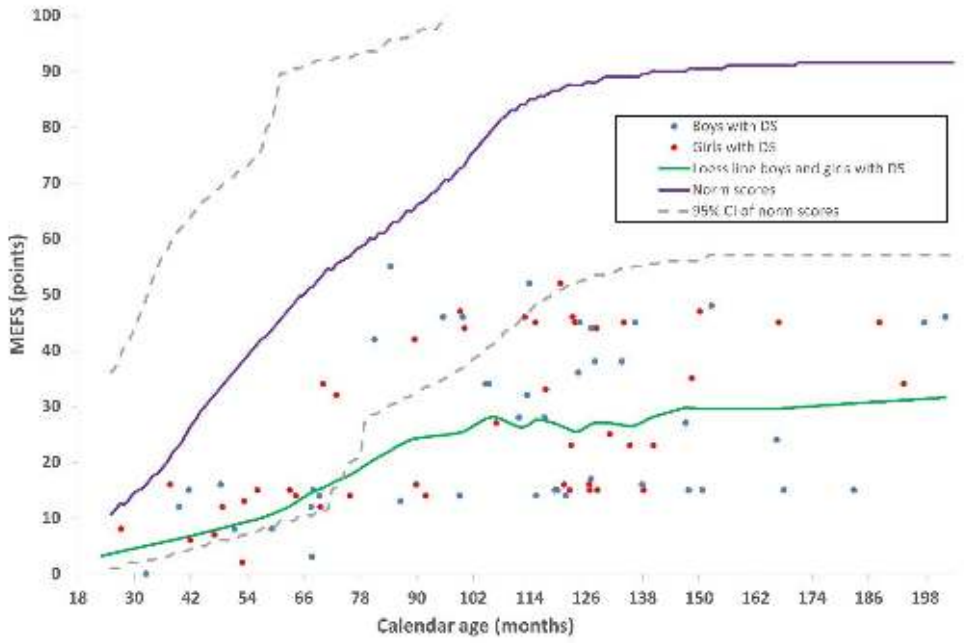


Figure 2. *Task-based executive functions*

Minnesota Executive Function Scale (MEFS) data of 86 children with DS as a function of calendar age together with normative data (n = 32,800, age range 24–216 months; Carlson[37]). Note lower MEFS scores in children with DS compared to the norm scores. Blue bullets: Measured boys with DS (n = 43). Red bullets: Measured girls with DS (n = 43). Green curve: Loess line fitted to the data of the children with DS pooled across boys and girls. Purple curve: Norm scores (mean) of typically developing children pooled across boys and girls. Grey dashed lines: upper and lower bound of the 95% confidence interval of norm scores of typically developing children.

The mean MEFS score in the children with DS was 26.2 ± 14.9 points, range 0 to 55, whereas the mean of the corresponding normative scores was 72.3 ± 22.4 points, range 15 to 92. The mean difference between the MEFS scores of children with DS and the norm scores for children of the same calendar age was significant, -46.1 ± 19.2 points, (*t*-test, $t(85) = -22.246$, $p < 0.001$).

In line with the norm scores, the MEFS scores of participants with DS increased in association with their calendar age ($r = 0.484$, $p < 0.001$). The magnitude of the lag in MEFS scores compared to norm scores also correlated with calendar age. With increasing calendar age, the MEFS scores of children with DS lie further below the norm scores ($r = 0.684$, $p < 0.001$, $B = -0.32 \pm$ SEM 0.04, $R^2 = 0.47$). As inferred from

the slope, B, of the regression line, the development of executive functions as assessed with the MEFS is about 30% slower in children with DS.

We also analysed the relation between the MEFS data and adaptive behaviour (expressed as a calendar age in months, estimated by the Vineland-S questionnaire). Towards that end, we compared the MEFS scores of participants with DS (n = 86) to normative data of children of the same adaptive behavioural age. On average, the MEFS scores of the children with DS coincide with the MEFS scores one could expect based on their Vineland adaptive behaviour (mean difference 0.6 ± 13.9 points, *t*-test, $t(64) = -0.339$, $p = 0.736$). Yet, it appeared that the correlation of MEFS scores of DS participants with their Vineland adaptive behaviour ($r = 0.545$, $p < 0.001$) was not significantly stronger than the correlation of MEFS scores in DS with their calendar age ($r = 0.484$, $p < 0.001$; $z = 2.51$, $p = 0.610$).

Children who successfully performed the MEFS test were on average older than those who did not (mean age 109.2 ± 41.5 and 86.6 ± 44.5, $t(102) = -2.075$, $p = 0.040$), and tended to have higher Vineland adaptive behaviour (mean 42.0 ± 12.22 and 35.1, $t(81) = -1.702$, $p = 0.093$).

4.3.3 BRIEF-P and BRIEF questionnaires

For a total of 89 (86%) children, parents returned the executive functions questionnaires. Some parents completed a questionnaire that did not meet the age range that we had specified, or filled in both BRIEF-P and BRIEF questionnaires. For the analyses below, we used all questionnaire results, provided the number of answered questions exceeded the minima specified in the BRIEF-P and BRIEF protocol (see Table 3b and c).

In Fig. 3, the raw GEC scores of the questionnaires BRIEF-P, BRIEF parents' and teachers' versions are plotted as a function of calendar age together with raw GEC norm scores. We found that the scores of children with DS were on average above the norm (poorer executive functions) in all three questionnaires (mean age-matched children BRIEF-P, 25.3 ± 17.5 points, *t*-test, $t(13) = 5.423$, $p < 0.001$; BRIEF parents' version, 17.9 ± 26.8 points, *t*-test, $t(45) = 4.568$, $p < 0.001$; BRIEF teachers' version, 40.1 ± 20.5 points, *t*-test, $t(28) = 10.535$, $p < 0.001$). None of the scores of our participants correlated with calendar age (all $p > 0.197$), as was the case with the norm scores. Only the teachers' ratings on the BRIEF negatively correlated with Vineland

adaptive behaviour (r = -0.368, p = 0.025) indicating that a higher level of adaptive behaviour was associated with better executive functions at school.

In none of the BRIEF-P or BRIEF questionnaires, we found a difference in mean age or mean Vineland adaptive behaviour between the children whose questionnaire was filled in and whose questionnaire was missing.

Table 3. *Questionnaire return*

Age ranges and numbers of filled BRIEF-P and BRIEF questionnaires

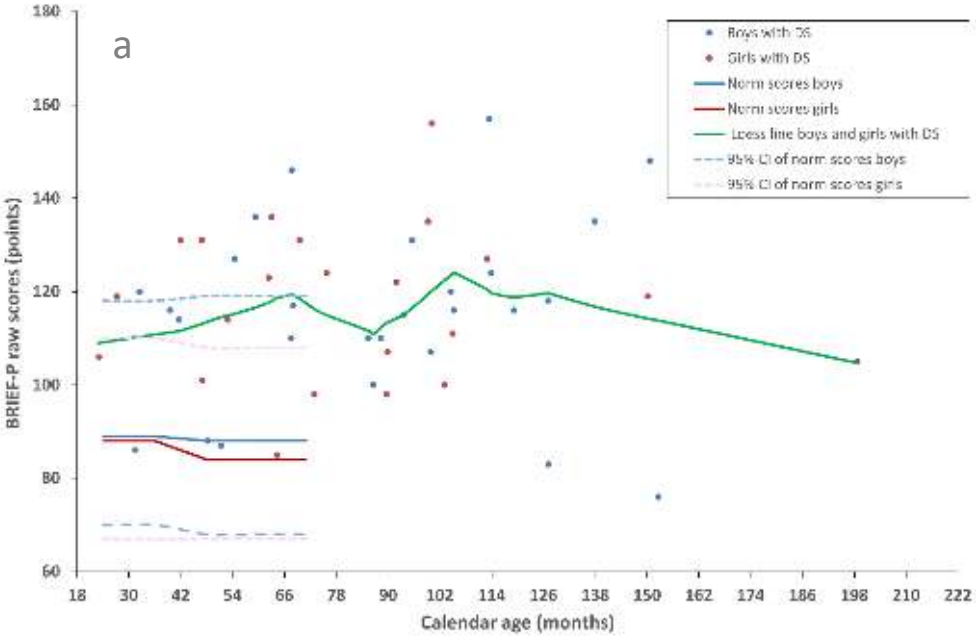
Questionnaires executive functions				
a **Age ranges of questionnaires executive functions**				
	Originally designed for age range	Adjusted age range to Down syndrome in our study		
BRIEF-P	2 - 5 years	2 - < 8 years		
BRIEF parents' version	5 -18 years	8 - 18 years		
BRIEF teachers' version	5 -12 years	8 - 18 years		
b **Number of questionnaires executive functions**				
	Questionnaires filled in	Meeting the age range of the study protocol	Not meeting the age range of the study protocol	Missing questionnaires meeting the age range of the study protocol
	n=	n=	n=	n=
BRIEF-P	49	30 (< 8 years)	19 (> 8 years)	11
BRIEF parents' version	50	44 (> 8 years)	6 (< 8 years)	19
BRIEF teachers' version	39	36 (> 8 years)	3 (< 8 years)	27
c **Number of parents returning combinations of questionnaires**				
	Only one questionnaire	Combination with BRIEF-P	Combination with BRIEF parents'	Combination with both BRIEF-P and BRIEF parents'
	n=	n=	n=	n=
BRIEF-P	35			
BRIEF parents' version	11	3		
BRIEF teachers' version	3		25	11

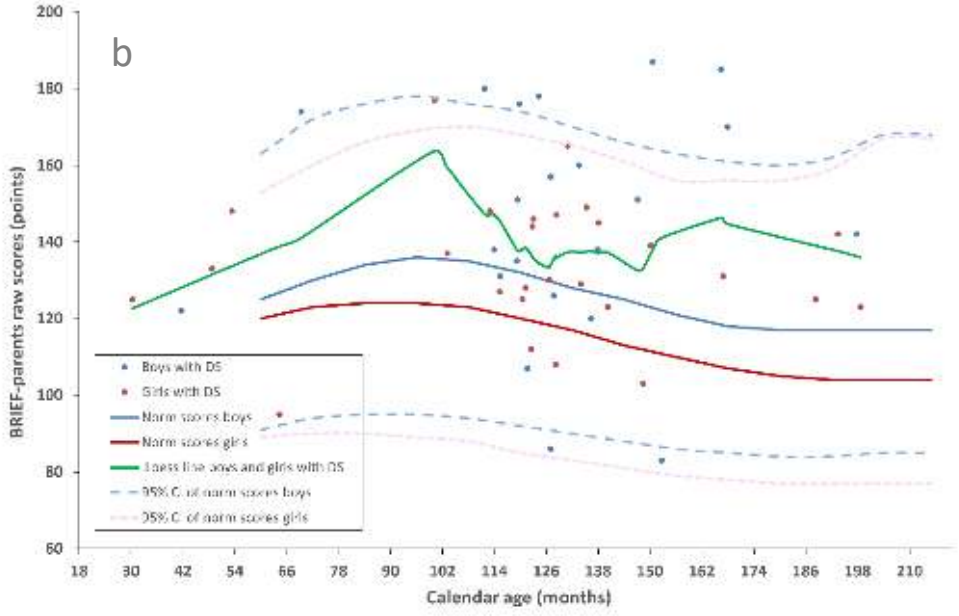
(a) *The age ranges for which the questionnaires were originally designed as well as the adjusted age ranges used of children with DS in the current study.*

(b) *The number of filled in questionnaires.*

(c) *The number of combinations of questionnaires BRIEF-P, BRIEF parents' version and BRIEF teachers' version) which were returned by the parents.*

n = number of participants.


a
Boys with DS
Girls with DS
Norm scores boys
Norm scores girls
Loess line boys and girls with DS
95% CI of norm scores boys
95% CI of norm scores girls
BRIEF-P raw scores (points)
Calendar age (months)


b
Boys with DS
Girls with DS
Norm scores Boys
Norm scores girls
Loess line boys and girls with DS
95% CI of norm scores boys
95% CI of norm scores girls
BRIEF-parents raw scores (points)
Calendar age (months)

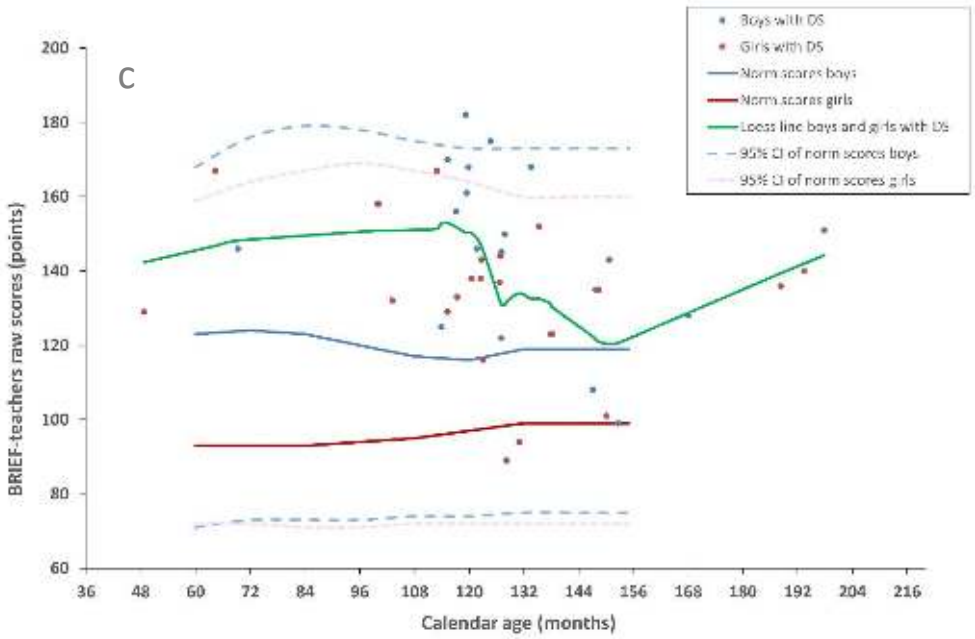


Figure 3. *Informant rated executive functions*

*(**a**) BRIEF-P results for children with DS younger than 8 years (n = 49) Normative data (n = 1747, age 2–5 years) from Gioia et al.[17,18]. (**b**) Parent's version of the BRIEF for children of 8 years and older with DS (n = 89). Normative data (n = 3333, age 5–17 years) from Huizinga et al.[20,21]. (**c**) Teacher's version of the BRIEF for children of 8 years and older with DS (n = 39). Normative data (n = 941, age 5–11 years) from Huizinga et al.[20,21]. Data of children with DS are typically above the norm indicating that children with DS scored poorer on this executive functions scale. Blue bullets: Measured boys with DS (BRIEF-P n = 27, BRIEF parents' version n = 22, teachers' version n = 18). Red bullets: Measured girls with DS (BRIEF-P n = 22, BRIEF parents' version n = 28, teachers' version n = 21). Green curve: Loess line fitted to the data from ratings on children with DS pooled across boys and girls. Blue curve: Norm scores (mean) of typically developing boys. Red curve: Norm scores (mean) of typically developing girls. Light blue dashed lines: upper and lower bound of the 95% confidence interval of norm scores of typically developing boys. Pink dashed lines: upper and lower bound of the 95% confidence interval of norm scores of typically developing girls.*

4.3.4 Visual acuity

We found poor distant visual acuity in the children in DS as well as a poor near visual acuity. Mean distant visual acuity was 0.43 ± 0.26 LogMAR (~0.37 decimal). Mean near visual acuity was 0.56 ± 0.32 LogMAR (~0.28 decimal). Their near visual acuity was on average poorer than their distant visual acuity (mean difference 0.11 ± 0.32 LogMAR,

paired *t*-test, *t*(73) = 2.900, p = 0.005). This is in contrast to typically developing children in whom no consistent differences between near and distant visual acuities are found[36]. The difference between near and distant visual acuity in children with DS did not correlate with their calendar age (r = -0.76, p = 0.520). Visual acuity measurements of our cohort are presented in comparison to the development of (distant) visual acuity during childhood in typically developing children (total n = 2985, age range 0–12 years, including Salomao et al.[38], n = 646, age range 0–30 months; Pan et al.[39], n = 1722, age range 30–72 months; Lai et al.[40], n = 212, age range 3–6 years; Huurneman et al.[35], n = 75, age range 4–8 years; Jeon et al.[41], n = 78, age range 5–11 years; Dobson et al.[42], n = 252, age range 5-12 years) in Fig. 4.

The average difference between distant visual acuity in children with DS and distant visual acuity of age matched typically developing children was 0.51 ± 0.25 LogMAR (~0.6 decimal) (*t*-test, *t*(90) = 19.597, p < 0.001) whereas this difference was 0.63 ± 0.30 LogMAR (~0.7 decimal) for near visual acuity (*t*-test, *t*(75) = 18.175, p < 0.001). These differences did not correlate with calendar age (both p > 0.5).

