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The Third Monitoring Report of the Early vs. Late Infantile Strabismus Surgery Study

The Early vs. Late Infantile Strabismus Surgery Study Group

Abstract The Early vs. Late Infantile Strabismus Surgery Study Group is a group of strabismologists and orthoptists from 58 clinics in 11 European countries. They investigate whether early or late surgery is preferable in infantile strabismus, in a non-randomised, prospective, multi-centre trial. Infants between 6 and 18 months of age receive a standardised entry examination and are then operated either before their second anniversary in clinics A, or between their 32nd and 60th month of age in clinics B. The children are evaluated at age six. After completion of the study, the two groups can then be compared regarding degree of binocular vision, angle of strabismus and visual acuity of the worse eye relative to the better. The current state of the study is reported here. Fifty-eight clinics have entered a total of 463 patients up to March 1996. Patient recruitment rates have been less than expected during the last months. Currently, 186 children have been entered in the early surgery group and 277 in the late surgery group Completeness of data and forms are excellent. Only 25 patients have definitively dropped out. There is no evidence for inhomogeneities between the two therapy groups concerning the distribution of the four most important prognostic factors: spherical equivalents, horizontal angle of squint, degree of amblyopia and limitation of abduction.

Key words Strabismus; surgery

Preliminary remark The analysis for this monitoring report was performed in March 1996. All Registration and other forms that reached the study centre before March 1st were included in the analysis. Please note: Throughout the report we use the designation 'entered' to characterise patients who are included into the study, monitored and evaluated at age 6. For all children with infantile, convergent strabismus age 6 to 18 months referred to a participating clinic for the first time, an Entry Examination form and an Examination form are filled out, even if any of these children is further excluded from the study for any reason. Data on children who might have taken part but did not do so for any reason, is obtained to get an impression of what is ex- and what is included in each participating clinic. Ac cordingly, the designation 'excluded' is used throughout this report to indicate all patients who were excluded and not entered into the study thereafter. All entered and excluded children are 'registered'.

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1 Participants Originally, 84 clinics from 14 countries did send a letter of intent to participate in the study. Forty-one of these elected to take part in the early surgery group and 43 in the late surgery group. They have been listed in the 1994 monitoring report (The Early vs. Late Infantile Strabismus Surgery Study Group, 1994). Fifty-eight of these (33 in the late and 25 in the early surgery group) have become active, i.e. did register children at the study centre.
The active participants are listed in Table 1.

TABLE 1. Listing of active participants per country. For each country, the country coordinating clinic with country coordinator is listed first (marked with 'CC'), followed by the other clinics in alphabetical order. Each entry consists of the clinic's name, the name of the clinic coordinator, and the assigned therapy group.

AU – Austria		
St. Pölten	Dr. Hildegard Luka (CC)	late
Graz	Dr. Andrea Langmann	late
Linz	Ass. Dr. Andreas Hajek	late
Salzburg	OAe Dr. Helga Thaller-Antlanger	late
Wien Hanusch-Krh.	Univ. Doz. Dr. S. Harrer	late
Wien II. Uni-Augenklinik	Prof. Dr. Arnulf Thaler	early
Wien Wilhelminenspital	Prof. Dr. Arnulf Thaler	early
Wiener Neustadt	Dr. Rudolf Pelz	late
B – Belgium		
Bruxelles	Prof. M. Spiritus (CC)	early
Edegem	Dr. Evens	early
CH – Switzerland		
Lausanne	Dr. Giorgio Klainguti (CC)	early
Zürich	Dr. Klara Landau	early
D – Germany		
Halle	Dr. R. Weidlich (CC)	late
Heidelberg	Prof. Dr. Gerald Kolling (CC)	late
Berlin Charité	Dr. Ebba-Ch. Schwarz	early
Berlin Steglitz	Dr. Jandeck	late
Dresden	PD Dr. Erika Sommer	late
Erlangen	Dr. G. Gusek	late
Frankfurt/M. Uni	Dr. A. Zubcov	early
Freiburg Uni	Prof. Dr. Kommerell	late
Hamburg Uni	Prof. Dr. Elisabeth Schulz	late
Homburg/Saar	Dr. B. Kaesmann	late
Köln Uni	Dr. F. Kaszli	late
München TU	PD Dr. T. Schmidt	late
München Uni	Prof. Dr. Boergen	late
Regensburg Uni	Prof. Dr. Lorenz	late
F – France		
Lyon	Dr. Bourron-Madignier (CC)	early
GB – Great Britain		
Dundee	Dr. C.J. McEwen	early
Liverpool	Dr Ian Marsh	early
London H. F. Sick Children	Dr. Chris Timms	early
I – Italy		
Firenze	Prof. Dr. Riccardo Frosini (CC)	late
Sassari	Prof. Dr. Francesco Carta	late

