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Effectiveness of routine population-wide orthoptic preschool vision screening tests at age 6–24 months in the Netherlands

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ABSTRACT.

Purpose: **The effectiveness of preverbal orthoptic tests at age 6, 9, 14 and 24 months in population-wide screening was assessed.**

Methods: **Two consecutive birth cohorts at 134 centres were compared. At general health screening visits, children born July–December 2011 were vision screened four times between 6 and 24 months with inspection, pupillary reflexes, eye motility, Hirschberg, cover test and monocular pursuit. Children born January–June 2012 were vision screened at general screening visits only in case of visually apparent abnormalities or positive family history. After referral, cause and severity of amblyopia were determined. Visual acuity was measured in all children at 36 and 45 months.**

Results: **The control and intervention group comprised 5649 versus 5162 children. Amblyopia was diagnosed in 185 (3.3%) versus 159 children (3.1%), outside of screening in 21 (11.4%) versus 25 (15.7%). Between 6 and 24 months, 44 (23.8%) versus 27 (17%) (RR = 0.67 [95% CI 0.42, 1.09]) were referred and after visual acuity (VA) measurement 120 (64.9%) versus 107 (67.3%). Of 109 versus 108 children with refractive or bilateral amblyopia, 94 (86.2%) versus 92 (85.2%) were detected with VA measurements. Visual acuity of the amblyopic eye, after referral, was not significantly different between groups (p 0.896), nor was the time to amblyopia diagnosis (intention to screen [p 0.55]; per protocol [p 0.11]).**

Conclusion: **The effectiveness of vision screening was not influenced by omission of orthoptic tests at general health screening at 6–24 months. Refractive and bilateral amblyopia were almost exclusively found by VA measurements.**

Key words: amblyopia – eye screening – paediatric screening – strabismus – vision screening

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Introduction

The Netherlands has one of the most extensive amblyopia screening systems worldwide (Sloot et al. 2015a, b). Children are screened seven times from birth to 5 years of age (Sloot et al. 2015a, b). In 1901, the first Child Healthcare (CHC) centre was opened in the Netherlands (de Preegeerlings et al. 2001). In 1960, measurement of visual acuity (VA) after three years of age was included. Preverbal orthoptic vision screening tests ('Vroegtijdige Onderkenning Visuele stoornissen (VOV)': early detection of visual disorders) were introduced in 1980 (Lantau et al. 1985; Loewer-Sieger et al. 1987). Preventive youth healthcare (YHC) physicians and nurses perform eye screening at CHC centres, as part of the screening for general health disorders and vaccinations, of all children younger than four years of age according to the national protocol ('Opsporing visuele stoornissen 0–19 jaar') (Coenen-van Vroonhoven et al. 2010). This includes inspection of cornea and pupil, pupillary reflexes, fundus reflex and eye motility at 1–2 and 3–4 months to detect congenital disorders like retinoblastoma and cataract. Preverbal orthoptic tests are performed at 6–24 months: Hirschberg test, cover test and pursuit movements, but no fundus reflex testing (Table 1) (Lantau et al. 1985; Loewer-Sieger et al. 1987; Coenen-van

Table 1. Examinations at child healthcare centres according to the National guideline.

Age	Inspection	Pupillary reflex	Fundus red reflex	Hirschberg test	Cover test	Quality of pursuit	Motility	VA APK	VA Landolt-C
1–2 m	X	X	X						
3–4 m	X	X	X						
6–9 m	X	X		X	X	X	X		
14–24 m	X	X		X	X	X	X		
36 m	X							X	
45 m	X								X
60 m	X								X

Age in months.
APK = Amsterdam Picture Chart, VA = visual acuity.

Vroonhoven et al. 2010). At 36 and 45 months, VA is tested, respectively, with the Amsterdam Picture Chart (APK) and the Landolt C. Visual acuity measurements are repeated at school at 54–60 months.

An overall participation rate of 97% of at least one visit in the first two years is reached (Juttmann 2001), because eye screening is imbedded in a population-based general healthcare screening and vaccination programme.

To evaluate the effectiveness of the amblyopia screening in the Netherlands, the RAMSES birth-cohort study ($N = 4624$) was performed. This study showed that preverbal screening contributed little to the detection of refractive amblyopia, while strabismus amblyopia was referred outside of screening in approximately half of cases (Groenewoud et al 2010).

The Optimization of Amblyopia Screening study (OVAS) was designed to assess whether and to what extent omission of orthoptic vision screening tests as part of general health screening between the age of 6–24 months would affect the detection of strabismus, refractive and combined-mechanism amblyopia and to confirm whether the omission of routine orthoptic vision screening tests between age 6–24 months would have no negative impact on the severity, time and total cases of amblyopia detected. Parts of these results concerning screening at age 6–9 months have been published earlier (Sloot et al. 2015a, b). In another previous study, the performance of CHC physicians with these orthoptic tests was assessed with semi-structured observations. We now report the outcomes of the total OVAS study, after 5-year follow-up.

Materials and Methods

Study design

A birth-cohort study was conducted with sequential control and intervention groups. The large sample size aimed for precluded individual randomization from a practical point of view. Based on their date of birth, participants were allocated for orthoptic vision screening tests as part of general health screening, the current standard in the Netherlands (control group, born between 1st of July and the 31st of December 2011) or general health screening without orthoptic vision screening (intervention group, born between 1st of January and the 30th of June 2012) at age 6–24 months. Parents in the intervention group were informed through an information leaflet about the change in screening protocol and could opt out of the study and request screening according to the national protocol. The nature of the intervention precluded participant blinding. All data were prospectively acquired in the Netherlands.

The Medical Ethical Review Committee of the Erasmus Medical Centre declared that the Medical Research Involving Human Subjects Act did not apply to this research proposal as it concerned population-based prevention and that the 'Besluit Publieke Gezondheid' (Dutch government 2008) applied (reference number MEC-2012-003). Permission was granted from the Dutch Health Care Inspectorate to deviate from the national screening guidelines. The study protocol and consent procedure adhered to the tenets of the Declaration of Helsinki.

Sample size calculation

We calculated the sample size for this comparative two-sampled non-inferiority study, based on the assumption that an incidence of only 2.7% amblyopia could occur, the most disadvantageous incidence threshold in the RAMSES study. In the RAMSES study, 2964 children had undergone the complete 7-years follow-up and vision testing, yielding an amblyopia diagnosis in 100 children (3.4%, 95% CI: 2.7–4.0%) (Groenewoud et al 2010). Using a type 1 error rate of 0.05 (α), a power of 80% (1-β, wherein the β (type 2 error) is 0.20) and a non-inferiority margin of 0.8%, we calculated that 5076 subjects were required per study group. We added a 5% anticipated loss to follow-up and dropout rate, yielding a minimum study population size of 10 660 children.

Screening examinations

All children were invited to visit the CHC centres at 6, 7.5, 9, 11, 14, 18, 24, 36 and 45 months of age for general health screening. In the first National protocol, vision screening should be performed at 6, 9, 14 and 24 months by CHC physicians. In a later version of the National protocol, vision screening was only obligatory at 6–9 and 14–24 months.