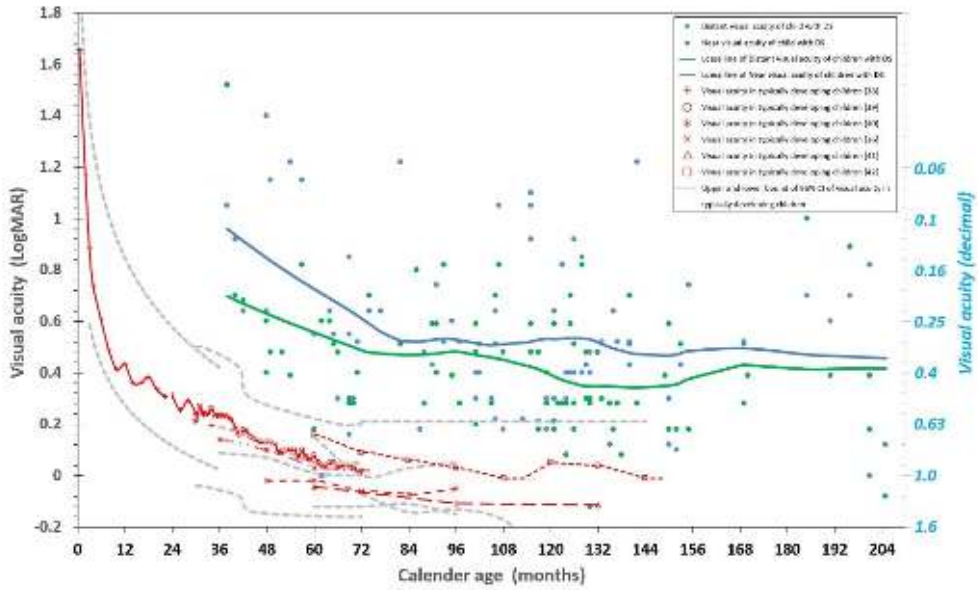


Figure 4. *Visual acuity*

Normative data from typically developing children (age 0–12 years) are shown in red[70] with upper and lower bound of the 95% confidence interval in grey dashed lines (extracted from the separate original studies[70]). Note that before the age of 30 months, visual acuity could be estimated only with a preferential looking test such as the Teller acuity chart (TAC)[71]. From the

age of 30 months, visual acuity could be assessed with symbols the child named, gestured or matched. Distant (green) and near (blue) visual acuity in our cohort of children with DS as a function of calendar age. Solid lines are Loess lines fitted to the data. Note the gradually improving visual acuity of children with DS and typically developing children. The acuities of the children with DS lie above the norm scores indicating that children with DS scored poorly on visual acuity, near visual acuity being even worse than distant visual acuity (mean difference 0.11 ± 0.32, paired t-test t(73) = -2.900, p = 0.005). Normative distant visual acuities were obtained from: Salomao et al.[38], (TAC, n = 646, 0–30 months, red crosses), Pan et al.[39] (HVOT, n = 1722, 30–72 months, red circles), Lai et al.[40] (Landolt-C, n = 212, 3–6 years, red stars), Huurneman et al.[35] (Tumbling E, n = 75, 4–8 years, red x-es), Jeon et al.[41] (Tumbling E, n = 78, 5-11 years, red triangles), Dobson et al.[42] (ETDRS, n = 252, 5–12 years, red squares). Grey dashed lines: upper and lower bound of the 95% confidence interval of the original norm data.

4.3.5 Associations between visual and cognitive impairments

We analysed the association of visual impairment (i.e., the difference between visual acuity of children with DS and the age-matched visual acuity norm scores), in particular distant visual impairment, with the lags in cognitive developmental scores of the children with DS (i.e., the difference in scores between children with DS and norm scores of Vineland adaptive behaviour, MEFS scores and BRIEF-P and BRIEF ratings). Following Papadopoulos et al.[44] and Metsiou et al.[43], we adjusted for possible confounding factors, age, gender and school attendance. We ran separate multivariate linear regressions on the lags in Vineland adaptive behaviour, MEFS scores and executive function ratings. Reported q-values are p-values adjusted for multiple testing with false discovery rate (FDR) correction.

Table 4. Association between visual acuity and Vineland adaptive behaviour

	r	q	B	SE B
Distant visual impairment	-0.396	0.001	-17.37	4.96
Calendar age	-0.964	<0.001	-0.846	0.03
Gender	0.171	0.164	0.287	5.48
School attendance	-0.23	0.055	-10.69	8.47
Model	-0.968	<0.001		

Multivariate analysis of the correlation between the lag in Vineland adaptive behaviour and distant visual acuity impairment adjusting for calendar age, gender and school attendance. R = partial correlation coefficient. q = significance of t-test adjusted for multiple testing with false discovery rate (FDR) correction. B (unstandardized coefficients) = slope. SE B = standard error of the mean of B.

The lag in Vineland adaptive behaviour was related to visual impairment; milder visual impairment was associated with a smaller lag in Vineland adaptive development (see Table 4).

We analysed the correlation between the developmental lag in Vineland adaptive behaviour and the magnitude of visual impairment, adjusting for their calendar age, gender and school attendance. These impairments were correlated ($r = 0.396$, $q = 0.001$). 94% of the variation in the lag of Vineland adaptive behaviour of the child with DS was explained by the model ($R^2 = 0.937$, model $r = 0.968$, $q < 0.001$). Here, both the magnitude of visual impairment and calendar age had a significant correlation with the lag in Vineland adaptive behaviour ($r = -0.40$, $q = 0.001$, $B = -17.37 \pm 5.0$ and $r = -0.96$, $q < 0.001$, $B = -0.85 \pm 0.029$, respectively). Going to school tended to correlate with the lag in Vineland adaptive behaviour ($r = -0.23$, $p = 0.055$, $B = -10.69 \pm 8.5$). The multivariate linear regression analysis showed that an impairment of one LogMAR line (0.1 LogMAR) in distant visual acuity was associated with a lag of 2 months in Vineland adaptive behaviour. One-month-older calendar age in DS was associated with 0.9 months of additive lag in Vineland adaptive behaviour.

The differences in scores of MEFS, BRIEF-P and BRIEF of the children with DS with respect to the norm scores of typically developing children were not correlated to the magnitude of visual impairment (all $p > 0.184$).

We also checked for a possible correlation of these cognitive developmental lags with nystagmus and strabismus (the presence of strabismus or size of the manifest angle), two common ocular disorders in DS that can influence visual acuity. In our data, the presence of nystagmus correlated with a lag in distant visual acuity ($r = 0.361$, $p = 0.001$). However, in none of these regression analyses on the cognitive developmental lags, we found significant correlations with nystagmus or strabismus.

4.4 DISCUSSION

The current multicentre study investigated adaptive behaviour, executive functions and visual acuity in children with DS, aged 2–16 years, in comparison to the age-matched norm scores of typically developing children. We used a parent-rated questionnaire for adaptive behaviour (Vineland-S) and a combination of parent-rated and teacher-rated questionnaires (BRIEF-P and BRIEF) as well as a task-based test (MEFS) for assessing executive functions. Visual acuity was assessed with symbol discrimination on visual acuity charts at distance and at near.

Compared to typically developing children, children with DS had a lower outcome on adaptive behaviour (Vineland-S), poorer outcome on executive functions according to both task-based (MEFS) and rating-based (BRIEF-P and BRIEF) assessment, and poorer visual acuity. Their near visual acuity was even worse than their distant visual acuity. Moreover, the lag in Vineland adaptive behaviour of children with DS was related to the severity of their visual impairment.

4.4.1 Adaptive behaviour

In line with previous studies[34,45–50], the children with DS in our study had weaker adaptive behaviour than typically developing children. As found by Papadopoulos et al.[44] in children with isolated visual impairments (i.e., without DS), older children with DS performed better in the current study too. But, they also showed a larger difference with typically developing children in comparison to younger children with DS. We found the lowest scores in adaptive behaviour in children with poorest visual acuities. This new finding in children with DS is in line with the reports of children with isolated visual impairment (without DS) by Sonckson and Dale[7], Dale and Sonckson[8], Tadic et al.[13] and Bathelt et al.[11].

Even when we analysed the influence of visual acuity in covariance with age, we found the lowest performance in the children with DS with the poorest visual acuities. This agrees with findings of Bathelt et al.[11]. They found poorer adaptive behaviour—in practical, social and conceptual composite scores—in children (without DS) with ascending levels of isolated visual impairment including mild to moderate and severe to profound visual impairments. As in afore mentioned studies in children with isolated visual impairment[7,8,11,13], we only used the assessments of distant visual acuity. Separate analyses of the influence of near visual acuity were omitted because there were too many missing data.

4.4.2 MEFS and BRIEF-P and BRIEF executive functions

In our study, children with DS had poorer executive function-outcomes than typically developing children in both task-based scores and in informant report ratings. This agrees with previous studies[51–57]. In executive functioning assessed with the MEFS, we found an association with calendar age. Older children with DS obtained higher MEFS scores, but they showed larger differences with norm data than younger children with DS. The scores show a large difference with age-matched norm scores, but this reduced MEFS performance is in line with the performance one can expect from their

adaptive behaviour (estimated with Vineland-S questionnaire and expressed in age, months). The lack of correlation of BRIEF-P and BRIEF ratings with calendar age in our study agrees with findings of Lee et al.[57] and the lack of correlation with age in norm data with findings of Gioia et al.[17] and Huizinga et al.[21,22].

The MEFS scores of the children with DS were not clearly associated with their visual acuity. Thus, the MEFS is suitable for children with visual impairment even though some vision is required to do the test.

4.4.3 Relation between adaptive behaviour scores and executive functions scores

Children with poorer adaptive behaviour showed a lower score on the MEFS, which is in line with a recently published study in children with DS by Sabat et al.[58]. The assessments they used resemble the combination of a questionnaire and a card sorting test, MEFS, we used: ABAS-II parents' and teachers' version[59,] and three executive functions tasks including the Wisconsin Card Sorting Test[60], respectively. Other researchers[56] also reported weaker performance on task-based executive functions tests in children with DS compared to children with normal development. In our study, we found an inverse correlation of Vineland adaptive behaviour with BRIEF-teachers' version but not with the parents' versions of the BRIEF and BRIEF-P questionnaires. Explanations for these discrepancies between ratings of executive functions by teachers and by parents include the possibility that teachers and parents are observing different behaviours or phenotypes. The more structured demands of school settings versus relatively less organized home activities may challenge the children in a different way[61,62].

So, different informants may validly contribute unique information from different perspectives.

In the current study, the MEFS scores of children with DS were comparable to the norm scores of typically developing children with the same level of adaptive behaviour. This relation shows the robustness of the Vineland-S and MEFS and underlines the suitability of the MEFS for use in children with DS.

4.4.4 Visual acuity, distant and near

The differences in distant visual acuity and in near visual acuity between children with DS and norm scores—poorer scores in children with DS—agree with previous publications[5,63]. These differences did not change with age because of a similar improvement with age in children with DS and in norm scores. Visual acuity develops slowly (see Fig. 4). Among other factors, the quality of the image on the retina in childhood ages is very important[64,65.] The image quality on the retina can be optimized by correction of refractive errors. In the current study, the children wore their habitual glasses or no corrections at all (i.e., usual care). But, this may not have been the optimal situation because the refractive error can change more rapidly in children with DS than in typically developing children[66].

However, children with DS do not complain because of low visual acuity. So, the need for adjustment of glasses may go unnoticed, unless regular screening is performed. In the literature, this was analysed by van Splunder et al.[67]. Prior to their large study on visual impairment in 1598 adults with DS in the Netherlands, visual impairment or blindness had remained undiagnosed in 40.6% of the persons. By contrast, typically developing children frequently do complain when their corrections are not optimal anymore. We, therefore, can expect that the typically developing children, from whom the norm scores were derived, getting usual care, had better corrections compared to the children with DS. Thus, non-optimal correction of refractive errors by suboptimal glasses may have played a role in the large difference in visual acuity between children with DS and typically developing children.

Apart from non-optimal corrections, other factors may have played a role. The abnormal morphology of the visual cortex in children with DS[4] induces impairment in cerebral visual processing, so called cerebral visual impairment (CVI)[68]. Thus, probably, the differences in visual acuity between children with DS and typically developing children also are the result of CVI in children with DS. CVI includes accommodative lags and crowding problems[69]. Accordingly, we found accommodative lags resulting in low near visual acuity and the poor crowded near visual acuity in all of our participants (see Table 2).

The observed difference between distant and near visual acuity in children with DS is mainly due to accommodative lags with non-optimal refractive corrections. In our RCT, we found that the difference between distant and near visual acuity in children with DS can be minimized with optical corrections tailored to the ocular disorders of

children with DS[27]. Wearing full correction of refractive error can maximize distant visual acuity and partly support near visual acuity. Additionally, wearing bifocal glasses, the extra correction for looking at short distances stimulates the development of near visual acuity[27] and thus reduces the difference between distant and near visual acuity in children with DS.

4.4.5 Strengths and limitations

Strengths of the current study include: the large sample size with a relatively rare and biologically well-defined condition (DS), the robust and standardised measurements that made data collection across multiple sites possible, the use of both task-based and informant-based measures of executive function, and the consideration of both adaptive developmental age (estimated from their adaptive behaviour in the Vineland-S questionnaire) and calendar age. In addition, this is the first study in children with DS to assess task-based executive functions with the MEFS.

Limitations of the study include the fact that normative data, being derived from other studies, may have been collected under different experimental conditions. However, all these studies included large groups (see Table 1). Norm scores of the Vineland-S and BRIEF-P had a limited age range (from 0 to 6 years and from 2 to 5 years, respectively), which limited comparisons with older children. Furthermore, as 90% of the included children needed updated glasses[27], a variable part of the visual impairments may have been due to insufficient correction of refractive errors. These avoidable impairments might have obscured a relation between executive functioning and the level of best-corrected visual acuity.

We also encountered difficulties in the acquisition of data, resulting in missing data. This was partly due to practical issues (no iPad with the MEFS test available), but mostly due to a lack of cooperation of the participants during the assessments on the one hand, and parental inattentiveness in returning completed questionnaires on the other. It is known that in children with DS, as in other children with cognitive disabilities, cooperation difficulties can emerge. In our cohort of children with DS, in which children were not selected because of high level functioning or cooperation, these difficulties were unavoidable. The local examiners all had volunteered to cooperate in this study and did their utmost to collect the data. Despite their motivation to obtain the necessary measurements, they sometimes had to skip a test, or stop the measurements according to the Dutch code of conduct relating to expressions of objection by people who are incapable of giving consent (2002).

However, of all the scores we collected, only the MEFS scores may have been affected by an age difference between the group of children whose scores were available and whose data were missing. By including young children with DS regardless of their developmental delay, it was unavoidable that we encountered children whose adaptive behaviour was not proficient enough to perform the MEFS test (designed for children without cognitive delay from the age of 2 years).

Finally, a cross-sectional analysis, as was performed in the current paper, has inherent limitations. It compares participants to estimate the development of skills with increase of age. In this particular case, it is obvious that the sample of children with DS is much more heterogeneous in terms of achieving adaptive skills or executive functions than a non-clinical typical developing sample. This clearly underlines the need for a longitudinal design in order to understand better the development of adaptive behaviour and executive functions in children with DS and its relation with visual acuity.

4.4.6 Implications of the differences found between DS and typically developing children

Children with DS attend regular schools or special schools, both with only a minority of children with DS. Being aware of the specific limitations in abilities of this syndrome can be a support to parents, teachers and other professionals in the management and guidance of children with DS. Regular, targeted screening can detect, specify and quantify the developmental lags and estimate the specific need of the individual child with DS. Interventions or adaptations might be developed and applied to support and stimulate development to, at least partly, reduce the developmental lags in children with DS. Optimizing visual functions with corrective glasses tailored to the ocular disorders of children with DS is one of these interventions. Possibly, besides improving visual functions, it may stimulate development on different levels, including adaptive behaviour and executive functions. A cumulative impact of one of the delays in development on other developmental processes, already mentioned and shown in children with isolated visual impairments[7,8,13], might also exist in children with DS. In the current study, a significant relation between visual acuity impairment and a lag in Vineland adaptive behaviour was found. It has still to be proven that interventions are useful in decreasing differences, which otherwise, according to our findings, get larger with increasing age. It is also not yet clear what the developmental range is in children with DS with optimal corrections and interventions.

4.4.7 Conclusions

Children with DS in the age range of 2–16 years are severely impaired in adaptive behaviour, executive functions and visual acuities (both distant and near). Larger impairments in Vineland adaptive behaviour are associated with larger impairments in visual acuity. This supports the idea that visual acuity plays a role in the development of adaptive behaviour, as previously suggested for visually impaired children without known developmental disorders. Furthermore, near visual acuity is more severely impaired in DS than distant visual acuity, presumably because of the accommodative lag in DS. These findings emphasize the necessity of regular screening during development in DS and, if possible, the application of interventions or adaptions.

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5

One-year effects of bifocal and unifocal glasses on executive functions in children with Down syndrome in a randomized controlled trial

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5 ABSTRACT

Purpose. Appropriate glasses can improve visual functioning of children with Down syndrome (DS), but it is unknown if such interventions influence their cognitive impairments.

Methods. In a randomized controlled trial with one-year follow-up, children with DS (2–16 years) were provided either bifocal glasses (add +2.5 Dioptres; n = 50) or unifocal glasses (n = 52). Executive functions were assessed pre- and post-intervention with the task-based Minnesota Executive Function Scale (MEFS) and with questionnaires, BRIEF-P and BRIEF, parents' and teachers' version. Intervention effects and associations between executive functions, (near) vision and ocular alignment were analysed.