TABLE 1, *continued*

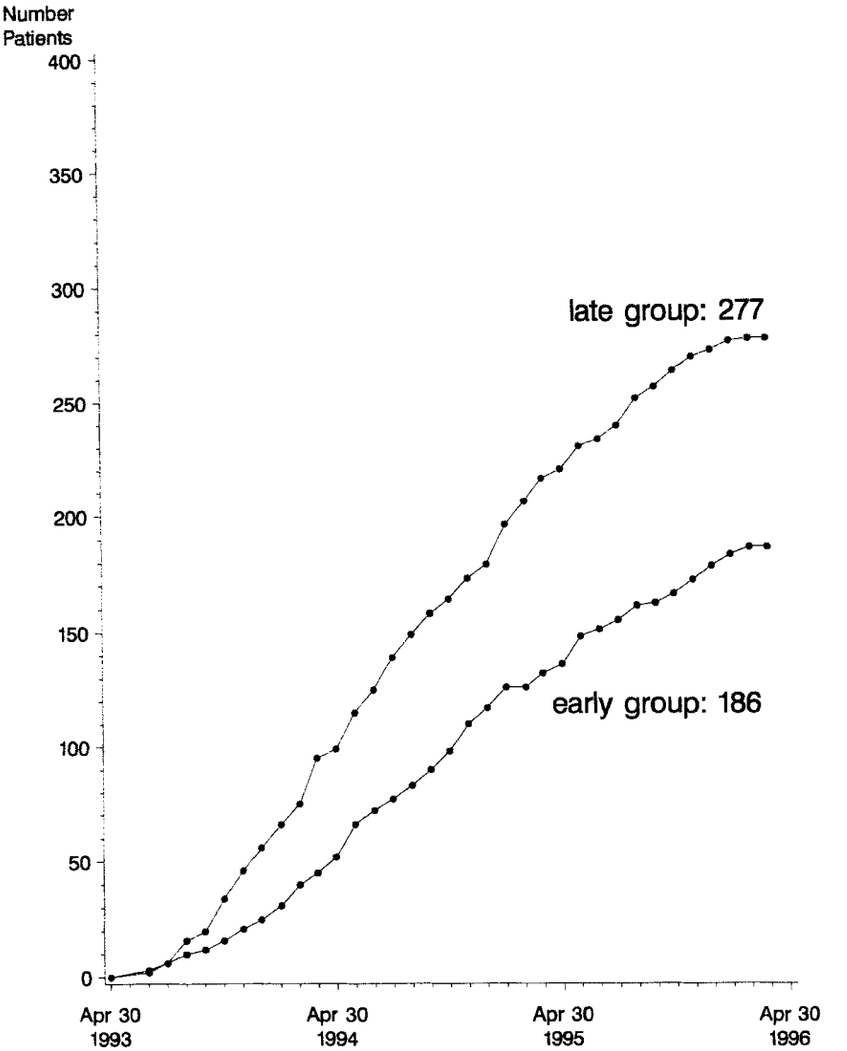
N–Norway		
Bergen	Dr. Olav H. Haugen (CC)	early
Aalesund	Dr. Geir Hanken	late
Forde Sentralsjukehuset	Dr. Leif Steene Eriksen	late
Haugesund	Dr. John Bore	early
Lillehammer	Dr. Tore Bulie	late
Tonsberg	Dr. Hans Petter Brinck	late
NL–Netherlands		
Amsterdam	Dr. L. Wenniger-Prick (CC)	early
Goes	Dr. A.G. Tjiam	early
Rotterdam Akademisch Z.	PD Dr. H.J. Simonsz	late
Rotterdam Oogziekenhuis	Dr. Jan–Tjeerd de Faber	early
S–Sweden		
Huddinge	Drs. Holmstroem / Lennerstrand (CC)	late
Boras	Dr. Gunnar Ladenvall	late
Danderyd	Dr. Agneta Wallin	late
Eskilstuna	Dr. Peter Furuskog	early
Jönköping	Dr. Birgitta Sunnqvist	early
Linköping	Dr. Peter Jakobsson	early
Sundsvall	Dr. Marlene Lindberg	late
Umeå	Dr. Kent Johansson	early
Vaexjö	Dr. Ingvar Axelsson	late
T–Turkey		
Istanbul Beyoglu	Dr. Birsen Acar (CC)	late
Adana	Dr. Guelhanim Haciyakupoglu	late
Ankara Hacettepe Univ.	Prof. Dr. Ali Sefik Sanac	early
Ankara Saglik Bakanligi	Dr. Saniye Demirci	early
Ankara Univ. Tup Fakultesi	Dr. Necile Erkam	early
Edirne Trakya Univ.	Prof. Dr. Nazan Erda	late
Izmir 9 Eyuel Univ.	Dr. Ayse Tulin Berk	early