Control (standard screening) group 6–24 months

Children born between July and December 2011 were vision screened according to the national protocol at 1–2 and 3–4 months with inspection of the eyes, pupillary reflexes, eye motility and red fundus reflex testing to rule out congenital eye disorders. At 6–24 months, the orthoptic vision

screening took place at least two times: at age 6–9 and 14–24 months. The examination consisted of inspection of cornea and pupil, pupillary reflexes, eye motility, Hirschberg test, cover test and pursuit movements (Table 1).

Intervention (reduced screening) group 6–24 months

Children born between January and June 2012 were eye screened at 1–2 and 3–4 months. These children attended general health screening visits at 6–24 months, but were only vision screened in case an eye abnormality was noticed or suspected by the screening physician or parent or in case of a positive family history.

Visual acuity measurements at 36–45 months in both groups

Visual acuity measurements were performed in both groups at the age of 36 and 45 months at the CHC centres with the APK and Landolt C chart, respectively. According to the national protocol, the result of the VA measurement can be sufficient or insufficient or the measurement itself fails (Table 2). Insufficient and failed measurements must be repeated within 3 months according to the national protocol, or the child had to be referred to an orthoptist, general practitioner (GP) or ophthalmologist. At 36 months, the VA measurement should be repeated with a VA of 5/10 for both eyes or with a VA above 5/10 with one-line difference between the eyes. In case of VA below 5/10 or a two-line difference, the child should be referred directly. At 45 months, the VA measurement should be repeated when at the first measurement the VA was above 0.5 decimal but with one-line difference between the eyes. In case of VA below 0.5 for either eye or a two-line difference, the child should be referred directly. If the result of the second VA measurement also proved insufficient, or failed, the child must be referred.

Data collection

Child healthcare centre

Vision screening data were collected from the electronic screening records from the CHC centres. The CHC organizations provided an Excel data set to the researchers. The follow-up visits at the CHC also provided information about children referred outside of screening.

Orthoptists

Orthoptists working in the study area were contacted and visited before the start of the study. Treating orthoptists provided clinical orthoptic data if the child was referred based on initials and date of birth. Some orthoptists also provided information about children from the selected cohorts, who were referred outside of screening by others than the CHC centres, like general practitioners or paediatricians. For each first hospital visit of a child in the two study arms, orthoptists filled out a standardized form about orthoptic examination, VA, diagnosis and treatment (Appendix 1). The treating orthoptists were asked to indicate whether the child (possibly) had amblyopia, and if amblyopia was suspected, whether it was strabismus, refractive, combined-mechanism or deprivation amblyopia (type of amblyopia).

Received data of the CHC centres were matched with the orthoptic data, provided with initials and date of birth, and thereafter anonymized by the researchers.

Data analysis

If one of the VA measurements (36, 45 or 60 months) at the CHC centre was sufficient according to the national protocol (Coenen-van Vroonhoven et al. 2010), the child was classified as having no amblyopia. If no or one failed or insufficient VA measurement was available, without orthoptic information, the child was classified as lost to follow-up. If the VA measurement was insufficient twice or had failed twice, and no orthoptic information was available, children were invited for extra VA measurements by the study orthoptist or the 60 months VA measurement result was requested from the CHC centre if available. If no extra VA result could be obtained, the child could not be diagnosed as amblyopic or non-amblyopic, but was classified as a separate loss-to-follow group because of a slightly higher chance of amblyopia.

When orthoptic information was available for children who had been referred at an age before VA measurement was possible, the amblyopia presence was based on the opinion of the treating orthoptist: amblyopia present: definitively, probably, probably not or not, fixation preference and the presence of an amblyogenic factor (strabismus, refractive disorder or deprivation).

When a VA measurement from the treating orthoptist was available, amblyopia diagnosis was based on the first VA measurement, before glasses adaptation. The orthoptists classified children into definitively, probably, probably not or no amblyopia. This classification was mainly based on a VA difference 2 logMAR lines difference between the eyes or a bilateral VA $\leq$ 0.5 snellen VA before glasses adaptation or strong fixation preference or amblyopic factor.

Table 2. Criteria for referral or repeat measurement, according to the Dutch National protocol for vision screening, for sufficient, insufficient or failed measurement at age 36 and 45 months with the Amsterdam Picture Chart* and Landolt-C (Coenen-van Vroonhoven et al. 2010; Telleman et al. 2019). *(not logMAR, however: 5/5, 5/6, 5/10, 5/15, etc.) (VA = visual acuity).

	36 months	45 months	
	Amsterdam picture chart	Amsterdam picture chart	With Landolt-C
VA measurement sufficient	Monocular VA $\geq$ 5/6 for both eyes	Monocular VA $\geq$ 5/5 for both eyes	Monocular VA $\geq$ 0.5 for both eyes
VA measurement insufficient	Monocular VA < 5/6 for one or both eyes One-line interocular difference*	Monocular VA < 5/5 for one or both eyes One-line interocular difference*	Monocular VA < 0.5 for one or both eyes Two-lines interocular difference
VA measurement failed	The measurement failed Only binocular VA obtained VA was measured of one eye only		

The research orthoptist (MT), researcher (FS) and ophthalmologist (HJS) determined the definitive presence, type and severity of amblyopia in both groups, taking all VA measurements, from both the CHC centres and the treating orthoptists, and the orthoptist's classification into account. If amblyopia was present, the type of amblyopia was defined based on the presence of an amblyogenic factor (strabismus, deprivation or refraction). Refractive amblyopia, for all age groups, was diagnosed when spherical equivalent between the eyes differed ≥ 1.00 dioptres or astigmatism with oblique axis, especially with opposite direction was present. Strabismus amblyopia was diagnosed when strabismus was determined by the orthoptist.

Statistical analysis

All analyses were performed with the statistical package for social sciences (SPSS, IBM Corp.) software, version 25.0.0.2. Statistical significance was set at the 0.05 level, and all testing was two-sided. Testing of categorical variables (e.g. two by two tables) was conducted with a Chi-squared test. We aimed to study and compare both groups, with respect to their time to referral and time to amblyopia diagnosis. The time to amblyopia analysis follows an intention to screen method (primary end-point). Secondarily, a per protocol analysis (no screening versus at least one screening test) was performed. These time to event analyses, including the corresponding hazard ratio's (HR) and figures, were performed with a Cox regression model for proportional hazards. In the sensitivity analysis, a covariate was added to the model to study its influence on the results. A Mann–Whitney *U*-test was performed to investigate difference in depth of amblyopia between the two groups (not normally distributed data).

Results

Inclusion

All children born in the area of and registered at the participating CHC centres were included at baseline. Inclusion into both study groups (n 10 811) was distributed equally across the 134 participating centres (p 0.13). The control group comprised 5649 children of whom 89 dropped out of the study (1.6%) prior to their first screening moment (moved out of the area, had no screening record or were non-users of the CHC centre). The intervention group included 5162 children with 100 dropouts, either prior to their first screening moment or because of declined participation (1.9%) (p 0.15) (Fig. 1). After excluding the dropouts, the total study population consisted of 10 622 children (5479 male, 5132 female) with 37 722 patient-years of on study exposure time. Loss to follow-up – at any time-point after the first screening visit – occurred equally in both groups with 491 / 5560 (8.8%) and 468 / 5062 (9.2%) cases, respectively (p 0.46) (Fig. 1). Loss to follow-up was mainly due to no VA measurement or relocation of the child.