Results. Intervention improved MEFS Total-scores in the bifocal group (p = 0.002; Cohen's d = 0.60) but not in the unifocal group (p = 0.191; Cohen's d = 0.24). Post-intervention, there was no intergroup difference (p = 0.120; Cohen's d = 0.34). Post-intervention, higher MEFS-scores were associated with better visual acuities (crowded near p = 0.025; uncrowded near p = 0.019; distant p = 0.045). Pre-post changes in MEFS-scores correlated significantly with improved ocular alignment (p = 0.040). Exploratory analysis of the questionnaires showed improved teacher-rated BRIEF-scores in both groups (bifocals: p = 0.014, Cohen's d = 1.91; unifocals: p = 0.022, Cohen's d = 1.46), with no intergroup difference (p = 0.594; Cohen's d = 0.23).

Conclusion. These results demonstrate positive effects of wearing better-correcting glasses on executive functioning in children with DS, suggesting a link between their visual and executive functioning. However, the relative contributions of distant and near vision need further study.

5.1 INTRODUCTION

Down syndrome (DS) is the most frequently occurring chromosomal anomaly; with an incidence of 14.6 in 10,000 live births[1,2]. The brain development in DS is slower and to a limited level compared to typically developing children[3-6]. As a result, children with DS have a varying degree of intellectual impairment with delayed cognitive and motor development[7]. The neurological deficits, as well as the ocular disorders specific for children with DS, hamper their visual acuity[8]. Reported prevalences of ocular disorders in children with DS differ between publications, but they are invariably higher than in typically developing children[5,8-21]. In 80 to 100% of the children with DS, reduced visual acuity, poorer than 0.3 LogMAR, (near visual acuity even more severely than distant visual acuity) and reduced contrast sensitivity are found. Accommodative lags (incapacity to accurately change the shape of the ocular lens to focus the image on the retina) occur in 50 to 90% of the children with DS, strabismus (squint) in 15 to 47%, nystagmus (involuntary eye movements) in 6 to 33%, and refractive errors inappropriate shape of the eye causing problems with focusing light accurately on the retina) are found in 40 to 90% (depending on the definition of the lower limit of refractive error) and these refractive errors are larger compared to typically developing children. The ocular disorders are mutually related and aggravate each other. For example, uncorrected refractive errors can hamper the development of visual acuity because there is no focused image on the retina. In specific refractive errors (hyperopia), accurate accommodation can focus the image on the retina, but the accommodation is associated with convergence stimulus, which may induce strabismus which on its turn induces amblyopia (lazy eye, low visual acuity). If accommodation is poor, the attempt to accommodate can induce strabismus and, as a result of strabismus, amblyopia. Nystagmus also hampers visual acuity, but low visual acuity aggravates nystagmus. More information about the ocular disorders in children with DS and the effect of bifocal on visual acuity and strabismus in children with DS is given in our previous publications[21,22].

Visual impairment can hamper cognitive development too. In visual impaired children without known developmental disorders, the level of visual impairment indeed correlates with deficits in cognitive development[23-27]. Cumulative debilitating consequences of early-onset visual impairment on cognitive, language and social skills are described in other studies[23,24,28]. Even children with mild to moderate visual impairment show reduced adaptive behaviour. They have more difficulties with skills that affect development and learning than normally-sighted typically developing

children[28]. However, in children with DS, it is still unclear whether the visual impairments aggravate their lag in cognitive development. If this relation exists, improving their visual acuity with optimal corrections in glasses tailored to the specific ocular disorders of children with DS could support cognitive development. Children with DS might also benefit from higher visual acuities because studies performed in the last two decennia show that their visuospatial memory is relatively preserved, and better than their verbal memory[29–32]. In addition, the recent review by Lukowski et al.[33] of studies on executive functions in children with DS underscores the relative strength in visual spatial working memory. Deficits occur in all domains of executive functions of children with DS—planning and goal directed behaviour, inhibitory control, cognitive flexibility and working memory—but children with DS perform worse on verbal working memory than on visuospatial working memory. The observed deficits in working memory are important in their own right, but its association with academic achievement in children with DS highlight its significance further[34].

Improving visual acuity with optimal corrections in glasses tailored to the specific ocular disorders of children with DS could be a first step to support their visuospatial working memory and their cognitive development. Correcting refractive errors in the way it is done in typically developing children is not optimal for children with DS, because of their specific mixture of ocular disorders. Full correction of refractive error is required because of the lag in accommodation. Moreover, the accommodation deficit may require different correction for looking at far and near distances. In small scale studies with bifocals in children with DS, good results were obtained in accommodative accuracy[35,36], near visual acuity and literacy skills[37,38] through the near addition. Adyanthaya et al.[39] studied the compliance with wearing bifocals. Of the children with bifocals, 89% were compliant whereas only 50% were compliant with unifocals. Al-Bagdady et al.[36] (n = 40, age range 5–14 years) found that accommodation was accurate in 38 (95%) children. Nandakumar et al.[37,38] reported that with bifocals, visual acuity improved more than 1.5 LogMAR and that 6 months later, literacy skills and school performance were improved too. However, this investigation did not include a control group, and focused only on a small group of children with DS that were pre-selected for their ability to read and write.

Triggered by these improvements in near visual acuity with bifocals[37,38], we set up a multicentre randomized controlled trial (RCT) in the Netherlands to study the effect of bifocals in comparison to unifocals on visual functions and cognitive development. Evaluated visual functions included distant visual acuity and near visual acuity– both uncrowded (i.e., charts with a clear spacing between the symbols) and crowded (i.e.,

symbols printed as close together as letters in a word) acuity, accommodative accuracy, strabismus, binocularity and stereopsis. After one year, the full correction of refractive error improved distant visual acuity in both intervention groups, but bifocals led to the largest improvement in near visual acuity and better ocular alignment (fewer children with strabismus and smaller angles of strabismus)[21,22]. The improved visual acuities were a good starting point to study the association with cognitive development too. Cognitive development was assessed by testing executive functions—neurocognitive skills that serve as a foundation for early learning[40].

The cross sectional analysis of our baseline measurements was, to the best of our knowledge, the first study to investigate the relation between lags in executive functions and visual impairments in children with DS[6]. This analysis showed a correlation between visual acuity and the level of adaptive behaviour as previously reported for visual impaired children without developmental disorders[23-28,41]. The observed correlation between visual acuity and the level of adaptive behaviour is a first indication that visual acuity might play a role in the development of executive functions in children with DS. However, at baseline, the children still wore their habitual glasses, glasses that were often not updated recently and that typically under-corrected for the children's refractive errors at the time of inclusion. Thus, in our previous study, we did not consider the effect of best-corrected visual acuity, nor did we analyse the 1-year cognitive development.

In the current paper, we assessed and compared the effects of two interventions improving visual acuity in children with DS, bifocals and unifocals, on cognitive development. We analysed the executive functions assessed in different ways and examined the relation between post-intervention visual acuity and the level of post-intervention executive functions. We hypothesized that if visual acuity influences cognitive development, intervention with glasses should have a larger effect on executive functioning after a whole year than shortly after the intervention. Second, if near visual acuity is of particular importance, we would expect a larger effect of bifocals than of unifocals. Third, we would expect a significant correlation between improvements in visual acuity and improvements in executive functions. Note, however, that distant and near visual acuity need not have the same effect on different measures of executive functions, as different measures of executive functions capture different facets of executive functioning[42,43].

5.2 METHODS AND PARTICIPANTS

To study the difference between the effect of bifocals in the intervention group and the effect of unifocal glasses, both with full correction of refractive error, we performed a multicentre randomized controlled trial in 15 participating locations in the Netherlands. Detailed descriptions of the methods and participants of this study have been published elsewhere[6,21,22]. Here, we reproduce part of the methods, for completeness and clarity.

The locations, 14 hospitals and one institute for the visually impaired, were geographically spread across the Netherlands serving rural and urban populations of diverse social economic status.

The included children from the participating institutes were randomly allocated to the two intervention groups with equal probability: bifocal group and unifocal group. The digital Web-based research data managing system, ResearchManager (2014, 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) effectuated the randomization in a permuted blocks randomization schedule, stratified by gender, age, and language development (parents report: speaking in 1 to 3 word sentences and speaking in 4 word or longer sentences). The intervention group, to which the child was assigned, was always known to the participant, the orthoptist and the investigator, because bifocal glasses are a visually prominent marker.

In both groups, full correction of refractive error measured using cycloplegia was applied. The bifocal segment top of the applied longline (flat-top or D-segment) bifocals with addition +2.5 dioptres, used in the bifocal group, was placed at the pupillary centre, as used in previous studies[35,36]. In those studies, good results were achieved in improving near vision and compliance in wearing these glasses. The children were seen on four occasions, T0 (baseline), T1 ~6 weeks, T2 6 months after inclusion, and T3, the final assessments one year after inclusion (see Fig. 1).

This project (Clinicaltrials.gov registration number NCT02241356, registration date 16/09/2014) was approved by the Dutch Medical Ethics Committee of the Isala Hospitals (NL48288.75.14/ METC: 14.0333) and confirmed by the local ethics committees of the participating clinics. All methods were performed in accordance with relevant guidelines and regulations[21,44,45]. The sample size was calculated with G*Power 346 according to results of former research[37] on near vision before and after

bifocals were used. To enlarge the inclusion number, we made some amendments to the protocol shortly after the trial commenced and these were approved again by the Medical Ethics Committee. Recruitment time, first planned for 6 months (from June to November 2015), was extended to 9 months (to February 2016), follow-up time was shortened from 1.5 year to one year (ending March 2017), and the age range originally limited from 2 to 14 years was extended to 18 years.

The current paper reports the effect of bifocals and unifocals, both with full correction of refractive error, on executive functions during one year follow-up. In our previous papers, we described the baseline assessments of executive functions[6] (Fig. 1, T0) and the effects of bifocals and unifocals on visual acuity[21], accommodative accuracy and strabismus[22].

5.2.1 Participants

A total of 119 children with DS between 2 and 16 years old were included after written informed consent was obtained from both parents of each child, and one parent in case of single parenthood. We included children from the age of two years, the youngest age at which bifocals can be used in the appropriate way by children with DS, because visual development takes place in the first years of life and the development of strabismus may be avoided when corrections for hyperopia are used from young ages (to avoid excess of accommodation attempt, which induces convergence). At the age of two years, most children with DS can sit and perform a task at a table. This task performance induces a viewing direction which is needed to use bifocal glasses in the appropriate way. All of the included children had (1) accommodative deficit, (2) not worn bifocals before, (3) ability to respond (verbally or non-verbally) to vision tests if they were older than 5 years, and (4) were able to sit on a chair while doing a task. 104 children came back for testing with their newly prescribed glasses and were included in the longitudinal analyses described in this paper.

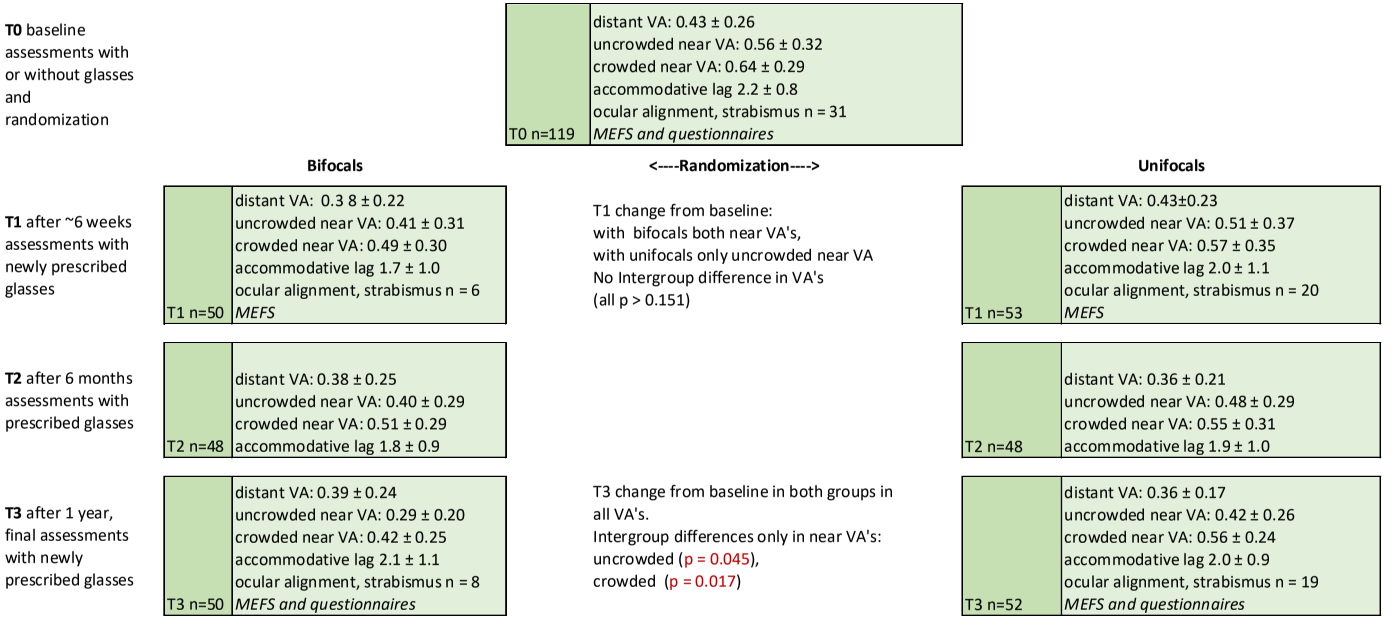

Figure 1. *RCT time-line*

RCT time-line

Study design with the number of children tested at each point in time (n), mean visual acuities (± standard deviation. Expressed in LogMAR), with significant short-term (T1) and 1-year (T3) changes, and type of executive function assessments at baseline (T0), shortly after receiving new glasses (T1), interim check for visual functions (T2) and after 1 year (T3).

Randomization was stratified by age, gender and level of verbal development.

VA = visual acuity, MEFS = Minnesota executive function scale, a task-based executive function test

5.2.2 Assessment procedures

Procedures for visual function examination and assessment of executive functions were protocoled. The participating orthoptists, local investigators from the 15 participating locations in the Netherlands, were trained to perform unfamiliar tests, to administer the MEFS as prescribed by Reflection Sciences, LLCTM, and to use the digital research data manager ResearchManager (2014). Additionally, each participating centre was visited by the principal investigator to review the procedures before the start and twice by an independent research monitor during the study to verify compliance of the local investigators with the research protocols.

A baseline visual function assessment was performed followed by executive functions assessment with the task-based test. At the end of the first and final visit, questionnaires were handed out to the parents to be filled out at home or were administered online by the parents or teachers, respectively.

If a 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[45] (Code of conduct in the Netherlands 2002, NVK Code of conduct in the Netherlands 2001). Reasons for missed data, be it a lack of cooperation or otherwise, were noted.

5.2.2.1 Visual functions

Visual functions were assessed at all four time-points (Fig. 1). At baseline (T0) the children wore their habitual corrections or no corrections when they did not use glasses. At all 3 time-points thereafter (T1, T2 and T3), the children wore their newly prescribed glasses.

Visual acuity. Visual acuity was assessed with verbal or non-verbal methods at distance (5 m or 3 m, according to the capacity of the child) and at near (40 cm) with symbol discrimination on visual acuity charts. Depending on the child's capacity, we used LEA symbols[47]or Kay pictures[48]. At 40 cm, we assessed both uncrowded (symbols with large spacing) and crowded (symbols arranged close to each other like letters in a word) near visual acuity with LEA symbols with absolute spacing[49,50].

Accommodative accuracy. Accommodative accuracy was assessed at 25 cm and 16.7 cm using the 'modified Nott method'[9,51,52]. The child looked at a small fixating object

at the close distance. Meanwhile, the streak retinoscope was moved closer and further away from the child's eyes to assess the distance of the exerted accommodation.

Strabismus and binocularity. In case of (nearly) straight eye position (evaluated with corneal light reflex at the beginning of the assessment) binocularity and stereopsis were assessed with one of several tests (TNO test (Lameris Ootech, Nieuwegein, The Netherlands), Titmus Fly (Stereo Optical Co., Inc., Chicago, IL), Lang Stereotest (Lang-Stereotest AG, Küsnacht, Switzerland), or positive base out 15 dioptre prism test), chosen by the orthoptist according to the developmental stage and cooperation of the child. After that, both manifest and/or latent strabismus angles were assessed with the prism cover test at 30 cm and 5 m, the Hirschberg corneal reflex test[53] and cover test at 30 cm and 5 m.

5.2.2.2 *Adaptive developmental behaviour*

The Vineland-Screener[54,55] (Vineland-S) was used to assess adaptive developmental behaviour at baseline (T0) only. The Vineland-S is a questionnaire for parents with 72 items. This questionnaire covers the four domains of adaptive behaviour: communication, socialization, daily living skills, and motor skills.

5.2.2.3 *Executive functions*

Executive functions (EF) were assessed with a task-based method and with questionnaires. Such methods are complementary to one another[55-58.] Task-based tests are like a snapshot, a momentary assessment mostly under optimal conditions. By contrast, rating based assessments provide a score of everyday executive functioning in the daily behaviour of the children in various settings.

Task-based: Minnesota executive function scale (MEFS). At T0, baseline, T1, the assessment with newly prescribed glasses after ~6 weeks, and at T3, the final assessments after one year, the participants themselves were tested using the task-based Minnesota Executive Function Scale[59,60] (MEFS). The MEFS is an engaging computer card-sorting game administered on an iPad one-on-one with the child. The MEFS test, suitable for the entire calendar age range of our participants, includes 7 levels of increasing difficulty, corresponding to the Total scores of 10, 20, 30, 40, 50, 60 and 90. The picture size of the MEFS test applied in our study is ~8 M which is visible for visual acuities of 1.5 LogMAR (3/100 Snellen equivalent) with an allowed viewing distance up to 15 cm.