An orthoptic form was received of 532 (out of 771) referrals in the control group versus 464 (out of 755) referrals in the intervention group. In addition, 84 forms in the control group and 108 forms in the intervention group were received of children referred outside of screening.

Attendance

Attendance to general health screening visits at 0–45 months was 7.95 ± 1.42 visits in the control and 7.71 ± 1.40 visits in the intervention group. The distribution of visits was slightly skewed with more visits in the control group. In the control group, a mean of 3.12 ± 1.07 orthoptic vision screening tests was performed at 6–24 months, as compared to 1.03 ± 1.06 screening tests in the intervention group. Complete absence of screening in the intervention group was achieved in 1989 children (39.3%), while 1598 (31.6%) underwent a single vision screening exam and 1475 (29.1%) children two or more vision screening tests (Fig. 2). Vision screening was allowed in the intervention group in case an eye abnormality was noticed or suspected by the screening physician or parent or in case of a positive family history.

Referral

After screening at 6–24 months in the control group, 173 out of 5560 (3.1%) children were referred, versus 123 out of 5062 (2.4%) children in the intervention group (Relative Risk (RR) = 0.78 [95% CI 0.62, 0.98]). Observation of strabismus by either parents or screening physician was the referral reason, in 80 (46.2%) versus 57 (46.3%) children. A visually apparent problem as nystagmus, microphthalmos, ptosis, dacryostenosis, cyst, anisocoria was the reason for referral in 11 (6.4%) versus 22 (17.9%) children. The preverbal screening test itself, at 6–24 months, as primary screening instrument, led to a referral in 28 (16.2%) versus eight (6.5%) children. Whether the strabismus was detected by observation only, or by the screening test, could not be determined in 43 (24.9%) versus 32 (26.0%) children. Four children in both groups were referred due to positive family history (2.3% vs. 3.3%) and seven children in the control group for other causes (4.0%).

Visual acuity measurements at 36 months led to 258 (4.6%) versus 267 (5.3%) referrals. Visual acuity (VA) measurement at 45 months led to 308 (5.5%) versus 350 (6.9%) children were referred. Extra VA measurements at 60 months led to another 32 (0.6%) versus 15 (0.3%) referrals.

In total, 771 children (13.9%) in the control group were referred based on screening, as compared to 755 children (14.9%) in the intervention group (p 0.11) (Fig. 3). Time to referral analysis demonstrated no significant (p 0.161) difference between both groups (HR 1.08, 95% CI 0.97–1.19) (Fig. 3).

Diagnosis and age of detection of amblyopia

After screening at age 6–24 months, from the 173 versus 123 referrals, 44 out of 5560 (0.79%) versus 27 out of 5062 (0.53%) children were diagnosed with amblyopia (RR = 0.67 [95% CI 0.42, 1.09] (Table 3). Other eye disorders were diagnosed in 29 (0.52%) versus 21 (0.41%) children (Table 3 and Appendix 1).

After VA measurements of the 598 referrals (out of 5560 children), 120 (2.2%) in the control group (36–60 months) were diagnosed with amblyopia versus 107 (2.1%) out of the 632 referrals (out of 5062 children) in the intervention group (Table 3). Other eye disorders were diagnosed in 31 (0.56%) versus 21 (0.41%) children (Table 3 and Appendix 1).

Amblyopia detected outside screening, for instance, after referral by a GP

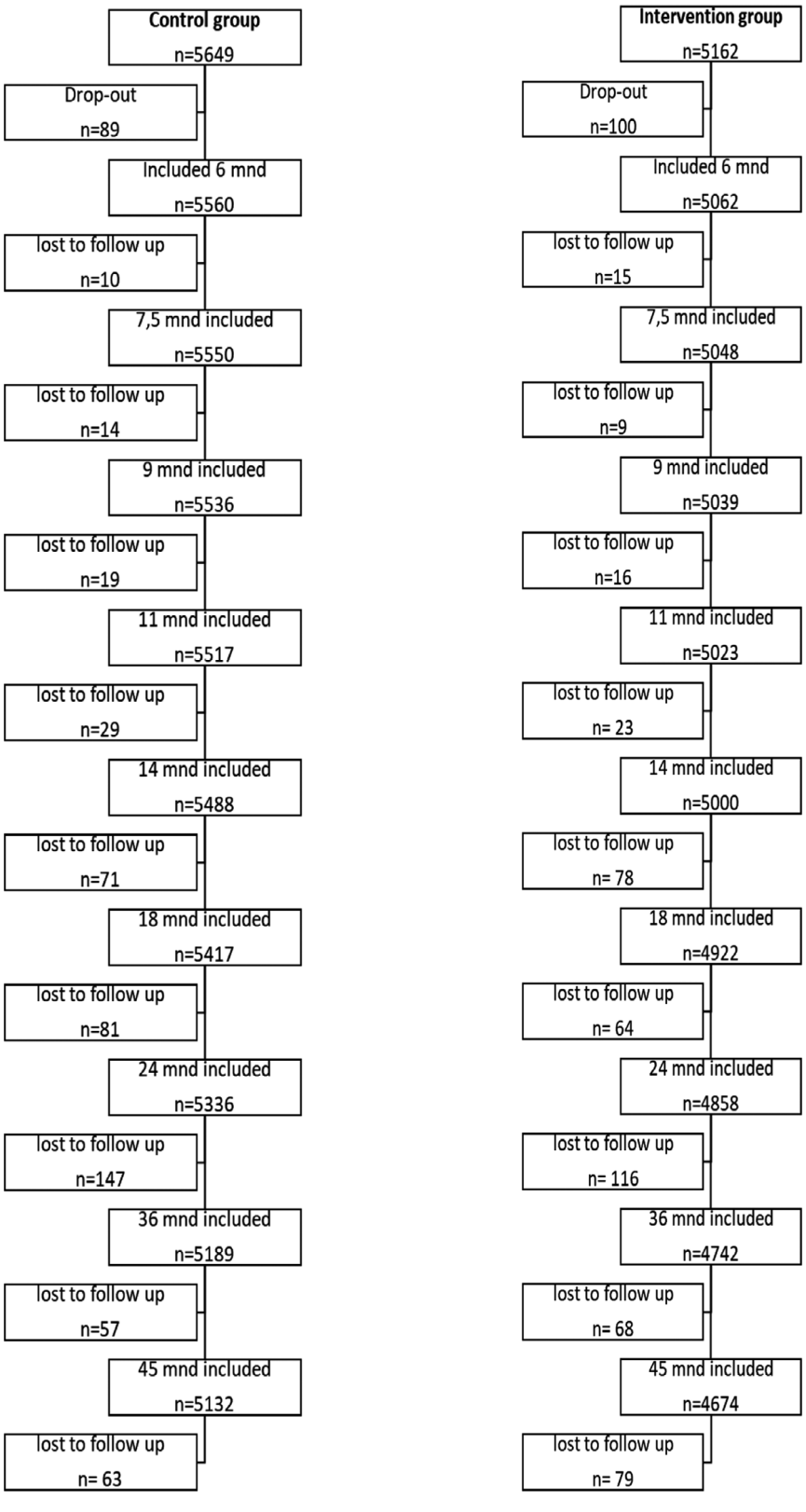

Fig. 1. Lost to follow-up per screening moment of the control group (n = 5649) and intervention group (n = 5162), the dropout for each study arm (89 vs. 100, p 0.15) and the loss to follow-up after each Child healthcare centre visit (in total 491 vs. 468, p 0.46). (n = number, mnd = months).

or after self-referral, yielded 21 (0.38%) versus 25 (0.49%) cases of amblyopia (Table 3), and other eye disorders in 21 (0.38%) versus 32 (0.63%) children (Table 3 and Appendix 1).

In total, 185 (3.3%) children in the control group and 159 (3.1%) children in the intervention group were diagnosed with amblyopia (p 0.613) as a result of referral by CHC centres, 6–60 months screening and referrals made

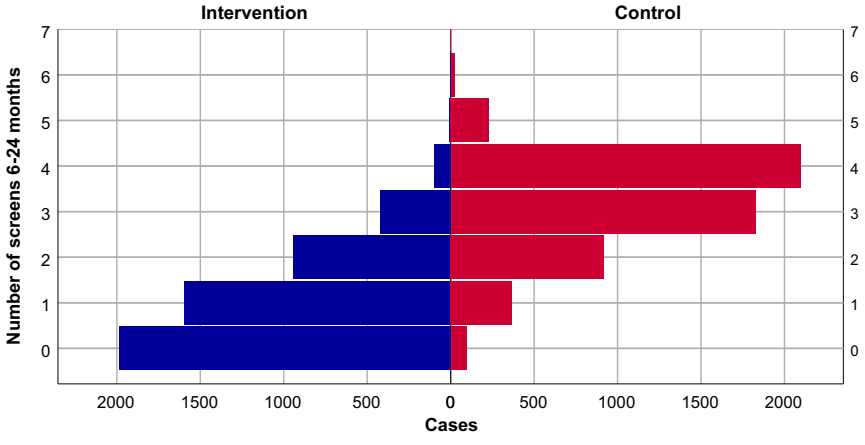

Fig. 2. Number of orthoptic vision screenings performed between 6 and 24 months. The national protocol in the control group indicated 2–4 orthoptic vision screenings during these moments. In the intervention group, all the children were invited for general screening, but the vision screening was performed on indication only.

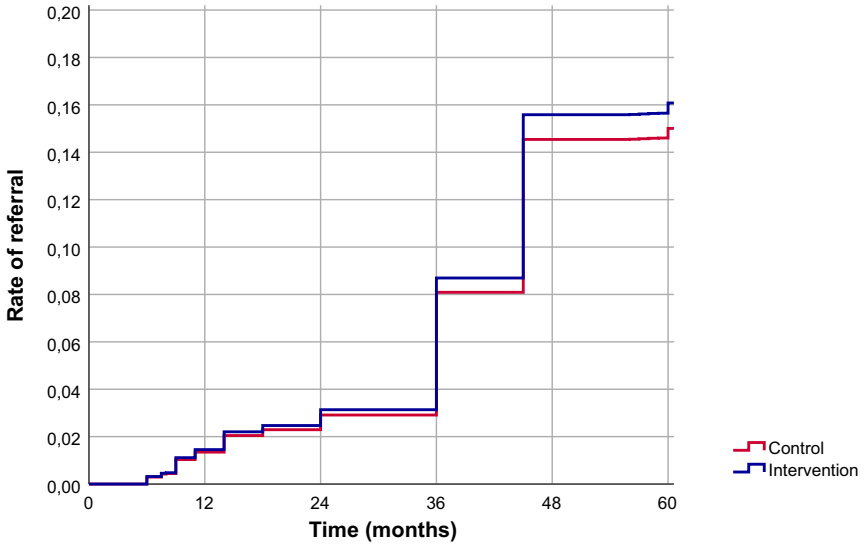

Fig. 3. Cumulative referral rate for vision screening between age 6–60 months.

outside of screening (Table 3, Fig. 4). Insufficient data were obtained in 234 (4.2%) in the control group versus 208 (4.1%) children in the intervention group. These children could not be classified as amblyopic because of insufficient or failed VA measurements twice and no available orthoptic data.

Based on the intention to screen analysis, there was no significant difference (p 0.55) between both groups in their time to amblyopia diagnosis. The corresponding HR was 0.98 (95% CI 0.79–1.21). Most amblyopia diagnoses were made after the VA measurements at 36 and 45 months, with no advantage in time to diagnosis by screening performed up to 36 months (Fig. 5a). A sensitivity analysis yielded an unchanged absence of a difference between both groups (i.e. no benefit of screening) after multivariate correction for the number of visits (HR adjusted (HRadj) 0.97, 95% CI 0.78–1.20), gender (Hradj 0.98, 95% CI 0.79–1.21) or children identified outside of the study (i.e. referred by general practitioners) (Hradj 0.97, 95% CI 0.78–1.20). The per protocol analysis, comparing those without any preverbal screening (n 2083) with children receiving ≥ 1 preverbal screening test (n 8539), also showed no significant difference (p 0.11) between both groups in their time to amblyopia diagnosis (HR 0.79, 95% CI 0.59–1.06) (Fig. 5b).

Positive predictive value

Vision testing performed at 36, 45 and 60 months yielded 3.2 times more amblyopia diagnoses (120 and 107 cases) than screening between 6 and 24 months (44 and 27 amblyopia cases, respectively). The positive predictive value between 6 and 24 months (i.e. a referral resulting in an amblyopia diagnosis) is 25.4% (95% CI 19.5–32.4%) for the control group and 22.0% (95% CI 15.6–30.1%) in the intervention group. The corresponding values for an amblyopia diagnosis based on referral after VA testing (36, 45 and 60 months) are 20.1% (95% CI 17.1–23.5%) versus 16.9% (95% CI 14.2–20.1%), respectively when children diagnosed with amblyopia based on vision testing (reference standard) are compared with an aggregate of all 6–24 months preverbal screening moments (index test), than screening in the control group has a sensitivity, specificity, positive and negative predictive value of 26.8%, 97.6%, 25.4% and 97.8%, respectively. Likewise, preverbal screening in the intervention group has a sensitivity, specificity, positive and negative predictive value of 20.1%, 98.1%, 22.0% and 97.8%, respectively.

Type of amblyopia

Strabismus amblyopia was detected in 50 versus 27 children, of whom 26 (52%) versus 12 (44%) were detected between 6 and 24 months, and 14 (28%) versus seven (26%) with VA measurements at 36–60 months. The other ten (20%) versus eight children (30%) were detected outside of screening.

Refractive amblyopia was detected in 60 versus 68 children, of whom five (8.3%) versus two (2.9%) with screening between 6 and 24 months and 54

Table 3. Amount of referrals, amblyopia cases, the positive predictive value (PPV) of amblyopia, other diagnosed eye disorders (Appendix 1) and the overall PPV of all diagnosed eye diseases (other and amblyopia). (VA = visual acuity, n = number).