Questionnaires: BRIEF-P (preschool), BRIEF parents' and BRIEF teachers'. At T0 and T3 (i.e., at baseline and after one year), we obtained informant based ratings from the children's parents and teachers in the Behaviour Rating Inventory of Executive Function (BRIEF-P or BRIEF) questionnaires[61–66]. The parents filled in the BRIEF-P questionnaire or the parents' version of the BRIEF depending on the calendar age of the child (in this study of children with DS, younger than 8 years or eight years and older, respectively). Teachers filled in the teachers' version of BRIEF. These questionnaires provide an ecologically valid real-world assessment of executive functions and yield complementary information to the task-based test[56]. The BRIEF and its subscales can generally be performed in a psychometrically sound manner among school-age children with DS[56,67]. In our analyses, we only considered the raw aggregated scores across domains, the raw Global Executive Composite (GEC). Normative GEC scores in both boys and girls on the parents' version of the BRIEF range between 72 and 216 and on the teachers' version between 73 and 219. In BRIEF-P the normative GEC scores lie between 189 and 63 for boys and girls. Higher scores represent greater levels of executive function impairment.

5.2.3 Statistical analyses

Statistical analyses were performed using the statistical package for social sciences (SPSS version 23, IBM., Chicago, IL) and the statistical software package "R" (version 3.6.2). We used mixed effects regression models with a random intercept estimated for each participant. R-code for the mixed effects regression analyses is made available on the data repository for this paper.

Adjustment for adaptive developmental age, assessed with the Vineland-S questionnaire, was not needed because calendar age and adaptive developmental age assessed with the Vineland-S questionnaire were tightly correlated (Pearson $r = 0.722$, $p < 0.001$ and r (partial adjusted for gender) $= 0.724$, $p < 0.001$).

For each intervention group, we first compared baseline MEFS, BRIEF-P and BRIEF results with post-intervention scores (pooled across T1 and T3). Then, we compared the post-intervention results between the two intervention groups. Thereafter, we analysed the relation between final visual acuities and post-intervention MEFS scores. In addition to the test statistics and confidence intervals, we report Cohen's d as a measure of effect size. According to common convention, we interpret Cohen's d effect sizes of 0.2, 0.5 and 0.8 as being small, medium and large, respectively.

To analyse and compare the effects of the interventions on performance in the MEFS test, we used the raw MEFS score, the Total score (further referred to as MEFS score), as opposed to its norm-referenced score, because children with DS have cognitive and motor developmental lags and their development is heterogeneous. We ran one mixed effects model on the MEFS scores obtained at T0, T1 and T3 with gender and age at T0 (in months) as covariates. As the post-intervention (T1 and T3) MEFS scores were not significantly different between the T1 and T3, we pooled the data from these two time-points to maximize statistical power.

Unfortunately, there were too many missing data for each of the baseline visual acuity measures to analyse the effect of intervention-related visual acuity changes on the change in MEFS score. To make best use of the data, we instead quantified the relation between visual acuity (i.e., visual acuity with newly prescribed glasses) and post-intervention MEFS scores. We only considered the data of visits T1 and T3. The analysis consisted of several steps. We first modelled the MEFS scores as a function of gender, age and intervention using the data from participants with no missing values. From the resulting mixed effects model, we then calculated adjusted MEFS scores, i.e., MEFS scores adjusted for gender, age and intervention for the participants with MEFS scores at T1 and/or T3. Then, we ran three separate mixed effects models for the adjusted MEFS scores with crowded near visual acuity, uncrowded near visual acuity and distant visual acuity as fixed effects, respectively. The missing data of near visual acuities and distant visual acuity would otherwise introduce changes in the coefficients for gender, age and intervention between these three analyses.

We also tested the association between the changes in ocular alignment and changes in MEFS scores between T0 and T1 by applying the Spearman rank-correlation test. In this analysis, only children with MEFS scores available at both T0 and T1 were included.

To analyse the results of the BRIEF-P and BRIEF questionnaires, we used the raw GEC scores (Global Executive Composit, i.e., the composite scores of all scales). We did not convert these scores to age-adjusted 'total scores' for typically developing children (as described in the manuals of the questionnaires) because children with DS have motor and cognitive delays.

Because questionnaire data were often missing, we had to limit our analyses of the BRIEF-P and the two versions of the BRIEF to an exploratory analysis of the complete cases. A paired *t*-test was used to analyse the differences between baseline scores

and final scores. An unpaired *t*-test was used to compare these differences between intervention groups. We calculated the lags of the children with DS compared to norm scores given in the manual of the questionnaires, i.e., score of the child with DS minus age-matched norm score, at T3, after 1-year(T3). We compared these developmental lags at final assessments to the lags found at baseline[6]. For completeness, and to be aware of possible biasing factors, we compared the group of children included in these analyses to the group of children excluded because of missing data.

5.3 RESULTS

At baseline, the bifocal and the unifocal group showed no statistically significant differences in calendar age, adaptive developmental age, uncrowded and crowded near visual acuities and distant visual acuity, accommodative accuracy, strength of habitual glasses, ocular alignment and executive functions as assessed with the MEFS and BRIEF-P or BRIEF[6,21,22].

5.3.1 MEFS

The MEFS was successfully administered in 86 (83%) participants at baseline (T0), in 82 (79%) participants at T1 when the children just started to use their new glasses, and in 94 (90%) participants at the final assessments (T3). MEFS scores were missing for various reasons. Either the child was too young or it did not understand the test (2, 5, 3 times at T0, T1 and T3, respectively), or the child was uncooperative (4, 5, 0 times respectively) or there were technical problems with the iPad (1, 5, 3 times respectively). For the remaining cases, no cause was described. In our analyses, only participants with baseline scores who had a follow-up score at T1 and/ or T3 were included (bifocals n = 41; unifocals n = 44).

5.3.1.1 Effect of the interventions on MEFS total scores

Post-intervention MEFS score were correlated with age (see supplementary Table S2) as they were at baseline[6]. Therefore, to investigate the effect of the treatments, we took into account gender and calendar age as possible confounding factors. We ran a mixed effects model for the effect of treatment on MEFS scores adjusted for gender and calendar age at baseline across all three time-points at which MEFS scores were collected (T0, T1 and T3). In these analyses, the follow-up scores were pooled across T1 and T3 since there were no significant differences between T1 and T3

(t(77) = -1.459, p = 0.149; Supplementary Fig. S1 and Table S1). The results are shown in Fig. 2. The mean MEFS score at baseline adjusted for gender and calendar age was 22.4 points (95% CI: 15.0, 29.7). On the post-intervention visits, the mean MEFS score was increased to 28.0 points (95% CI: 20.5, 35.5) in the bifocal group, and to 24.6 points (95% CI: 17.1, 32.1) in the unifocal group. In the bifocal group, the medium effect difference in mean MEFS scores between the post-intervention scores and baseline scores was 5.6 points ((95% CI: 2.1, 9.0); p = 0.002; Cohen's d = 0.60 (95% CI: 0.22, 0.98)). In the unifocal group this difference was small, only 2.26 points, and not statistically significant ((95% CI: -1.1, 5.7); p = 0.191; Cohen's d = 0.24 (95% CI: -0.12, 0.03)). The post-intervention difference in mean MEFS scores between the bifocal group and the unifocal group of 3.3 points ((95% CI: -0.9, 7.5); p = 0.120; Cohen's d = 0.34 (95% CI: -0.09, 0.77)) had a small effect size and was not statistically significant.

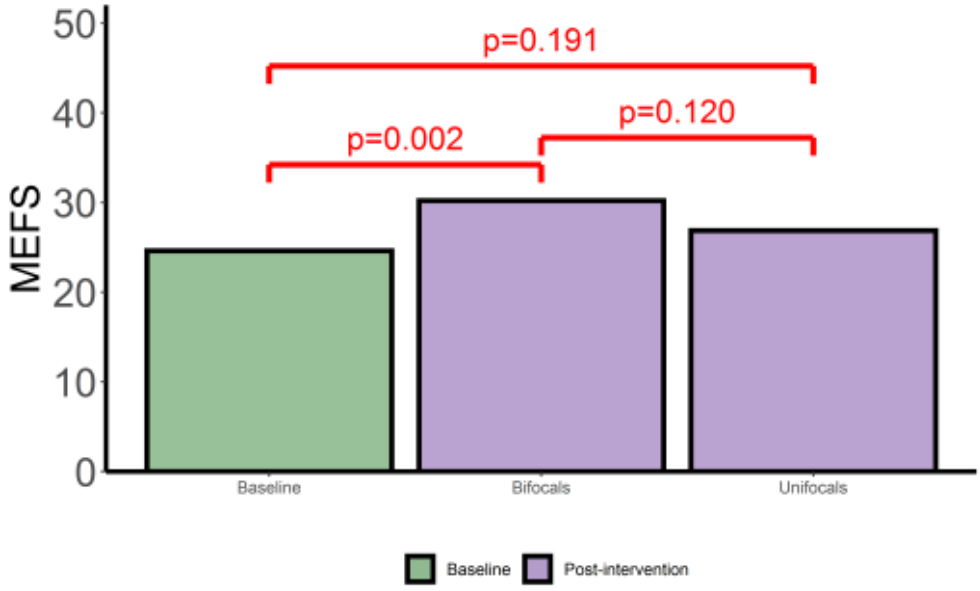

Figure 2. Effect of the interventions on MEFS

Note the significant post-intervention improvement of MEFS scores in the bifocal group. The intervention had no significant effect on the MEFS scores in the unifocal group. Post-intervention values (pooled across T1 and T3) were not significantly different between the two groups.

Thus, the effect of treatment on MEFS scores was significant between baseline and post-intervention measurement in the intervention group. However, there was no significant difference in MEFS score between the two intervention groups after the intervention. After the initial improvement with the new optical corrections in the bifocal group, the longitudinal analysis of the MEFS scores showed no significant progression over the one-year follow-up period. Nevertheless, we did obtain some clues that improving near vision may be helpful since the 2.5 dioptres addition for near vision in the bifocals was associated with an average medium-effect improvement of 5.6 points in Total MEFS score with respect to baseline MEFS performance.

5.3.1.2 Cross-sectional relation between visual acuity and the level of post-intervention MEFS scores

At baseline, we found no significant association between visual acuity and MEFS scores[6]. However, at this point in time, most participants were not yet wearing full corrections for their refractive errors, or the correction was out-dated[21]. New prescriptions were given to both groups (bifocal and unifocal) according to the refractive error that was measured at the start of the study. It is therefore of interest to analyse the effect of post-intervention visual acuity on the level of post-intervention MEFS scores.

We found that the crowded near visual acuity, uncrowded near visual acuity and distant visual acuity with newly prescribed glasses were associated significantly with post-intervention adjusted MEFS scores (see Fig. 3). The slopes for these relations were of similar magnitude and all negative (Table 1), indicating that after full correction of refractive error, better visual acuity was associated with better MEFS performance. Before pooling of the data across T1 and T3, we verified that there was no statistically significant difference in MEFS scores between T1 and T3.

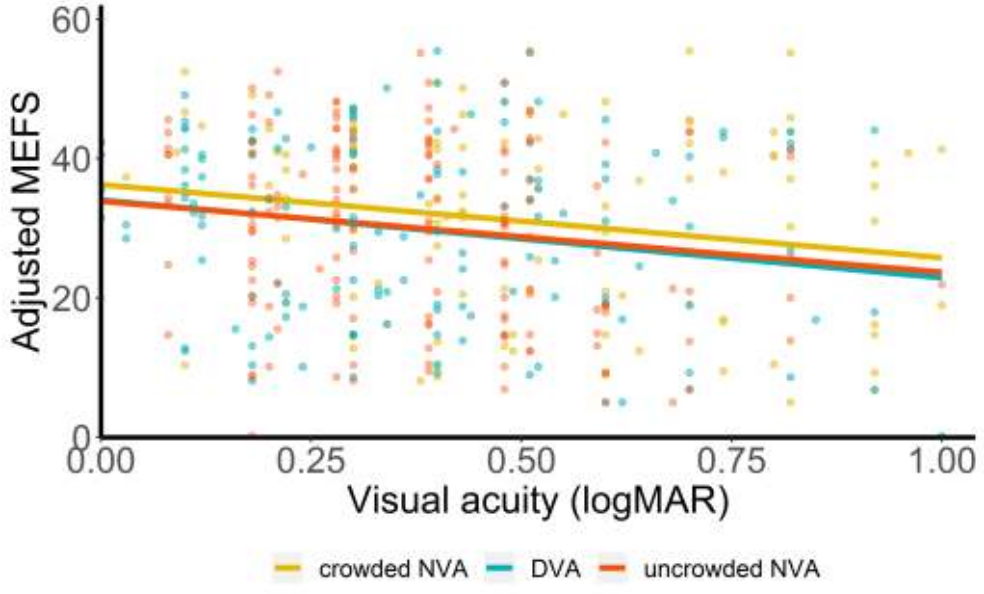

Figure 3. *Post-intervention relations between visual acuity and MEFS scores*

Post-intervention MEFS scores, adjusted for gender, age and intervention, correlated significantly with each of the three post-intervention visual acuity measures (LogMAR): crowded near visual acuity (orange), uncrowded near visual acuity (red) and distant visual acuity (blue). Individual data points are from T1 and T3. Solid lines are mixed-effects regression lines. Note that better MEFS scores are associated with better post-intervention visual acuities and vice versa.

Table 1. *Post-intervention relations between visual acuity and MEFS scores*

(See Figure 3.) Fixed effects coefficients of the mixed-effects regression analysis. Post-intervention MEFS scores were adjusted for gender, age and intervention, and pooled across T1 and T3.

Cohort's mean visual acuity with newly prescribed glasses	Cohort's mean adjusted MEFS score	Slope
Crowded near visual acuity		
0.51 LogMAR	0.31 points (95%CI: 28.1, 33.8)	-10.5 (95%CI: 19.8, -1.3), p = 0.025
Uncrowded near visual acuity		
0.4 LogMAR	29.8 points (95%CI: 27.1, 32.4)	-10.2 (95%CI: -18.6,-1.8), p = 0.019
Distant visual acuity		
0.39 LogMAR	29.7 points (95%CI: 27.1, 32.3)	-11.2 (95%CI; -22.0, -0.3), p = 0.045

5.3.1.3 Association between MEFS score changes and changes in ocular alignment

Ocular alignment facilitates visual functions as binocularity (merging the images of both eyes in the brain), accommodation endurance (eyes staying focused at the same near distance for a longer time), stereopsis (depth perception through interpretation of the minimal differences between the image of the right and left eye) are important in social situations for having eye contact. Possibly, these functions may also play a role in the development of executive functions. We, therefore, analysed if the change in MEFS scores from baseline to T1 is associated with the change in ocular alignment measured at T1, shortly after the children started wearing the newly prescribed glasses[22]. In this analysis, we found a significant positive rank-correlation between change in ocular alignment and change in MEFS scores in the bifocal group (n = 36, rho = 0.343, p = 0.040), indicating that children with improved ocular alignment had improved in MEFS scores. We did not find such a significant rank-correlation in the unifocal group (n = 37, rho = -0.084, p = 0.620), in which the change in strabismus was not statistically significant[22].

5.3.2 BRIEF-P and BRIEF questionnaires

In line with our findings at baseline[6], a year after the intervention, we found no significant correlation between the informant report scores of executive functions and performance of the children on the MEFS test (see supplementary Table S2). Unfortunately, all three questionnaires suffered from large percentages of missing scores at both time-points, T0 and T3, (missing questionnaires, baseline: BRIEF-P 26%, BRIEF parents' version 30% and BRIEF teachers' version 43%. Final assessment: BRIEF-P 47%, BRIEF parents' version 46% and BRIEF teachers' version 46%). For this reason, in an attempt to still report on all outcome measures[68], we only did an exploratory analysis of complete cases on the difference between baseline ratings (T0) and final ratings (T3). Participants with baseline and T3 data on BRIEF-P (bifocals n = 17; unifocals n = 14), or on BRIEF parents' version (bifocals n = 15; unifocals n = 16) or on BRIEF teachers' version (bifocals n = 10; unifocals n = 13) were included in these analyses.

5.3.2.1 One year effect of bifocals and unifocals on BRIEF-P and BRIEF scores

After one year, ratings on the teachers' version of the BRIEF (Global executive composit, GEC) were significantly better than at baseline

(change bifocal group: − 21.9 points (95% CI: -38.3, − 5.5), t(9) = 3.029, p = 0.014; Cohen's d = 1.91 (95% CI: 0.42, 3.41)); change unifocal group: -16.7 points (95% CI: -30.6, 2.8), t(12) = 2.625, p = 0.022; Cohen's d = 1.46 (95% CI: 0.23, 2.68). However, this improvement was not significantly different between the two intervention groups (*t*-test, *t*(21) = -0.541, p = 0.594; Cohen's d = 0.23 (95% CI: -0.60, 1.05)). Scores on the parents' ratings BRIEF-P and BRIEF were not significantly different between T0 and T3 (BRIEF-P: t(30) = -0.937, p = 0.336; Cohen's d = 0.34 (95% CI: -1.05, 0.37; BRIEF parents' version: t(30) = 0.980, p = 0.335; Cohen's d = 0.35 (95% CI: -1.06, 0.36)). The mean improvement assessed by the teachers was -19.0 points (95% CI: -28.7, -9.2; t(22) = 4.035, p = 0.001; Cohen's d = 1.68 (95% CI: 0.73, 2.63).

For completeness, we checked for differences between the children with completed teachers' questionnaires at both time-points (baseline and final ratings) and those excluded because of missing or incomplete teachers' questionnaires. The children included in the complete-case analysis tended to have higher adaptive developmental behaviour assessed with the Vineland-S questionnaire compared to the excluded children (49.9 months (95% CI: 45.9, 53.9) and 45.2 months (95% CI: 41.9, 48.5) respectively, *t*-test, *t*(53) = 1.772, p = 0.082; Cohen's d = 0.49 (95% CI: -0.06, 1.04)). There were no differences in age, visual acuities or MEFS scores.

Because of the missingness in both the questionnaires and visual functions and the small number of children with (improved) strabismus we were not able to analyse the associations between parent-rated and teacher-rated executive functions with visual acuities and ocular alignment.

5.4 DISCUSSION

The current multicentre RCT is the first longitudinal study to examine the effect of bifocals and unifocals on task-based executive functions (assessed with MEFS) and rating-based executive functions (assessed with BRIEF-P and BRIEF) in children with DS. The included children were 2 to 16 years old and all received full corrections of their refractive error for distant vision. Although we found no significant differences between the interventions after one year and shortly after the intervention, within the bifocal group there was a change. In this group, the post-intervention MEFS scores were improved significantly compared with the participants' baseline performance.

The effect size of this one-year change in the bifocal group was medium, whereas the improvement of the unifocal group was statistically small and not significant.

Unfortunately, we could not test reliably if there was an association between improvements in visual acuity and improvements in MEFS scores (Data were too sparse to compute enough pre-post difference pairs). However, our cross-sectional analysis of the post-intervention data showed that better post-intervention MEFS scores were associated with better post-intervention visual acuities (crowded near visual acuity, uncrowded near visual acuity, and distant visual acuity). For participants that had strabismus at baseline, improved ocular alignment with bifocals was associated with improved MEFS scores. Exploratory analysis of the questionnaire data indicated that improvements in executive functioning were also noted by teachers (teachers' version of BRIEF), with a large effect size, but not by parents (BRIEF-P and parents' version of BRIEF). After a year, teachers reported fewer problems with executive functioning regardless of the intervention type.

5.4.1 MEFS

The MEFS is a visual test in which verbal instructions are given, partly supported by visually demonstrated instructions of swiping the picture in the right box. Thus, one might doubt about its value when testing children with low visual acuities. Therefore, we verified the picture size (~8 M). The pictures presented in this test are of good contrast and large enough to be easily discriminated by children with limited visual acuity, as poor as 1.5 LogMAR. The mean uncrowded near visual acuity of the participants of our study was 0.58 ± 0.34 LogMAR[21]. None of our participants had an uncrowded near visual acuity poorer than 1.4 LogMAR at baseline. In our previous publication on the baseline measurements of this cohort[6], we checked the association of the children's scores with their visual acuity at baseline. We found no statistically significant association. Thus, we could conclude that the MEFS test is suitable for children with visual impairment because the pictures are large enough to be seen by these children, also without optical correction for near vision.

After one year, treatment effects on MEFS scores were not significantly different between the two intervention groups and the longitudinal analysis showed no significant progression over the one-year follow-up period. Perhaps the follow-up period was too short to find statistically significant differences between the two intervention groups. Shortly after participants started wearing their new glasses, near visual acuity (uncrowded and crowded) had improved on average, but it was not until

a year later that the effect of bifocals on near vision exceeded the effect of unifocals[21]. Possibly, after a longer follow-up, when the near-vision differences between the intervention groups have developed and had more time to influence the development of executive functions, the better near vision in the bifocal group could lead to a significant difference in the MEFS scores between the intervention groups. Better near visual acuity might also help children with DS to sustainably enhance their visuospatial short term memory by training, as suggested by other authors[69,70]. However, to study the effects of better near vision on the development of executive functions in children with DS, future studies may need longer follow-up times.

Unfortunately, we could not leverage the longitudinal design of the study to its full potential; there were too many missing baseline measurements of visual acuity (mostly at near) to test if changes in executive functions are directly associated with changes in a child's visual acuity. Otherwise, we might have been able to account for part of the between-subject variability in the intervention effects. However, we could examine the cross-sectional association between the level of visual acuity and the level of MEFS performance observed after the interventions. We previously found no significant association between baseline visual acuity and baseline MEFS scores[6]. We only found an association between baseline visual acuity and adaptive developmental behaviour (assessed with the Vineland-S questionnaire). However, at baseline, participants were not yet wearing full corrections for their refractive errors. Our finding that better post-intervention visual acuities do correlate significantly with better post-intervention MEFS scores is in line with and extends previous cross-sectional studies in visual impaired children without known developmental disorders[23–27]. It also agrees with and extends the findings of Tadic et al.[41] who compared attentional processes of visual impaired preschool children (without DS and cerebral visual impairment (CVI)) and typically developing children with normal vision. In their cross-sectional study[41], they reported that visual impairment significantly reduces the capacity of a young child to regulate attention between people and objects, and that in case of visual impairment, the ability to establish attention on toys and maintaining of attention is lower than in children with normal vision.

5.4.2 Informant reported executive functions

After one year, only teachers reported a substantial improvement of ~20 points. This statistically large improvement (Cohen's d = 1.7) after either intervention represents an ~50% reduction of the lag found in the baseline scores of the children with DS

relative to age-matched norm scores of typically developing children. At baseline, the mean difference in the teachers' version of the BRIEF scores compared to the age-matched norm scores was 40.1 points (95% CI: 32.3, 47.9)[6]. Although teachers reported an improvement, parents did not report an improvement in the executive functions of their children with DS. Such a discrepancy between parents' and teachers' ratings of behaviour is not uncommon[71,72]. Poor to moderate agreement was observed in children with DS[73,74], without DS[72,75,] in twins with attention deficit hyperactivity disorder[42], and analysed in a review already in 1987[71] and more recently in 2008[43]. Explanations for the discrepancies include the possibility that parents and teachers are observing different behaviours and phenotypes, particularly given the more structured demands at school settings versus less organized home activities, placing different demands on children depending on the setting[42,43]. So, different informants may validly contribute different unique information from different perspectives. Additionally, activities at home may be different from those at school. School activities might include more visually guided activities, which could be more directly influenced and facilitated by better visibility and visual memory support owing to better seeing with new glasses in both intervention groups.

The studies of Daunhauer et al.[76,77] can also help understand the apparent disagreement between parents and teachers. Their findings include that teachers do encounter the changes in executive functions and are able to rate them in a questionnaire on executive functions. In their cross-sectional study in elementary students with DS, aged 7.86 ± 1.75 years, they demonstrated that executive function skills scored by teachers was the only statistically significant predictor of overall school performance in elementary students with DS[76]. They mention the following two implications. First, executive functions may play a more prominent role in academic contexts for children with DS than was previously noted in literature. Second, their findings suggest that improving executive functions may be of particular use for improving overall school performance in DS. Their findings are an additional motivation to find interventions that can improve executive functions in children with DS. Bifocals with full corrections of refractive errors could be one of them.

5.4.3 Strengths and limitations

Some of the strengths of the current study are already reported in our previous publications. These include the longitudinal design and the large sample size with a relatively rare biologically well-defined condition (DS). The participants were recruited

from rural and urban populations of diverse social status and attended both regular schools and schools for children with special needs, in order to attain a cohort that represents the general Dutch population of children with DS. Further strengths were the multimodal and multi-informant evaluation of intervention efficacy; the robust and standardized measurements that made data collection across multiple sites possible, the use of the combination of both task-based and informant-based measures of executive function differentiating between parent ratings and teacher ratings. The need to obtain reports of both types of observers is highlighted by many authors because of the difference in fundamental behaviours they observe[42,43,75]. Besides the need for different observers in different situations, the combination of task-based assessments (a momentary assessment mostly under optimal conditions) and rating-based assessments (scoring everyday behaviour) is complementary in typically developing children[56,57,62,75], in preterm preschoolers[58] and in children with DS[78]. Studies applying such a combination of task-based scores and raters' information are scant in young children with DS, except for a few studies[78,79].

Additionally, the current paper focuses on a novel question, i.e., whether visual functions (acuity and ocular alignment) are associated with the level of cognitive performance.

A further strength is the refined visual acuity assessment used in the current study to analyse the association of visual acuity and executive functions, instead of broad visual impairment categories, which were used in previous studies[24,25], and which do not specify visual acuity at different distances. In our study, we found different timelines for development of uncrowded and crowded near vision and could study the differences between distant and near vision which go unnoticed if these facets of vision are not independently measured. In DS, the difference between distant and near visual acuity is typical if not corrected accordingly, because of their accommodative lag and cerebral visual impairment[21]. Analyses of the correlations with other developmental measures, such as MEFS, were possible because of the refined assessments of visual acuity.

One of the limitations of our study is the limited follow-up time of one year. In children with DS, development is slow. Where a time lapse of one year in typically developing children is often long enough to detect development, in children with DS it may have been too short to detect significant progress in MEFS scores in the unifocal group or a possible difference in MEFS scores between the intervention groups. To reveal differences in slowly developing processes, longer follow-up times are necessary.

Possibly, the development of executive functions induced by better visual functions is one of these slow developments, which need time to reach statistically significant differences between baseline and final assessments and between the interventions.

The large age range can also be taken as a limitation. Developmental steps of visual acuity but specially in executive functions are not the same during one year in the youngest ages than in the older ages because of non-linearities in the developmental curve. Especially in children with DS, development is heterogenous. In our study, we included children from the age of two. This is the youngest age at which bifocal use could be expected in the appropriate way. We corrected refractive errors also for near distances in the bifocal group, at the youngest ages possible in order to stimulate the development of visual functions.

The possibility that different teachers might have completed ratings on the same child due to the nature of the trial spanning 12 months might be another limitation. We did not monitor that, because the teachers remained anonymous. Longer follow-up times would have exacerbated this issue even more.

The biggest limitation of our study was the large amount of missing datafor the three versions of BRIEF questionnaires. We tried to deal with this limitation by performing an exploratory analysis of complete cases in order to report the results for all outcome measures. The missing visual acuity data, in particular at baseline, also limited longitudinal analyses. We could not enter all the visual acuity variables in a mixed effects model to analyse the changes in executive functions in relation to changes of visual acuity. We therefore had to limit our analyses to cross-sectional data from the post-intervention visits.

5.4.4 Overall evaluation of the interventions

After the interventions, the MEFS scores were significantly improved in the bifocal group but not significantly in the unifocal group. Post-intervention, children with better visual functions, crowded and uncrowded near visual acuity and distant visual acuity, showed higher MEFS scores. Children with improvements in ocular alignment typically improved in MEFS scores.

Only explorative analyses could be performed on the BRIEF-P and BRIEF data. Teachers, but not parents, rated improved executive functions in both intervention groups. However, these findings need replication in larger samples with longer follow-up. Such studies could explore if the better post-intervention ratings by

teachers and task-based scores on executive functions in DS are a developmental phenomenon or only the result of better visual functioning. Notwithstanding the acuity improvements as a result of bifocals, children with DS wearing appropriate bifocals still lag behind in visual acuity (far and near) compared to typically developing children[6].

5.4.5 Conclusion

After full correction of refractive error, better distant and near vision were associated with higher executive function scores on task-based test administered at near, the MEFS. However, there were not enough data to test such an association with informant reported scores.

Nevertheless, teachers' ratings suggest that at school, children show improved executive functions when wearing full corrections of their refractive error.

The +2.5 addition in the bifocals with full correction of refractive error improved near vision more than the full correction of refractive error alone, and bifocals also improved the conditions to achieve better task-based executive function scores on the MEFS.

On the basis of our findings, we suggest to optimize visual functions in children with DS by prescribing them optimal corrections for both distant and near vision to maximize their developmental chances. We found that good corrections for children with DS are up-to-date full corrections of refractive error in bifocals with an addition of +2.5 dioptres for near vision. Further longitudinal research is needed to investigate if improved visual functions indeed boost the development of executive functions in DS.

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SUPPLEMENTARY MATERIALS

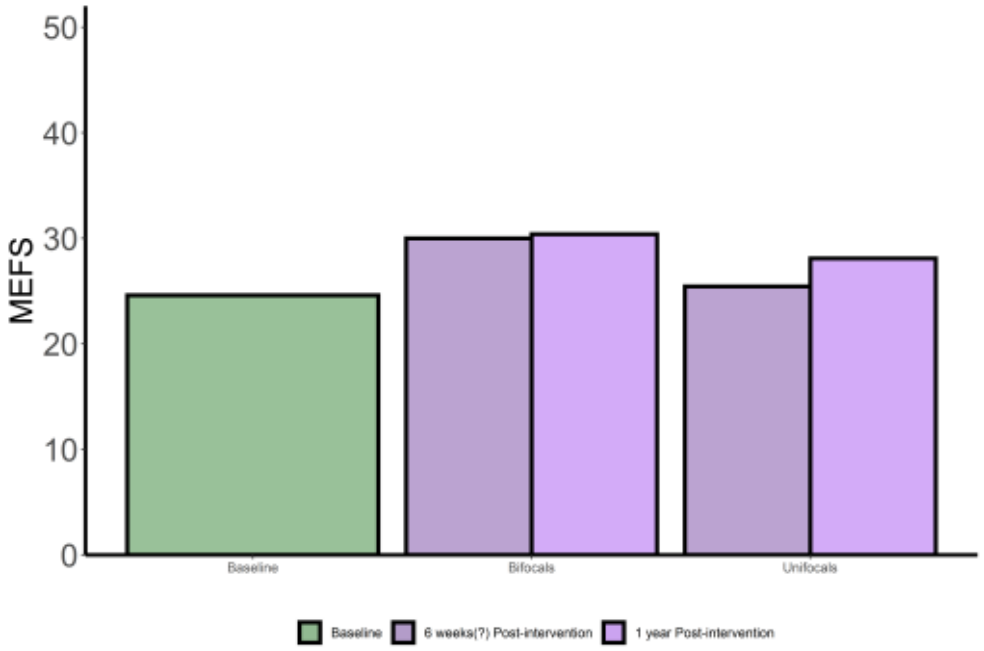

Figure S1. *Effect of the interventions on the MEFS controlled for age and gender*

Note the significant post-intervention improvement of MEFS Total scores in the bifocal group at T1 (after ~6 weeks) and T3 (after 1-year). The intervention had no significant effect on the MEFS scores in the unifocal group. Post-intervention values were not significantly different between the two groups, as shown in Table S1.

Table S1. *Comparisons of the effects of interventions on MEFS controlled for age and gender*

Comparison	Difference in MEFS score	Standard Error	P value
Bifocals T1 vs baseline	5.39	2.16	0.013
Bifocals T3 vs baseline	5.79	2.05	0.005
Bifocals T3 vs T1	2.03	2.29	0.863
Unifocals T1 vs baseline	0.82	2.09	0.694
Unifocals T3 vs baseline	3.49	2	0.083
Unifocals T3 vs T1	2.51	2.14	0.228
T3 (Bifocals vs Unifocals)	4.44	2.78	0.098
T1 (Bifocals vs Unifocals)	2.35	3	0.376

This table lists comparisons of the effects of the interventions on the MEFS Total scores between different time-points, baseline, T1 (~6 weeks post-intervention), T3 (final assessment, 1 year post-intervention), as shown in Fig. S1. Note the significant post-intervention improvement of MEFS Total scores in the bifocal group at T1 (after ~6 weeks) and T3 (after 1-year). Within the intervention groups, short-term (T1) and long-term (T3) effects were comparable ($p > 0.1$).

Table S2. *Post-intervention rank-correlations*

	T3 MEFS Total scores	T3 BRIEF-P	T3 BRIEF parents' version	T3 BRIEF teachers' version	T3 age (months)
T1 MEFS Total scores	rho=0.680 p<001 n=78		rho=-0.385 p=0.030 n=32	rho=-0.163 p=0.372 n=32	
T3 MEFS Total scores		rho= 0.008 p=0.963 n=33	rho=-0.295 p=0.077 n=37	rho=-0.054 p=0.751 n=37	rho=0.397 p=0.001 n=93
T3 BRIEF-P					rho=0.101 p=0.535 n=40
T3 BRIEF parents' version				rho=0.180 p=0.280 n=38	rho=-0.015 p=0.930 n=38
T3 BRIEF teachers' version					rho=-0.609 p<0.001 n=38

The table only list rank-correlations for data sets with a sample size of n ≥29 participants. Smaller data sets do not have sufficient statistical power to detect even large effect size (rho ≥0.50) correlation with Type I and Type II errors of 0.05 and 0.80, respectively [Spearman Correlation: 2-tailed (statisticssolutions.com)]. Note, that this table should be interpreted with caution since each correlation measure is derived from a different subgroup of children.

6

Main findings

6 MAIN FINDINGS

6.1 GENERAL SUMMARY

In this thesis the effects of bifocals and unifocals in children with DS are compared. The work reveals important beneficial effects of bifocals over unifocals on visual functions, and shows that supporting near vision with bifocals has a positive influence on adaptive behaviour and executive functions too. Full correction of refractive error also had positive effects.