	Age in months	Group	Referral, n	Amblyopia, n	PPV Amblyopia (%)	Eye disease, n	PPV all diagnoses (%)
Preverbal screening	6 months	Control	17	5		2	
6–24 months		Intervention	13	3		2	
	7.5 months	Control	10	3		1	
		Intervention	5	0		0	
	9 months	Control	32	6		5	
		Intervention	28	3		5	
	11 months	Control	18	1		7	
		Intervention	14	3		3	
	14 months	Control	44	11		8	
		Intervention	27	5		7	
	18 months	Control	20	8		1	
		Intervention	5	1		0	
	24 months	Control	32	10		5	
		Intervention	31	12		4	
Total preverbal screening		Control	173	44	25.4	29	42.2
6–24 months		Intervention	123	27	22.0	21	39.0
VA at 36–60 months	36 months	Control	258	72		17	
		Intervention	267	60		12	
	45 months	Control	308	42		11	
		Intervention	350	44		8	
	60* months	Control	32	6		3	
		Intervention	15	3		1	
Total VA measurements		Control	598	120	20.1	31	25.3
36–60 months		Intervention	632	107	16.9	21	20.3
Total all screening visits		Control	771	164	21.3	60	29.1
6–60 months		Intervention	755	134	17.7	42	23.3
Referrals outside of screening		Control	47	21		21	
		Intervention	59	25		32	
Total screening 6–60 months and		Control	818	185	22.6	81	32.5
referrals outside of screening		Intervention	814	159	19.5	74	28.6

* Optional extra vision exam in case of exam failure at 45 months.

(90%) versus 62 (91.2%) with VA measurements at 36–60 months. One (1.7%) versus four children (5.9%) were detected outside of screening.

Combined-mechanism amblyopia was detected in 17 versus 16 children, of whom seven (41.2%) versus nine (56.3%) were detected between 6 and 24 months and four (23.5%) versus four (25%) with VA measurements at 36–60 months. Six (35.3%) versus three (18.8%) were detected outside of screening.

Bilateral amblyopia was detected in 49 versus 40 children, of whom five (10.2%) versus two (5%) with screening between 6 and 24 months and 40 (81.6%) versus 30 (75%) with VA measurements at 36-60 months. Four (8.2%) versus 8 (20%) were detected outside of screening.

Deprivation amblyopia was detected in two versus four children. Both children in the control group were detected between 36 and 60 months. One child in the intervention group was detected between 6 and 24 months, one between 36 and 60 months and two outside of screening.

Type of amblyopia was unknown in seven versus four children.

Figure 6 shows the type of amblyopia detected. Figure 7 shows the cumulative percentage of total amblyopia detected separated in type of amblyopia.

There was no significant difference between the number of amblyopia cases between the two groups; 185 children (3.3%) in the control group versus 159 children (3.1%) in the intervention (p 0.613). There were slightly more strabismus and slightly less refractive amblyopia cases in the control group. Strabismus amblyopia was diagnosed earlier.

Severity of amblyopia

The logMAR VA of the amblyopic eye was equally distributed between both groups (Fig. 8). The logMAR VA difference between both eyes was equally distributed between study groups (p 0.733, Mann–Whitney-U test) (Fig. 9).

Severe amblyopia (VA under the 0.25 decimal) was diagnosed in 55 versus 45 children. Moderate amblyopia (VA 0.25–0.5 decimal) was diagnosed in 83 versus 74 children. Mild amblyopia (VA higher than 0.5 decimal) was diagnosed in 15 versus 11 children. Severity was unknown in 32 versus 29 children.

There was no significant difference between both groups regarding the vision of the amblyopic eye in the severe amblyopia group (VA under 0.25 decimal, above 0.6 logMAR) (p 0.274). There was no significant difference between both groups regarding the vision of the amblyopic eye in the moderate to severe amblyopia group (VA under 0.50 decimal, above 0.3 logMAR) (p 0.549).

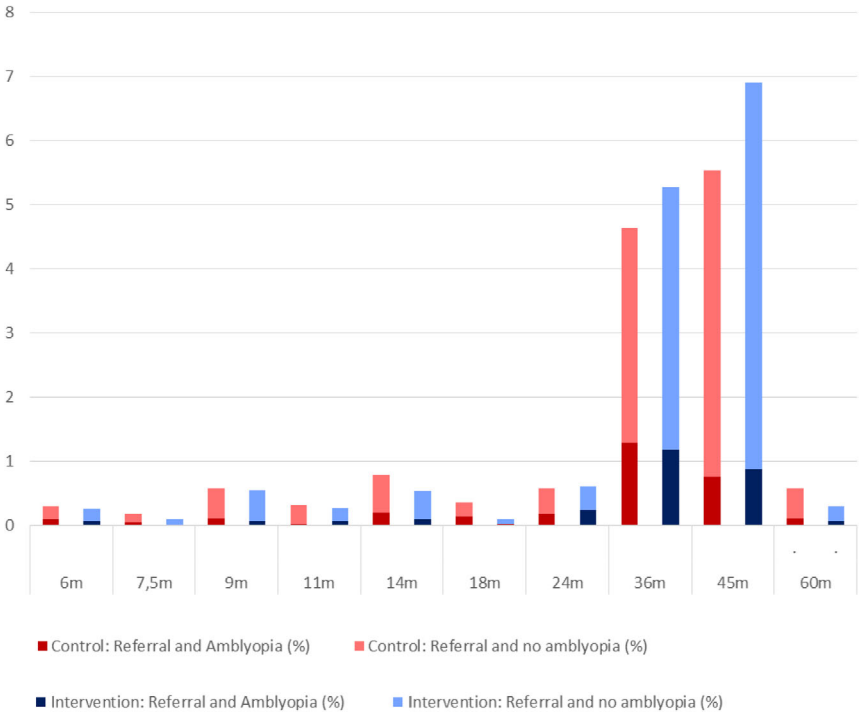

Fig. 4. Referral and amblyopia cases detected at each screening moment (m = months) (in percentages).

Discussion

This study demonstrated that omission of routine preverbal eye screening tests between the age of 6–24 months in the Netherlands did not lead to significant differences in amount of children referred, in total cases of amblyopia detected or in time of detection. Nor was there a significant difference in the severity of the detected amblyopia. The most important reason for referral at age 6–24 months was observed strabismus or a visually apparent eye disorders noticed by the parents. These disorders will be detected regardless of formal vision screening. Strabismus amblyopia was mainly detected before the age VA could be measured. Refractive amblyopia and bilateral amblyopia on the other hand were detected, almost exclusively, with the VA measurements between 36 and 60 months. Visual acuity measurements at 36–60 months yielded far more amblyopia cases compared to the screening between 6 and 24 months with even expenses. Only 0.8% from the 3.3% amblyopia in the control group and 0.5% from the 3.1% amblyopia in the intervention group were detected with preverbal screening. More strabismus amblyopia cases were detected in the control group. This difference only became apparent after the VA measurements.

Amblyopia is more responsive to treatment in children younger than seven years of age (Holmes et al. 2011). As there was no significant difference in time to referral and severity of amblyopia, omission of eye screening between 6 and 24 months does not seem to affect the effectiveness of amblyopia treatment. With the VA measurements at 45 months, children will be referred and receive treatment well before the age of seven. In ongoing research, we will assess whether there is a difference in amblyopia treatment received between children referred from the control versus the intervention group.