6.1.1 Results of the RCT regarding visual acuity (chapter 2)

- After one year of wearing the newly prescribed glasses, a larger improvement of near visual acuity (NVA) was achieved with bifocals compared to unifocals. Mean improvements of the uncrowded NVA in the bifocal and unifocal group were 0.23 LogMAR (95% CI: -0.34, 0.80) and 0.12 LogMAR (95% CI: -0.47, 0.71), respectively, with bifocals yielding 0.095 LogMAR (95% CI: 0.003, 0.187)($F = 4.180$, $p = 0.045$) better improvement. Even larger improvements and larger intergroup differences were found for crowded NVA (mean improvements bifocals: 0.31 LogMAR (95% CI: -0.24, 0.86); unifocals: 0.16 LogMAR (95% CI: -0.35, 0.75); mean intergroup difference 0.17 (95% CI: 0.033, 0.31), $F = 6.194$, $p = 0.017$).
- Distant visual acuity (DVA) had improved in both groups with full correction of refractive error (mean improvement bifocals: 0.07 LogMAR (95% CI: -0.34,0. 48; unifocals: 0.08 LogMAR (95% CI: -0.35, 0.51)), but there was no difference between the two groups after one year of wearing the newly prescribed glasses (mean intergroup difference: 0.021 LogMAR (95% CI: 0.052, 0.094), $F = 0.334$, $p = 0.565$).
- Despite the acuity improvements achieved with either interventions, distant and near visual acuity of children with DS still lagged that of typically developing children (all $p < 0.001$).

6.1.2 Results of the RCT regarding ocular alignment, accommodative accuracy and binocularity (chapter 3)

- Bifocals reduced the manifest angle of strabismus after a few weeks - a reduction that remained throughout the one-year follow-up ($U = 1000.5$, $p = 0.010$). Unifocals, however, had no effect on the angle of strabismus, not even after one year.
- Neither bifocals nor unifocals had effects on accommodative accuracy and refractive errors or on the presence of stereopsis and binocular vision over the course of one year (all $p > 0.212$).

6.1.3 Findings regarding adaptive behaviour and executive functioning (Chapters 4 and 5)

- The developmental delay in adaptive behaviour (Vineland-S questionnaire) of children with DS as well as their lag in task-based executive functions (MEFS test) increased with calendar age (adaptive behaviour: $r = 0.965$, $p < 0.001$; MEFS: $r = 0.684$, $p < 0.001$).
- After wearing the newly prescribed glasses for one year, executive functions assessed with the task-based MEFS had improved compared to baseline only in the bifocal group (mean improvement: bifocals 5.6 points (95% CI: 2.1, 9.0), $p = 0.002$, Cohen's $d = 0.60$; unifocals: 2.26 points (95% CI: -1.1, 5.7), $p = 0.191$, Cohen's $d = 0.24$). The difference between the groups was not statistically significant (intergroup difference 3.3 points (95% CI: -0.9, 7.5), $p = 0.120$).
- Higher follow-up scores for task-based executive functions (MEFS) were associated with better visual acuities (uncrowded NVA, slope -10.2 (95% CI: -18.6, -1.8), $p = 0.019$; crowded NVA, slope -10.5 (95% CI: -19.8, -1.3) $p = 0.025$; and DVA, slope -11.2 (95% CI: -22.0, -0.3), $p = 0.045$) and improved ocular alignment ($rho = 0.343$, $p = 0.040$).

6.1.4 Further insights of clinical and practical relevance

- Children with DS were able to learn how to use bifocals in the appropriate way, and were compliant in wearing the bifocals during the one-year follow-up [de Weger et al. 2020] (see chapter 3).

- A time effect in developing visual acuity was revealed. After a few weeks of wearing the newly prescribed glasses, the bifocal group had made progress in both uncrowded and crowded NVA, while the unifocal group had made progress in uncrowded NVA only. Visual acuity developed further in both groups and after one year, both groups had made progress in both NVAs, but in the bifocal group, NVA had improved more [de Weger et al. 2019] (see chapter 2).
- At baseline, mean uncrowded NVA was poorer than DVA (mean difference 0.11 LogMAR (95% CI: -0.52, 0.74), $t(73) = 2.900$, $p = 0.005$) [de Weger et al. 2019, 2021a] (see chapters 2 and 4). After one year of wearing the bifocals, however, NVA was no longer poorer than DVA in the bifocal group ((mean VA) uncrowded NVA 0.32 LogMAR (95% CI: -0.05, 0.69); crowded NVA 0.35 LogMAR (95% CI: -0.10, 0.8) and DVA 0.38 LogMAR (95% CI: -0.09, 0.85) [de Weger et al. 2019] (see chapter 2).
- The effect of bifocals on strabismus developed much faster than the effect that these glasses had on near visual acuity [de Weger et al. 2020] (see chapter 3).
- The correlation at baseline between visual impairment and delay in adaptive behaviour suggests that visual acuity plays a role in the development of adaptive behaviour in children with DS, as it also does in visually impaired children without known cognitive disorders [de Weger et al. 2021a] (see chapter 4).
- Exploratory analyses of teachers' ratings of executive functions (BRIEF questionnaires) indicate that children with DS show significantly improved executive functions at school after one year of using their newly prescribed glasses. Because school tasks depend on visual guidance, the improved visual acuity resulting from the interventions may have helped them performing these [de Weger et al. 2021b] (see chapter 5).
- Children with DS have heterogenous and varying phenotypes regarding ocular disorders, visual functions, adaptive behaviour and executive functions. This heterogeneity, with the added complexity of slow development and variations in attention span and cooperation were a challenge for both the acquisition and the analysis of the data. Longer follow-up times and larger study populations are needed in future studies [de Weger et al. 2019, 2020, 2021a, 2021b] (see chapters 2,3,4,5).

6.2 GENERAL DISCUSSION

Besides comparing the effects of bifocal and unifocal glasses on visual functions in a large cohort of Dutch children with DS, this thesis addressed two novel questions. Firstly, are visual functions (acuity and ocular alignment) associated with the level of cognitive performance in DS? Secondly, can the bifocals intervention reduce the impairments in cognitive functions in DS?

Small-scale studies with bifocals had already reported improvements in near visual acuity in selected children with DS [Stewart et al. 2005, Nandakumar et al. 2010]. This thesis extends these findings by demonstrating improvements in both uncrowded and crowded NVA and significant reductions in strabismus angle in a much larger, representative population of children with DS. Reduced visual input presents a major obstacle to the acquisition and building of fundamental developmental skills in early and later childhood [Keil et al. 2017]. Other authors [Sonksen & Dale 2002, Bathelt et al. 2018] found that in visually impaired children without known developmental disorders, the level of visual impairment indeed correlates with deficits in cognitive development. Additionally, knowledge about executive function is of importance for those who teach visually impaired students, particularly in special schools, where the pupils' executive functions is especially vulnerable [Heyl & Hintermair 2015].

We studied possible associations among developmental delays in children with DS, because we hypothesized that a known cumulative impact of multiple developmental delays in children with visual impairment [Sonksen & Dale 2002, Dale & Sonksen 2002, Dale & Salt 2007, Tadic et al. 2009] also exists in children with DS. However, these associations had not been studied yet in children with DS.

In our study we applied a developmental approach. This approach, to describe and understand how outcomes emerge and develop throughout childhood, has developed in the last hundred years. At that time the focus of research on individuals with intellectual disability had gradually shifted more towards assessing abilities and achievement potential in multiple developmental domains than on determining an overall IQ or other singular performance measures [Fidler et al. 2008]. A notion that is critical to understanding change over time throughout a child's development is, that development involves multiple, mutual, and continuous interaction of different functions in the developing system. With this developmental approach, we obtained new insights. It revealed associations between the level of visual functioning and the

level of adaptive behaviour and cognitive performance [de Weger et al. 2021a and 2021b] (see chapters 4 and 5), further elaborated on under heading 'Children's performance in adaptive behaviour and executive functioning'.

6.2.1 Study design

To answer the research questions outlined in the Introduction (see chapter 1), we designed a multicentre randomized controlled trial to study the effects of bifocal spectacles compared to unifocals on visual functions and executive functions in children with DS. Both spectacles had full correction of refractive errors for distant vision as assessed in cycloplegia. The bifocals had S +2.5 dioptre in straight-top near addition placed at the pupillary centre. To attain a cohort that represents the Dutch population of children with DS we included children, aged 2 to 16 years, from rural and urban populations of diverse social and economic status who were attending both regular schools and schools for children with special needs. We included children as young as 2 years, because this is the youngest age for children with DS to be able to sit at a table doing a playing task while looking down at their hands or toy. This is the viewing direction needed to use the bifocals at short viewing distances. As visual acuity develops during the first years of life [Braddick & Atkinson 2011], stimulating interventions for its development should be provided at this young age.

We applied multimodal and multi-informant evaluation of intervention efficacy, robust and standardized measurements that made data collection across multiple sites possible, and used a combination of both task-based (objective) and informant-based (questionnaires) measures of executive functions, while taking care to differentiate between parent ratings and teacher ratings. Many authors emphasize the need to obtain reports from both parents and teachers because of the fundamentally different behaviours they get to observe [Hartman et al. 2007, Polanczyk & Jensen 2008, Netson et al. 2011]. Besides the need for different observers in different situations, the combination of task-based assessments (a momentary assessment mostly under optimal conditions) and rating-based assessments (scoring everyday behaviour) is complementary in observing children [Isquith et al. 2013, Toplak et al. 2013, Gioia et al. 2000, 2003, Netson et al. 2011, Loe et al. 2015, Daunhauer et al. 2017]. Studies applying such a combination of task-based scores and raters' information in relation to young children with DS, are few in number [Daunhauer et al. 2017, d'Ardhuy et al. 2015].

The established cohort representing the Dutch population of children with DS and the multimodal and multi-informant evaluation of the executive functions are important strengths of this study.

6.2.2 Data acquisition

We encountered considerable challenges in all assessments due to the characteristically developmental heterogeneity of children with DS. This resulted in missing data, which made some of the analyses complicated or limited. Children with DS have a heterogeneous phenotype in the anatomy of the eye (refractive errors), visual functions, adaptive behaviour and executive functions. Visual acuity can vary over time as a developmental change in cerebral visual impairment (CVI). Their attention span and cooperation are heterogeneous and may vary over time. For this reason, we could not always perform all assessments planned for a given time-point in our study, which resulted in incomplete series of repeated assessments. In addition, inattentiveness of the parents resulted in unreturned questionnaires. Other authors also encountered difficulties because of a lag in cooperation and fluctuations in attention and concentration due to the cognitive delay of the participating children with DS [Courage et al. 1994, 1997; Woodhouse et al. 1996; McCullough et al. 2013, Doyle et al. 2016, 2017]. In this study, we therefore analysed the portion of variance that can be explained by regression to the mean, which also reflects variance in performance [Pocock et al. 2016, Barnett et al. 2005, Oldham 1962, Trochim 2006, Tu & Gilthorpe 2007].

6.2.3 Visual acuity

Visual acuity was assessed in considerable detail [de Weger et al. 2019] (see chapter 2). We differentiated between distant and near visual acuity, and we distinguished between uncrowded and crowded near visual acuity. Children with CVI (a disorder found in all children with DS) might encounter more difficulties with crowded visual acuities. It can be a limiting factor, not only in reading, writing and mathematics, but also in observing crowded images. The above-mentioned differentiation in near visual acuity assessment, was not provided in earlier studies of children with DS. It allowed us to obtain novel insights in differentiated visual developments for these different visual acuities. Even with bifocals, crowded near visual acuity needed more time to improve than uncrowded near visual acuity. Both

aspects of near vision needed time to develop and did improve further during the one-year follow-up.

The majority of the participants in our study were hyperopes, who, until then, did not receive full correction of their hyperopia. After the first visit, these participants received, on average, more than one dioptre additional correction for distant vision. The results of just the updated distance correction of refractive error in both groups showed more improvement of distant and near visual acuities on the second visit than expected, possibly because the children's habitual glasses contained outdated and insufficient corrections at baseline. In future studies, the update of the distance correction should be checked prior the start of the study. Clinically relevant in our study are the significantly greater improvements with bifocals (compared to unifocals) of uncrowded and crowded near visual acuity after one year [de Weger et al. 2019] (see chapter 2) and in ocular alignment (reduction of strabismus) already after a few weeks of using the newly prescribed bifocals [de Weger et al. 2020] (see chapter 3).

From the time-line of changes after both prescriptions, we conclude that the application of a new correction trial, as is offered in demonstration frames, is useless, because visual acuity improvements can often be measured only after weeks, months or even a year. The short-term use of the probal glasses will provide no indication of the end result on visual acuity that develops in the course of weeks, months or a year. This finding, and the fact that people with cognitive impairment do not complain about low visual acuity [van Splunder et al. 2006], emphasizes the importance of regular objective measurement of refractive errors (in cycloplegia) and updated prescriptions for glasses with full corrections of refractive errors. Wearing these full corrective glasses will help to avoid amblyopia [Joly & Franko 2014, Coats & Paysse 2015, Adams 2004, Maconachie & Gottlob 2015].

After one year of wearing the bifocal glasses, near visual acuity was no longer poorer than distant visual acuity in children with DS. Both visual acuities (distant and near) had improved to reach a performance plateau of ~0.3 LogMAR. Possibly, this limitation of development of acuity, compared to typically developing children, reflects their differences in the brain and in the development and the morphology of the visual cortex in children with DS [Becker et al. 1991, Morton 2011]. This interpretation agrees with findings of Zahidi et al. [2018]. Notwithstanding the improvements obtained through optimized corrective glasses, i.e., bifocals with full corrections of refractive error with addition S +2.5 for near vision (separation line of the straight-top

bifocals placed at the pupil), the visual acuities in children with DS do not reach those of typically developing children.

In groups with large heterogeneity (inter- and intra-participant variances), it is more difficult to detect real change. The mean changes in near visual acuity measured on a LEA symbols LogMAR visual acuity chart in the bifocal group are notable. The improvements in the bifocal group, which exceeded 0.2 LogMAR, (uncrowded NVA 0.23 LogMAR (95% CI: -0.34, 0.80) and crowded NVA 0.31 LogMAR (95% CI: -0.24, 0.86)) with significant intergroup differences ($p = 0.045$ and $p = 0.017$, respectively, smaller improvements in the unifocal group), are notable considering the coefficients of reliability of these measurements [Arditi et al. 1993, Kheterpal et al. 1996, Moganeswari et al. 2015]. These mean improvements in the bifocal group are significant statistically, because these are improvements of large effect sizes (Cohen's $d = 1.03$ in uncrowded NVA and Cohen's $d = 1.18$ in crowded NVA), but also clinically. These improvements are not expected in an average development of children with DS during one year. The developmental curve of visual acuity found at baseline in our cohort [de Weger et al. 2021a] (see chapter 4], showed a visual acuity consistently poorer compared to the norm scores and that stabilized at around the age of six years, which was little later than the stabilizing age of four years in DS found by Zahidi et al. [2018].

Crowding is often found in CVI [Hoyt 2013, Guideline CVI 2019]. Children with DS, who have CVI by definition [Sakki et al. 2018, Wilton et al. 2021], experience crowding as a barrier in many daily visual tasks, at school and in particular in digital tasks including games. The improvements found in the teacher-rated BRIEF questionnaires [de Weger et al. 2021b] (see chapter 5) support the idea that a substantial improvement in crowded near visual acuity could provide a boost to the visually guided activities at school. Perhaps it also helps them increase their social participation.

The improvements in near visual acuity achieved with bifocals in children with DS are important considering the statistics of visual impairment published by the World Health Organization (WHO) [Resnikoff et al. 2004] and VISION2020 [Vision 2020]. According to data published by Vision2020, uncorrected refractive errors were the worldwide leading cause of visual impairment in 2002. In the Netherlands, the highest prevalence of avoidable visual impairment and blindness is found among the elderly in nursing and care homes (44%: 70,000), among the cognitive impaired (19%: 20,600) and among independently living people aged 50 years and older

(2%: 198,000). These numbers reflect the importance of appropriately correcting refractive errors, also in population groups who typically do not complain about low visual acuity. Many children with DS are impaired for near distances if the limit of 0.5 LogMAR (WHO) is applied. In our cohort of children with DS, ~60% had near visual acuities poorer than 0.5 LogMAR prior to the intervention. After one year of wearing bifocals, this number had decreased to 15%. Thus, through the use of bifocals, we were able to reduce the percentage of avoidable visual impairment in children with DS. The results of our RCT hopefully will result in the reduction of impaired near vision by the application of bifocals in the future.

6.2.4 Compliance

Compliance in wearing the bifocals was high in our study [de Weger et al. 2020] (see chapter 3). All children who were prescribed bifocals indeed wore them (parents' report) and came in for follow-up during the whole year of our study. This agrees with findings of Adyanthaya et al. [2014] on compliance and with other studies on bifocals in children with DS [Al-Bagdady et al. 2009, Stewart et al. 2005, Nandakumar & Leat 2010]. In the retrospective study of Adyanthaya et al. [2014], 89% of the children with bifocals were compliant. In their unifocal group, 50% of the children were compliant.

6.2.5 Refractive errors

Although the group average of the refractive errors did not significantly change over the course of one year [de Weger et al. 2020] (see chapter 3), in individual cases, the refractive errors had increased more than 0.5 dioptres after one year. In these cases (37% of our cohort) new prescriptions were needed after the end of our study. This finding agrees with previous findings in children with DS [Cregg et al. 2003, Haugen et al. 2001b], and emphasizes the need for regular screening and objective measurement of refractive errors during their development.