The positive predictive value (PPV) was low for all screening moments. In the Netherlands, the general health screening is performed by youth healthcare physicians and nurses, which makes screening much cheaper than screening performed by orthoptists, but might lead to a lower PPV. Another factor that influences the PPV is the low prevalence of amblyopia. For the VA measurements at 45 months, the low PPV might be an underestimation because children were already under orthoptic control due to the VA measurements at 36 months. Due to the higher age, CHC personnel might have referred children quicker because of fear of missing amblyopia at this age and because they depend more on the VA measurements at 45 months. The high specificity and high negative predictive value can be explained by the large sample size and the low incidence rate of amblyopia.

There was a high response rate from the treating orthoptists (532 out of 771 referrals in the control group and 464 out of 755 referrals in the intervention group) which minimized the lost to follow-up. Some information could not be retrieved because: (i) some children were first referred to their general practitioners and they might not have referred the child further to an orthoptist; (ii) parents were unaware of the referral; (iii) parents did not comply with the referral; and (iv) some orthoptic clinics changed during the long follow-up. (Tjiam et al. 2011; Telleman et al. 2019). With no received orthoptic information, we might have missed some amblyopic children. Children, who could not be classified as amblyopic due to two or more failed or insufficient VA measurements at the CHC centre without orthoptic information, hold the highest potential risk to be amblyopic. As this group was similar between groups 234 (4.2%)

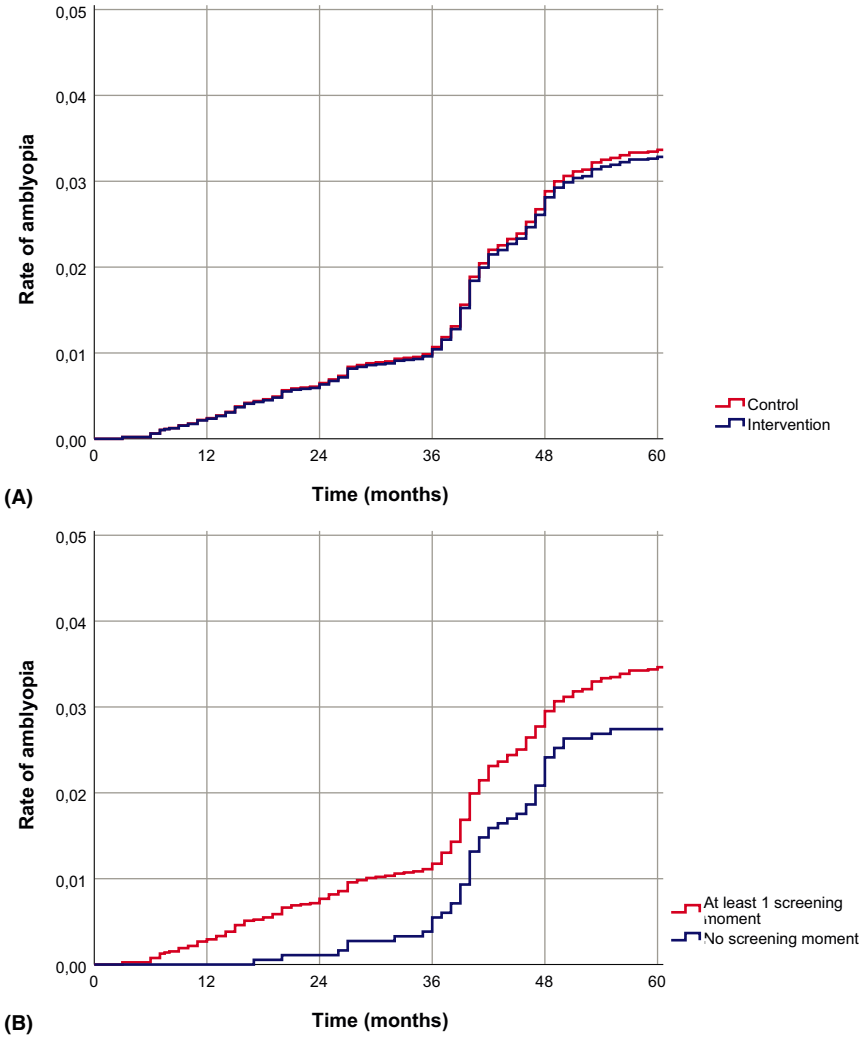

Fig. 5. (A) Time to amblyopia diagnosis intention to treat analysis. (B) Time to amblyopia diagnosis per protocol analysis.

versus 208 (4.1%), we expect the amount to be the same in both groups. Because only the orthoptic information from the first measurement was analysed, the orthoptic assessment at a young age (i.e. before VA could be measured) might have missed some children with micro strabismus. Moreover, children with high anisometropic amblyopia might have had a micro strabismus which was not recognized at the first orthoptic visit. The high amount of children with bilateral amblyopia could be explained as only the orthoptic information of the first VA measurement was recorded. Therefore, the amblyopia diagnosis was based on the VA before glasses adaptation.

The small difference in type of amblyopia between the groups, slightly more strabismus amblyopia and slightly less refractive amblyopia in the control group, could be explained by the age of diagnosis. Children in the control group were diagnosed a bit earlier and because anisometropia tends to increase with age. Children in the control group were more likely to be classified as amblyopic due to strabismus than amblyopia due to refractive error. Also, the same criteria for refractive amblyopia were used for all ages.

The strength of this study is the large sample size, (8% of the Dutch birth rate was included) with a long follow-up (37722 patient-years exposure time) and high attendance rate. The incidence of amblyopia (3.3% versus 3.1%) is comparable to literature (Friedman et al. 2009).

A limitation of the study is that only the referred children had an orthoptic eye examination. Due to the large sample size, it was not possible to provide all children with an orthoptic examination. Most children had two VA measurement (36 and 45 months) at the CHC centres. The observational study by Sloot et al. (2017) showed a good performance of the VA measurements at the CHC centres. Therefore, children with a sufficient VA measurement at the CHC centre were classified as not amblyopic. As a consequence, very mild amblyopia could have been missed. Mild amblyopia, however, would have a much lower impact than moderate to severe amblyopia.

Another limitation of the comparison was that all children did attend their regular screening visits at the CHC centres and that physicians may have detected more cases than physicians who were not trained to perform eye examinations: (i) the physicians were used to specific eye screening within the general health screening examination; (ii) they actively had to