Because children with DS do not complain about decreased visual acuity, parents, and professionals alike, do not always notice the need for adjustment of a child's glasses. The children with DS depend on a well-functioning health care system that is able to cope with the high prevalence and variability of ocular disorders and the atypical development in children with DS.

6.2.6 Ocular alignment, accommodation and convergence

We found that after using bifocals, accommodative accuracy [Leat & Gargon 1996], assessed through distance corrective glasses, had not improved [de Weger et al. 2020] (see chapter 3). This is in line with the study of Nandakumar & Leat [2010], but not with the earlier study of Al-Bagdady et al. [2009]. Al-Bagdady et al. [2009] reported improved accommodative accuracy after terminating the use of bifocals in a few children with DS, but such findings have not been reported since.

The persisting lag of accommodation that our study confirmed can be explained by a permanent insufficiency of neural control. The accommodative system of children with DS may have the physical capacity to respond to a given stimulus with an appropriate amplitude, but the neural control of the system is defective [Cregg et al. 2001]. The amount of accommodation elicited does not reflect the maximum amplitude of accommodation like in presbyopes. Children with DS have a consistent degree of underaccommodation at all viewing distances [Woodhouse et al. 1993, Cregg et al. 2001]. Thus, bifocal glasses are permanently needed to correct for the accommodative inaccuracy and optimize near visual acuity in children with DS.

Doyle et al. [2016, 2017] reported that children with DS can in fact converge accurately on near visual fixation objects, provided that the accommodative effort is cancelled. In our study, we found a similar effect with bifocals. Bifocals minimized the accommodative effort and shortly after the children started with bifocals, strabismus was reduced. This is an important finding (in line with Haugen & Hovding [2001a]) as non-surgical interventions for strabismus are preferred because of contraindications for anaesthesia in DS [Borstlap et al. 2011]. Optical correction as a treatment for esotropia in DS is also much more economical, because surgery under anaesthesia is far more expensive.

Our cohort contained too few children with exotropia or very large-angle esotropia to allow for a reliable analysis of the effects of our interventions on these strabismus angles. Their numbers are low because our study population reflected the usual prevalence of strabismus angles in the DS population (32% in our study and 19 to 40% in literature [Watt et al. 2015, da Cunha et al. 1996, Haugen & Hovding 2001a]). Studies specifically aimed at the treatment of exotropia or large-angle esotropia in children with DS are needed to reveal possible treatments of those rare strabismus angles in DS. It is unknown if the near triad in children with DS includes the complex vergence and cyclovergence of the eyes in vertical viewing directions, as it

does in people without DS [van Rijn & van den Berg 1993, Mok et al. 1992]. It also is unknown if this cycloversion might have a role in the disruption of binocularity and the onset or appearance of strabismus.

Future research is needed to generate fundamental knowledge on differences in the cortex and pRF functions with possible underrepresentation of small receptive fields or differences in visuo-oculomotor connections in children with DS. Such items of fundamental knowledge could provide better understanding of some of the observations in our study. The differences compared to children without DS and a possible link between underaccommodation and an additional cyclovergence movement of the eye in vertical gaze shifts during convergence could possibly contribute to the disruption of binocularity, the appearance of strabismus, apparent amblyopia or low visual acuity in children with DS. These possible contributions to the visual functions also need future research.

6.2.7 Children's performance in adaptive behaviour and executive functioning

Adaptive behaviour (rated using the Vineland-screener questionnaire) and executive functioning (assessed with the task-based MEFS test and observer-based BRIEF-P and BRIEF questionnaires) of children with DS was weaker than that of typically developing children [de Weger et al. 2021a] (see chapter 4). This is in line with the findings of Sabat et al. [2020]. In our study, the adaptive behaviour scores improved with increasing age, as in children with isolated visual impairments [Papadopoulos et al. 2011]. The MEFS scores of children in our cohort on average were in line with their adaptive behaviour scores, but showed a large inter-participant variance compared to norm scores. Although on average we found improvement with increasing age on the adaptive behaviour scores and the task-based executive function scores (as in norm scores), the delay (compared to norm scores) increased with increasing age. This may be of consequence for the timing of interventions. Starting interventions timely in children with DS seems important to avoid increasing delays and cumulative effects from visual impairment associated with performance impairment. The cumulative effects of visual impairment and performance impairment are well documented in children with isolated visual impairment [Sonksen & Dale 2002, Dale & Sonksen 2002, Dale & Salt 2007, Tadic et al. 2009, Bathelt et al. 2016] and also seem to exist in children with DS.

In our study after one year of wearing the new glasses (unifocal and bifocal), higher visual acuities (relative to group mean) correlated with higher executive functions in the MEFS total scores [de Weger et al. 2021b] (see chapter 5). In the bifocal group, where near visual acuities (both uncrowded and crowded) had developed significantly more at the end of our study than in the unifocal group [de Weger et al. 2019] (see chapter 2), we also found a significant improvement in the MEFS total scores compared to baseline, whereas in the unifocal group the improvement was non-significant [de Weger et al. 2021b] (see chapter 5).

Only the teachers' BRIEF-P and BRIEF questionnaires, not the parents' ratings, showed an improvement in executive functions after one year (regardless of the intervention group). Exploratory analysis of the teachers' rating showed a ~50% reduction of the lag relative to typically developing children in the course of one year [de Weger et al. 2021b] (see chapter 5). The discrepancy between the teachers' and the parents' ratings can be explained by differences of behaviour and phenotype in different settings [Hartman et al. 2007, Polanczyk & Jensen 2008]. Additionally, the tasks at school might include more structured and visually guided activities than the tasks at home. On the other hand, a scoring urge of the professionals could have played a role as a consequence of the lack of blinding the participation in our study. Their drive to see improvement could have biased their interpretation and evaluation of the child's behaviour. This interpretation would assume, however, that the teachers remembered the various scores they gave the child a year earlier.

Daunhauer et al. [2014, 2017] found that executive function skills rated by teachers are the only statistically significant predictors of overall school performance. They mention two implications. Firstly, executive functions may play a more prominent role in school contexts for children with DS than has previously been noted in the literature. Secondly, improving the executive functions may be of particular use for improving overall school performance in children with DS. Their findings strengthen the motivation to find interventions that aim to improve executive functions in children with DS. Bifocals with full corrections of refractive errors could be one of these.

6.2.8 Limitations of our study

Development in children with DS is slow and one year follow-up proved to be a limiting factor. While a time of one year is often long enough to detect visual and general development in typically developing children, it probably is too short in children with DS to detect significant progress in general development [de Weger

et al. 2021b] (see chapter 5). To reveal differences in slowly developing processes, longer follow-up times are necessary. Possibly, the improvement of executive functions as a result of better visual functions (visual improvement was still going on during the year of follow-up [de Weger et al. 2019] (see chapter 2)) is one of these slow developments which need time to build up and distinguish between the interventions.

The large heterogeneity in general development in children with DS was a limitation in our study. We sought to include a representation of the Dutch DS population, but the heterogeneity in this population was larger than in previous studies with selected children with DS, who could all read and write. To offset the larger heterogeneity and the difficulties in obtaining all measurements, we would have needed a larger sample size. Because the sample size was relatively small in relation to the heterogeneity of the included population in our study, only large effects between group means could be detected. The investigation of subtler group differences may have been underpowered [Button et al. 2013]. Inclusion of a larger number of participants would have decreased this limitation. Future studies which include a representation of the DS population of children should include a larger number of children.

The wide age range (calendar age) of the included children also had its drawbacks. Developmental steps in visual acuity but especially in executive functions during one year in the youngest children compared to the older children are quite different because of non-linearities in the developmental curve.

Blinding was not possible in our study, because of the visibility of the near addition in bifocals, the difference in the notations in the prescriptions, and difference in the prices between bifocal and unifocal glasses. As the type of intervention was always evident to the parents, the participants, the orthoptists, the teachers and the investigator, they knew to which group the child was assigned. The lack of blinding could have induced bias in evaluations, although we found improvement after both interventions. The developmental improvements one can expect from growing one year older, were adequately taken into account in the various analyses and their interpretations in the discussions. We displayed the baseline scores in executive functions (rated in questionnaires and task-based), adaptive behaviour and visual acuity (distant and near) against calendar age in developmental curves to visualize the expected development in children with DS in relation to the expected improvements with age in norm-scores [de Weger et al. 2021a] (see chapter 4).

Parent and teacher ratings may be less accurate than direct standardized testing and may be susceptible to biasing effects. These ratings may reflect unrealistic parental expectations of the performance of the child or, in case of the teachers, a scoring urge of the professional. In our study, where blinding was not possible, these biasing factors may have played an even more prominent role.

The biggest limitation of our study was the notable amount of missing data in baseline assessments and in the three different BRIEF questionnaires, which made longitudinal analyses difficult. Therefore, we had to limit our analyses to analyses of complete cases, cross-sectional analyses of the post-intervention visits or, in case of the BRIEF questionnaires, to exploratory analyses.

6.3 GENERAL CONCLUSIONS

In conclusion, wearing glasses with full correction for distance and near refractive errors has positive effects on distant visual acuity, near visual acuity and executive function in children with DS, which suggests that there is indeed a link between visual and executive functioning.

The +2.5 dioptre addition in the bifocals with full correction of refractive error improved near vision more and reduced strabismus more effectively than the full correction of refractive error without addition. Bifocals improved the conditions for achieving better task-based executive function scores on the task-based test, MEFS. A correlation was found between better visual acuity and better scores in adaptive behaviour and executive function development. However, the relative contributions of distant and near vision to the development of executive functions need further study.

In view of the results after one year of follow-up, the prescription of bifocals (near addition +2.5 dioptres) with full correction of refractive error in children with DS improves their visual functions as well as their educational and developmental prospects.

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Appendices

NEDERLANDSE SAMENVATTING

In dit proefschrift worden de effecten van bifocale (longline, additie +2,5 met scheidingslijn op pupil) en unifocale brillen, beide met volledige correctie van de brekingsafwijking, bij kinderen met Downsyndroom vergeleken. Het werk toont belangrijke gunstige effecten van een bifocaal boven een unifocaal aan. Bovendien wordt aangetoond dat ondersteuning van het nabijzien met een bifocale bril daarnaast ook nog een positieve invloed heeft op adaptief gedrag en executief functioneren. Ondersteuning met unifocale glazen met volledige correctie van de brekingsafwijking blijkt eveneens positieve effecten te hebben.

Resultaten

Resultaten van de RCT met betrekking tot gezichtsscherpte (hoofdstuk 2)

- Na een jaar dragen van de nieuw voorgeschreven bril werd een grotere verbetering van de gezichtsscherpte nabij (NVA) bereikt met bifocale glazen in vergelijking met unifocale glazen. De gemiddelde verbeteringen van de uncrowded NVA (symbolen met witruimte ertussen) in de bifocale en unifocale groep waren respectievelijk 0,23 LogMAR (95% CI: -0,34; 0,80) en 0,12 LogMAR (95% CI: -0,47; 0,71), waarbij bifocale brillen 0,095 LogMAR (95% CI: 0,003; 0,187) ($F = 4,180$, $p = 0,045$) grotere verbeteringen opleverden. Nog grotere verbeteringen en grotere intergroepsverschillen leverde de bifocale bril voor crowded NVA (symbolen vlak naast elkaar zoals letters in een woord) (gemiddelde verbeteringen bifocaal: 0,31 LogMAR (95% CI: -0,24; 0,86); unifocaal: 0,16 LogMAR (95% CI: -0,35; 0,75); gemiddeld intergroepsverschil: 0,17 LogMAR (95% CI: 0,033; 0,31), $F = 6,194$, $p = 0,017$).
- De gezichtsscherpte veraf (DVA) verbeterde in beide groepen door de volledige correctie van de brekingsafwijking (gemiddelde verbetering bifocale bril: 0,07 LogMAR (95% CI: -0,34; 0,48); unifocale bril: 0,08 LogMAR (95% CI: -0,35; 0,51)). Er was geen verschil in DVA tussen de twee groepen na één jaar dragen van de nieuw voorgeschreven bril (gemiddeld intergroepsverschil: 0,02 LogMAR (95% CI: -0,05; 0,09), $F = 0,334$, $p = 0,565$).
- Ondanks de gezichtsscherpteverbeteringen die met beide interventies werden bereikt, bleven de gezichtsscherpte veraf en nabij van kinderen met Downsyndroom achter bij die van normaal ontwikkelende kinderen (alle $p < 0,001$).

Resultaten van de RCT met betrekking tot oogstand, accommodatie-nauwkeurigheid en binoculariteit (hoofdstuk 3)

- In de groep met bifocalen verminderde de manifeste scheelzienshoek al na een paar weken - een vermindering die bleef bestaan gedurende het follow-up jaar (U = 1000,5, p = 0,010). In de groep met unifocalen had de bril geen effect op de scheelzienshoek, zelfs niet na één jaar.
- Gedurende het jaar follow-up hadden noch bifocale, noch unifocale brillen effect op de accommodatie-nauwkeurigheid en brekingsafwijkingen of op de aanwezigheid van stereopsis en binoculair zien (alle p > 0,212).

Bevindingen met betrekking tot adaptief gedrag en executief functioneren (hoofdstukken 4 en 5)

- Het verschil in ontwikkeling gemeten met de Vineland-S vragenlijst (achterstand in adaptief gedrag) tussen goedzienden en kinderen met Downsyndroom evenals hun achterstand in taakgerichte executieve functies (MEFS test) nam toe met de (kalender)leeftijd (adaptief gedrag: r = 0,965, p < 0,001; MEFS: r = 0,684, p < 0,001).
- Na een jaar dragen van de nieuw voorgeschreven brillen werden de executieve functies opnieuw gemeten met de op taak gebaseerde test (MEFS). Alleen in de bifocale groep verbeterden deze functies ten opzichte van baseline (gemiddelde verbetering: bifocaal 5,6 punten (95% CI: 2,1; 9,0), p = 0,002, Cohen's d = 0,60; unifocaal: 2,26 punten (95% CI: -1,1; 5,7), p = 0,191, Cohen's d = 0,24). Het verschil tussen de groepen was niet statistisch significant (intergroepsverschil 3,3 punten (95% CI: -0,9; 7,5), p = 0,120).
- Hogere follow-up scores voor taakgerichte executieve functies (MEFS) waren geassocieerd met betere gezichtsscherpte (uncrowded NVA, helling -10,2 (95% CI: -18,6; -1,8), p = 0,019; crowded NVA, helling -10,5 (95% CI: -19,8; -1,3), p = 0,025; en DVA, helling -11,2 (95% CI: -22,0; -0,3), p = 0,045) en verbeterde oogstand (rho = 0,343, p = 0,040).

Verdere inzichten van klinische en praktische relevantie

- Kinderen met Downsyndroom waren in staat om de bifocale bril op de juiste manier te leren gebruiken en droegen de bifocale bril goed tijdens het jaar follow-up [de Weger et al. 2020] (zie hoofdstuk 3).

- Er werd een tijdseffect in de ontwikkeling van de gezichtsscherpte gevonden. Na een paar weken dragen van de nieuw voorgeschreven brillen had de groep met bifocale bril vooruitgang geboekt in zowel uncrowded als crowded NVA, terwijl de groep met unifocale bril alleen vooruitgang had geboekt in uncrowded NVA. In beide groepen ontwikkelde NVA verder en na een jaar hadden beide groepen vooruitgang geboekt in zowel crowded als uncrowded NVA, waarbij de verbeteringen in NVA in de bifocale groep significant groter waren [de Weger et al. 2019] (zie hoofdstuk 2).
- Aan het begin van de studie was uncrowded NVA slechter dan DVA (gemiddeld verschil 0,11 LogMAR (95% CI: -0,52; 0,74), t(73) = 2,900, p = 0,005) [de Weger et al. 2019, 2021a] (zie hoofdstukken 2 en 4). Na een jaar dragen van de bifocale bril was NVA echter niet meer slechter dan DVA in die groep ((gemiddelde gezichtsscherpten) uncrowded NVA 0,32 LogMAR (95% CI: -0,05; 0,69); crowded NVA 0,35 LogMAR (95% CI: -0,10; 0,8) en DVA 0,38 LogMAR (95% CI: -0,09; 0,85) [de Weger et al. 2019] (zie hoofdstuk 2).
- Het effect van een bifocale bril op scheelzien ontwikkelde zich veel sneller dan het effect van de bifocale bril op de gezichtsscherpte [de Weger et al. 2020] (zie hoofdstuk 3).
- De correlatie tussen de visuele beperking en de achterstand in adaptief gedrag aan het begin van de studie suggereert dat gezichtsscherpte een rol speelt in de ontwikkeling van adaptief gedrag bij kinderen met Downsyndroom, zoals dat ook het geval is bij visueel beperkte kinderen zonder bekende cognitieve stoornissen [de Weger et al. 2021a] (zie hoofdstuk 4).
- Uit de exploratieve analyses van de door leerkrachten ingevulde executieve functies (BRIEF vragenlijsten) blijkt dat kinderen met Downsyndroom na een jaar op school significant verbeterde executieve functies laten zien met de nieuw voorgeschreven brillen. Omdat schooltaken veelal visueel zijn, kan de door interventies verbeterde gezichtsscherpte hen geholpen hebben deze taken uit te voeren [de Weger et al. 2021b] (zie hoofdstuk 5).
- Kinderen met Downsyndroom hebben verschillende oogafwijkingen en verschillende afwijkingen in visuele functies, adaptief gedrag en executieve functies. Deze heterogeniteit in combinatie met hun trage ontwikkeling en variërende aandachtsspanne en medewerking vormt een uitdaging voor zowel de verwerving als de analyse van de onderzoeksgegevens. Langere follow-up tijden en grotere studiepopulaties zijn nodig in toekomstige

studies [de Weger et al. 2019, 2020, 2021a, 2021b] (zie hoofdstukken 2,3,4,5).