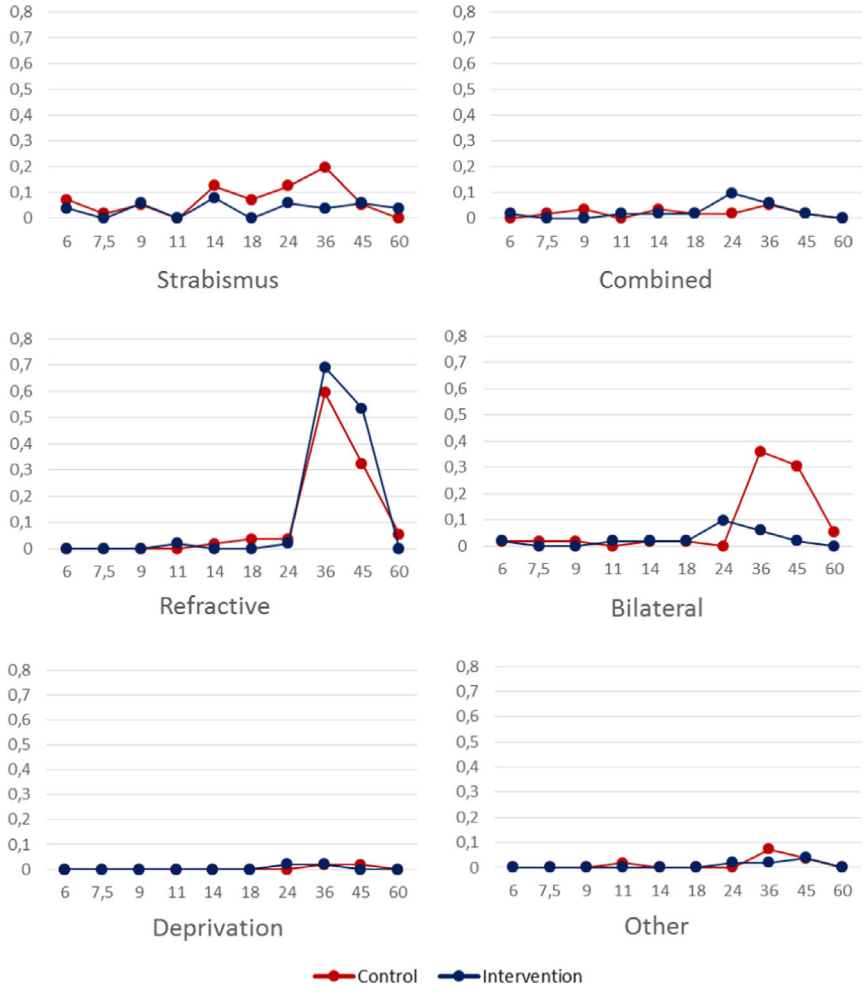

Fig. 6. Type of amblyopia detected (*y*-axis, %) for each age of screening (*x*-axis, months) for the control and intervention group.

omit eye screening in the intervention group; and (iii) they had to exclude conspicuous eye disorders and a positive family history in the intervention group, all raising their level of attention for eye disorders.

Photoscreening is not part of the vision screening programme in the Netherlands. Photoscreening is used to detect risk factors for amblyopia and is in some countries suggested as a replacement for preverbal vision screening or even VA measurements. However, it is still unclear how much amblyopia will be prevented if glasses are prescribed early. The Pediatric Eye Disease Investigator Group et al. (2019) did not find a significant reduction in the development of strabismus, nor better stereo acuity, nor better VA when prescribing glasses at age 1–2 years to moderate hypermetropic children (+3 up to +6) compared to no prescription of glasses. In Flanders, Belgium, photoscreening has been introduced recently as a temporary add-on screening to VA measurements at one and two-and-a-half years of age. Implementation of photoscreening resulted in increase of prescriptions of glasses from 4.7% to 6.4% (Bostamzad et al. 2020).

The rate of failed VA measurements with the Landolt C at 45 months is currently assessed, as the VA measurements at 36 months already proved to be insufficient in 32.1% at 36 months with the APK (Telleman et al. 2019). Similar rates have previously been reported for Lea Symbols and HOTV (Kvarnström & Jakobsson 2005). Difference between VA measurement at 36 and 45 months will be further investigated as to compare the use of different VA charts, testability at different ages and diagnosis and treatment after referral. Preverbal vision screening is not only performed in the Netherlands but also in the majority of countries throughout Europe. Large differences, however, exist in type and amount of screening tests and screening personnel (Sloot et al. 2015a, b). Our results could, therefore, be informative for other countries that want to evaluate, extent, implement or disinvest their own preverbal vision screening.

In conclusion, routine eye screening tests between the age of 6–24 months can be omitted without any negative impact on amblyopia detection or its severity. Strabismus or visually apparent disorders was diagnosed regardless of formal preverbal vision screening. Refractive amblyopia is not discovered with preverbal eye screenings before the age VA can be measured.

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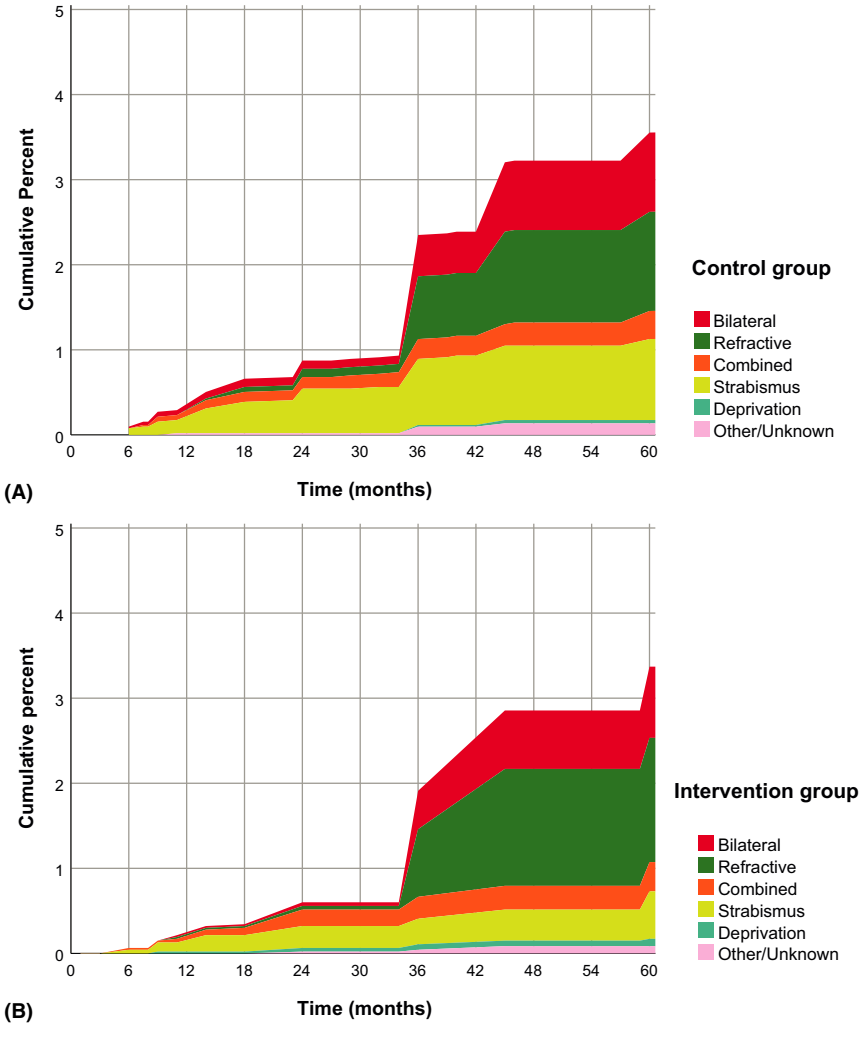

Fig. 7. Cumulative percent of amblyopia detected separated for each type of amblyopia for each screening moment for the control group (A) and intervention group (B).