Conclusie

Samenvattend heeft het dragen van een bril met een volledige correctie van de brekingsafwijking veraf- én nabij (de bifocale bril) positieve effecten op zowel de gezichtsscherpte veraf en nabij als op het executief functioneren van kinderen met Downsyndroom, wat suggereert dat er bij deze groep inderdaad een verband bestaat tussen hun visueel en executief functioneren.

De +2,5 dioptrie additie in de bifocale bril met volledige correctie van de brekingsafwijking verbeterde het nabijzien meer en verminderde het scheelzien effectiever dan de volledige correctie van de brekingsafwijking zonder additie. Bifocale brillen verbeterden de uitgangssituaties voor het ontwikkelen van executieve functies. Er werd een correlatie gevonden tussen betere gezichtsscherpte en betere scores op adaptief gedrag en ontwikkeling van executieve functies. De relatieve bijdragen van veraf- en nabijzien aan de ontwikkeling van executieve functies moeten echter verder worden onderzocht.

Gezien de resultaten na één jaar follow-up, lijkt het voorschrijven van bifocale brillen (additie +2,5 dioptrie) met volledige correctie van de brekingsafwijking bij kinderen met Downsyndroom zinvol, vanaf de leeftijd dat zij zittend een taakje kunnen uitvoeren.

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Yvonne Kras, jou, en ook Laura van der Helm die tijdelijk de taken overnam, wil ik heel hartelijk bedanken voor jullie ondersteunde taken tijdens de start en de uitvoering van het onderzoek. Dit was een erg drukke tijd, er moest toen vaak veel tegelijk gebeuren.

De vriendelijke en positieve sfeer tussen de collega's van CNS, allen bezig met een onderzoek, Bianca Huurneman, Annemiek Barsingerhorn, Karlijn Woutersen, Anna Geuzeveld en anderen bij de Lab meetings heeft me goed gedaan.

Graag wil ik ook nog stilstaan bij de mensen die een rol hebben gespeeld bij het begin van dit onderzoek. Roel Borstlap die door mij, als orthoptist, uit te nodigen bij het op te zetten Downteam in Assen in 1993 mijn speciale interesse voor deze doelgroep heeft aangewakkerd. Jeanette Slooff, die ik in 2011 leerde kennen bij het meeschrijven aan de Update van de Multidisciplinaire Richtlijn voor de Medische Begeleiding van Kinderen met Downsyndroom. Jij toonde steeds je medewerking en interesse voor dit onderzoek. Birgite Swartjes, met wie ik samen de literatuur doorzocht op oogafwijkingen bij Downsyndroom voor een voordracht daarover. Jij ondersteunde me met jouw schrijfvaardigheid in het Nederlands. Margaret Woodhouse die nog met me meedacht bij het ontwerp van dit onderzoek. Esther de Vries, jij gaf via het DOC bekendheid aan het onderzoek. Wouter Koeners die zijn kennis op het gebied van bifocale glazen met me deelde. Zo wil ik ook alle mensen en partijen bedanken die meegewerkt hebben aan het bereiken van ouders om hen de mogelijkheid tot meedoen aan het onderzoek te kunnen aanbieden.

Uitzicht, bestaande uit ODAS, Oogfonds, Novartis en LSBS, ben ik zeer erkentelijk voor de financiële steun tijdens de eerste jaren en Bartiméus, bedankt voor jullie financiële bijdrage tijdens de laatste jaren van dit onderzoek.

Theo, wat fijn dat jij je naast je kennis van de Engelse taal ook wilde verdiepen in het thema van dit onderzoek. Wat ben ik blij met jouw laatste hand om de Engelse taal op een hoger niveau te tillen. Dank je wel.

Mijn paranimfen, Marianne Horn en Marjan Vaessen, bedank ik dat zij mij bijstonden.

Ook thuis zijn deze jaren niet ongemerkt voorbij gegaan. Leonoor, Reinier, ook al woonden jullie niet meer thuis, dit hebben jullie zeker ondervonden. Reinier, jouw opmerking na het halen van mijn master Evidence Based Health care, 'mama, waarom ga je niet promoveren?', staat mij nog steeds bij. Leonoor, jouw geduldige hulp bij de opmaak van het boekje was zo welkom. Wim, jij hebt mij vele weekenddagen moeten missen omdat ik achter mijn laptops zat. Dit traject werd wel een enorm project. Je hebt veel stress voor me weggenomen door steeds weer bereid te zijn technische problemen voor me op te lossen. Jouw vaardigheden waren ook zeer welkom bij het maken en steeds verder verfijnen van de figuren en illustraties om deze in de juiste vorm en kwaliteit op te kunnen leveren. Dank voor al je steun en geduld gedurende al die jaren.

ABOUT THE AUTHOR

Christine Zijlstra was born on January 27, 1959 in Warrenton South Africa, from Dutch parents. During her youth, the family moved to different countries, such as Malaysia, the Netherlands and then Peru, where Christine grew up. During her parents' stay in Pakistan in 1976, she returned to the Netherlands for her secondary education and graduated from the Ronald Holst College at Hilversum, Atheneum-B. After an aborted physical geography study and completing a training as a master goldsmith, and a few years of practising her craft, she started her training in orthoptics. On the basis of her orthoptics training achievement she was invited to do a traineeship at the Freiburg University Hospital by Prof. Dr. med. G. Kommerell and Dr. H.J. Simonsz. Having obtained her diploma of orthoptics in 1988, she found employment at the practice of Dr. M.H. Gobin, strabologist in Antwerp, who was also affiliated with the university of Leiden.

In the wake of a relocation to the northern part of the Netherlands, she revived her interest in hospital work and founded two new orthoptic hospital practices, respectively at the Wilhelmina Ziekenhuis Assen and the Bethesda Ziekenhuis Hoogeveen. At the Wilhelmina Ziekenhuis Assen, paediatrist Dr. R. Borstlap invited her to join the newly founded Down-team as first orthoptist to undertake the examination of visual functions of children with DS. Meanwhile she did stand-in work at different locations, including an ophthalmologist practice in Groningen, the Aeromedical Institute and KLM-Health services. In addition, she taught refresher courses for general practitioners and doctors in youth health care and was a member of the quality committee of the Dutch association of orthoptists (NVvO). From 2002-2004, she worked also as orthoptics information specialist at the Nederlands Paramedisch Instituut, NPI (Dutch allied health services centre). In this setting, she was able to broaden her interest in the field of scientific research publications and evidence based health care.

In 2005, she registered for the master course Evidence Based Practice in Health Care at the Amsterdam University (Academic Medical Centre) where, in 2007, she received her academic master degree. In 2009, she started her work at the Bartiméus Institute for the Visually Impaired in the Netherlands, where she was invited to do in-depth research in relation to ocular disorders of children with Down syndrome and become co-author of the chapter 'Visual acuity and ocular disorders' of the updated guideline for treatment of children with Down syndrome issued by the Dutch Association of Paediatric Medicine in 2011.

At that time, her career faced a new challenge. She realized that a specific approach was needed for treating the ocular disorders that are particular to children with DS, and that research was needed into a tailor-made intervention for specific ocular disorders in children with DS. Together with Dr. F.N. Boonstra, ophthalmologist for the visually impaired, she initiated a lobby for financial support and designed the present randomized controlled trial. In 2013, a research grant was obtained from Uitzicht, a cooperation of ODAS, Oogfonds, Novartis and LSBS. The research project she envisioned was created at the Donders Institute of Radboud University Nijmegen, with Dr. H.H.L.M. Goossens and Dr. F.N. Boonstra as co-supervisors, in cooperation with the Department of Research and Innovation of the Isala Clinics, the Stichting Down Syndroom, SDS (the Dutch Down Syndrome Foundation), TNO (the Netherlands Organisation for Applied Scientific Research), DOC (Down Research Consortium), and the 15 participating treatment locations.

Since 2011, as a clinical epidemiologist, she has been teaching courses to support scientific research and evidence based practice and research designs in quantitative and qualitative research at the Academy of the Isala Clinics in Zwolle and also at Bartiméus.

From 2011-2020 she was board member and chairman of the Stichting tot Bevordering der Orthoptie, which awards a prize, the Jonkers' Prize, to the author of the best scientific publication originating from the global Dutch speaking language community, in the field of the development and/or pathophysiology of binocular vision or the therapy of impaired binocular vision. At Bartiméus, she has been a member and chairman of the expertise centre/group for visually impaired children.

Christine de Weger-Zijlstra has been married to Wim de Weger since 1984 and they are proud to be parents of a daughter, Leonoor (1988) and a son Reinier (1993).

LIST OF PUBLICATIONS

2021	De Weger C, Boonstra FN, Goossens J. One-year effects of bifocal and unifocal glasses on executive functions in children with Down syndrome in a randomized controlled trial. Sci Rep. 2021;11:16893. doi: 10.1038/s41598-021-96308-5. https://pubmed.ncbi.nlm.nih.gov/34413362/
2020 - 2021	de Weger C, Boonstra FN, Goossens J. Differences between children with Down syndrome and typically developing children in adaptive behaviour, executive functions and visual acuity. Sci Rep. 2021;11:7602. doi: 10.1038/s41598-021-85037-4. https://pubmed.ncbi.nlm.nih.gov/33828124/
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2019	de Weger C, Swartjes B. 'Kinderen met Down zien dichtbij beter met een bifocale bril'. Down+up 2019, 128: 42-49.
2018 - 2019	de Weger C, Boonstra N, Goossens J. Effects of bifocals on visual acuity in children with Down syndrome: a randomized controlled trial. Acta Ophthalmol. 2019;97:378-393. doi:10.1111/aos.13944. https://pubmed.ncbi.nlm.nih.gov/30367541/
2014	de Weger C, Boonstra FN, Goossens J. Onderzoek in Nederland naar het effect van een bifocale bril bij kinderen met Downsyndroom. VISUS 2014, 4:10-11.
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2014	de Weger C. Is een bifocaal beter voor uw kind? Dow+up 2014,108 winter: 36.
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2012 de Weger C, Swartjes B. De meest geschikte screeningsmomenten voor oogafwijkingen bij kinderen met Downsyndroom. TvO 2012, 2: 66-72.

2011 Co-auteur 'Update multidisciplinaire richtlijn voor de medische begeleiding van kinderen met Downsyndroom', hoofdstuk: Gezichtsscherpte en Oogheelkundige Afwijkingen, van de NVK, Nederlandse Vereniging voor Kindergeneeskunde.

2010 de Weger C, Van Den Brom HJ, Lindeboom R. Termination of amblyopia treatment: when to stop follow-up visits and risk factors for recurrence. J Pediatr Ophthalmol Strabismus. 2010;47:338-346. doi:10.3928/01913913-20100218-03. http://www.ncbi.nlm.nih.gov/pubmed/20210280

Geselecteerd als CME (continuing medical education) artikel.
Vermeld in Current Medical Literature,2011;21(2);86.

LIST OF PRESENTATIONS

2022	Congress of the NOG, the Dutch society of ophthalmologists, Groningen, The Netherlands.
2022	Congress of the IOA in Liverpool, UK, postponed to 2022.
2022	Congress VISION2020 Dublin, Ireland, postponed to 2021 and later postponed to 2022.
2020	Webinar / Symposium of the SDS, The Dutch foundation for Down syndrome, in Leiden, The Netherlands: 'Down door een andere bril bekeken'.
2020	Congress of the NOG, the Dutch society of ophthalmologists, Groningen, The Netherlands.
2019	Congress of CVRS, Child Vision Research Society in Pisa, Italy.
2019	Congress of the SOE, European Society of ophthalmology in Nice, France.
2019	Symposium of the NVvO, Dutch association of orthoptists, Amersfoort, The Netherlands.
2019	Congress of the NOG, the Dutch society of ophthalmologists, Maastricht, The Netherlands.
2017	Symposium Kinderoogheelkunde (Child ophthalmology), Tilburg, the Netherlands.
2017	Congress VISION2017, international society for low vision and rehabilitation, The Hague, the Netherlands.
2016	Symposium NVK, Dutch association of paediatric medicine, Dordrecht, The Netherlands.
2016	Congress COM, cataract and optometrist meeting, Manchester, UK.
2012	Symposium 'Syndrome of Down', NVvO and OVN, a collaboration of both the Dutch associations the optometrists and orthoptists, De meest geschikte screeningsmomenten voor oogafwijkingen bij kinderen met Downsyndroom.

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RESEARCH DATA MANAGEMENT PAGE

Beyond improving visual acuity in children with Down syndrome. The effect of bifocals.

This research followed the applicable laws and ethical guidelines. Research Data Management was conducted according to the FAIR principles. The paragraphs below specify in detail how this was achieved.

Ethics.

This thesis is based on the results of human studies, which were conducted in accordance with the principles of the Declaration of Helsinki. The Dutch Medical Ethics Committee of the Isala Hospitals (and confirmed by the local ethics committees of the participating clinics) has given a positive advice to conduct these studies to the Dean of the Faculty, who formally approved the conduct of these studies (Number NL48288.75.14/ METC: 14.0333). This research was financially supported by ODAS, Oogfonds, Novartis and LSBS (Uitzicht 2013-23 to F.N.B. and J.G., and Bartimeus Institute to F.N.B. and C.d.W.). These financial parties had no influence on the design and the progress of the study.

Data management system

We used the digital Web-based research data managing system, ResearchManager 2014, 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.

Findable Accessible

The data of this dissertation are stored in the Repository. The table below details where the data and research documentation for each chapter can be found on the Donders Repository (DR).

The data in the Data Sharing Collection (DSC) on the Donders Repository (DR) can be shared after any reasonable request. Please contact Christine de Weger or Jeroen Goossens. All data archived as a Data Sharing Collection remain available for at least 10 years after termination of the studies.

Informed consent was obtained on paper following the Centre procedure. The forms are archived in the cooperating locations of this multicentre RCT for 10 years after termination of the studies.

Chapter	DAC	RDC	DSC	DSC License
2. Effect of bifocals on visual acuity	- Raw data export ResearchManager Isala - Raw data export MEFS - Randomization - Data set short	- Dropouts and exclusions	- Data set short	RU-HD-1.1
3. Bifocals reduce strabismus				
4. Differences between children with DS and norms				
5. One-year effects of bifocals on executive functions		- Dropouts and exclusions - Post-intervention analyses MEFS	- Data set short - Post-intervention analyses MEFS	RU-HD-1.1

DAC = Data Acquisition Collection, RDC = Research Documentation Collection, DSC = Data Sharing Collection

Interoperable, Reusable

The raw data are stored in the DAC in their original form. The datasets for RDC and DSC are stored in the Repository ensuring that data remain usable in the future.

Privacy

The privacy of the participants in this thesis has been warranted using random individual subject codes. A pseudonymization key linked this random code with the personal data. This pseudonymization key was stored at the participating location that was only accessible to members of the project who needed access to it because of their role within the project. The pseudonymization key was stored separately from the research data. Data in chapters 2, 3, 4 and 5 are not identifiable and can be shared on any reasonable request.

DONDERS GRADUATE SCHOOL FOR COGNITIVE NEUROSCIENCE

For a successful research Institute, it is vital to train the next generation of young scientists. To achieve this goal, the Donders Institute for Brain, Cognition and Behaviour established the Donders Graduate School for Cognitive Neuroscience (DGCN), which was officially recognised as a national graduate school in 2009. The Graduate School covers training at both Master's and PhD level and provides an excellent educational context fully aligned with the research programme of the Donders Institute.

The school successfully attracts highly talented national and international students in biology, physics, psycholinguistics, psychology, behavioural science, medicine and related disciplines. Selective admission and assessment centres guarantee the enrolment of the best and most motivated students.

The DGCN tracks the career of PhD graduates carefully. More than 50% of PhD alumni show a continuation in academia with postdoc positions at top institutes worldwide, e.g. Stanford University, University of Oxford, University of Cambridge, UCL London, MPI Leipzig, Hanyang University in South Korea, NTNU Norway, University of Illinois, North Western University, North-eastern University in Boston, ETH Zürich, University of Vienna etc.. Positions outside academia spread among the following sectors: specialists in a medical environment, mainly in genetics, geriatrics, psychiatry and neurology. Specialists in a psychological environment, e.g. as specialist in neuropsychology, psychological diagnostics or therapy. Positions in higher education as coordinators or lecturers. A smaller percentage enters business as research consultants, analysts or head of research and development. Fewer graduates stay in a research environment as lab coordinators, technical support or policy advisors. Upcoming possibilities are positions in the IT sector and management position in pharmaceutical industry. In general, the PhDs graduates almost invariably continue with high-quality positions that play an important role in our knowledge economy.

For more information on the DGCN as well as past and upcoming defences please visit: http://www.ru.nl/donders/graduate-school/phd/

BEYOND IMPROVING VISUAL ACUITY IN CHILDREN WITH DOWN SYNDROME

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