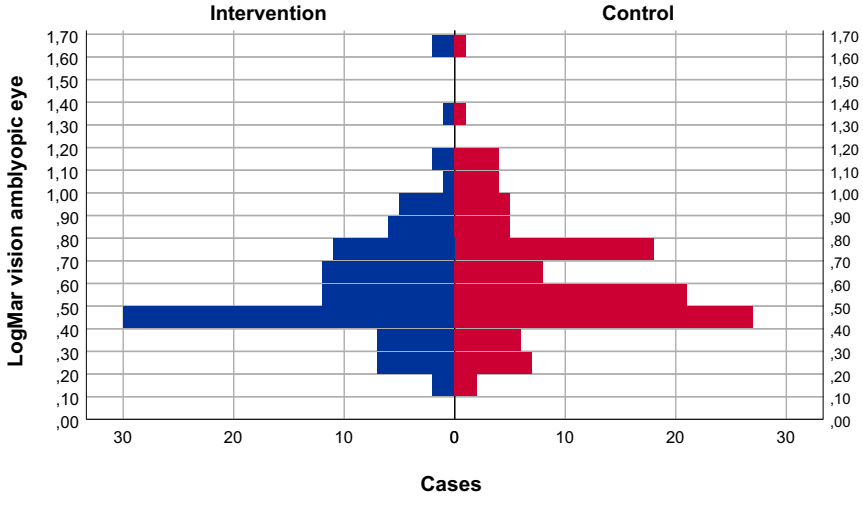

Fig. 8. Frequencies of the visual acuity (logMAR) of the amblyopic eye for the intervention and control group.

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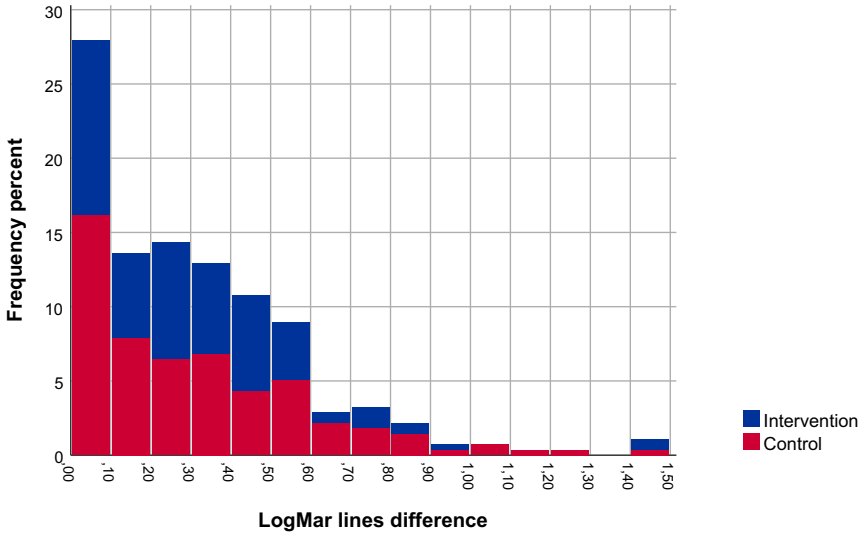

Fig. 9. Stacked histogram of the logMAR difference between eyes in children diagnosed with amblyopia.

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http://clinicaltrials.gov: NCT01675193

Appendix 1

Name orthoptist: _____ Hospital: _____

Initials patient: _____ Date of visit: _____

Date of birth: _____ Referral from: _____

Was patient treated elsewhere before?

Yes / No Where: _____ Treatment: _____

Is there a amblyopia present to your opinion?

Definitively Probably Probably not Not

Cause of amblyopia

Strabismus Anisohypermetropia Combined Deprivation

Cause: _____

Strabismus

Infantile esotropia Accommodative esotropia Exotropia Microstrabismus

Other: _____

VA after optimal correction

OD _____ APK Lea Numbers/letters Tumbling E Landolt-C

OS _____ APK Lea Numbers/letters Tumbling E Landolt-C

Fixation free alternating Fixation short No fixation Fixation excentrisch

Refraction after cycloplegia: Autorefraction / Skia

OD S _____ C _____ x _____

OS S _____ C _____ x _____

Notes:

_____

Glasses

Yes / No _____ D undercorrection

Occlusion

Yes _____ hours per day _____ days per week No

Strabismus surgery

Planned / Performed Date: _____ Operation: _____

Follow-up

Non / Control _____ months at: orthoptist / ophthalmologist

Remarks

_____

_____

_____

		Control group		Intervention group	
		Referral by CHC center	Referral by other	Referral by CHC center	Referral by other
Refractive error without amblyopia	Myopia	15	1	10	5
	Hypermetropia	5	2	1	
	Astigmatism	3		1	
Strabismus without amblyopia	Esotropia	3	3	3	2
	Exotropia	9	2	3	1
	Decompensating phoria	5	2	2	
	Unspecified strabismus				1
Motility disorders	Duane syndrome	3		1	
	Brown syndrome	2		1	
	n. VI				1
	n. IV	1			
	Marcus gun jaw winking				1
Nystagmus			1		1
Oculo motor apraxia				1	
Eyelid disorders	Ptosis	4	1	4	
	Cyste			1	3
	Hordoleum	1			
	Strand between the eyelids	1			
	Entropion				1
	Haemangioma		1		1
Dacryostenosis		5	3	8	6
Anisocoria				1	2
Retina disorders	Albinism				1
	Leber		1		
	Cone dystrophy	1			1
	Unspecified				1
	Papil disorder			1	
Other eye or adnexen disorders	Sturge weber		1		
	Splinter removal		1		
	Goldenharr				1
	Suspected CVI			1	
	Choroidale naevus	1			
	Conjunctivitis		2		
	Adenovirus			1	
	Iris scratch				1
	Coloboma			1	2
	Gray spot sclera			1	
Total other eye disorders without amblyopia		**59**	**21**	**42**	**32**

		Control group		Intervention group	
		Referral by CHC centre	Referral by other	Referral by CHC centre	Referral by other
Refractive error without amblyopia	Myopia	15	1	10	5
	Hypermetropia	5	2	1	
	Astigmatism	3		1	
Strabismus without amblyopia	Esotropia	3	3	3	2
	Exotropia	9	2	3	1
	Decompensating phoria	5	2	2	
	Unspecified strabismus				1
Motility disorders	Duane syndrome	3		1	
	Brown syndrome	2		1	
	n. VI				1
	n. IV	1			
	Marcus gun jaw winking				1
Nystagmus			1		1
Oculo motor apraxia				1	
Eyelid disorders	Ptosis	4	1	4	
	Cyste			1	3
	Hordoleum	1			
	Strand between the eyelids	1			
	Entropion				1
	Haemangioma		1		1
Dacryostenosis		5	3	8	6
Anisocoria				1	2
Retina disorders	Albinism				1
	Leber		1		
	Cone dystrophy	1			1
	Unspecified				1
	Papil disorder			1	
Other eye or adnexen disorders	Sturge weber		1		
	Splinter removal		1		
	Goldenharr				1
	Suspected CVI			1	
	Choroidale naevus	1			
	Conjunctivitis		2		
	Adenovirus			1	
	Iris scratch				1
	Coloboma			1	2
	Grey spot sclera			1	
Total other eye disorders without amblyopia		59	21	42	32