2 Patient enrolment

2.1 PLANNED AND ACTUAL PATIENT RECRUITMENT Patient recruitment rates have been less than expected during the last months. Currently, 186 children have been entered in the early surgery group and 277 in the late surgery group (Figure 1). This is an average recruitment of 5 children per month in both groups. If this tendency would remain constant until the end of the recruitment period on October 31st, 1996, we would reach a total of approximately 230 early operated and 320 late operated children only, as compared to expectations of 280 and 380 patients based on the data from last year's monitoring report (The Early vs. Late Infantile Strabismus Surgery Study Group, 1995).

2.2 PATIENTS ENTERED AND PATIENTS EXCLUDED PER CLINIC Table 2 gives an overview of patients entered and excluded per clinic. The columns contain the number of patients entered into the study and the number of patients excluded, for early and late surgery, respectively. The ratio of entered to excluded children varies considerably per clinic. For all clinics, however, the ratio is very similar with 186:160 for the early and 277:243 for

Fig. 1. Patient recruitment.



the late surgery group. When comparing Table 2 with the results from last year's report, the ratio of entered to excluded children is similar. Most clinics contributed patients with entry rates similar to the past. The reason for the reduced entry rates is that some clinics are dramatically less active than before.

2.3 LISTING OF EXCLUSION CRITERIA EMPLOYED The reasons why excluded patients did not enter the study are listed in Table 3 (multiple reasons possible).

2.4 DELAY BETWEEN ENTRY EXAMINATION AND PATIENT REGISTRATION The median delay between the Entry Examination and receipt of the Patient Registration form at the study centre was 11 days. 73% of all forms were received within 4 weeks as compared to 77% in the last report.

TABLE 2. Entered and excluded children per clinic.

Clinic	*Entered early surgery*	*Entered late surgery*	*Excluded early surgery*	*Excluded late surgery*
AU – Austria				
Graz	0	8	0	1
Linz	0	2	0	8
Salzburg	0	3	0	2
St. Pölten	0	17	0	16
Wien Hanusch-Krh.	0	16	0	21
Wien II. Uni-Augenklinik	12	0	19	0
Wien Wilhelminenspital	11	0	17	0
Wiener Neustadt	0	21	0	11
	23	**67**	**36**	**59**
B – Belgium				
Bruxelles	28	0	14	0
Edegem	3	0	2	0
	31	**0**	**16**	**0**
CH - Switzerland				
Lausanne	18	0	13	0
Zuerich	2	0	5	0
	20	**0**	**18**	**0**
D – Germany				
Berlin Charité	13	0	14	0
Berlin Steglitz	0	2	0	3
Dresden	0	10	0	21
Erlangen	0	24	0	18
Frankfurt/M. Uni	15	0	15	0
Freiburg Uni	0	35	0	19
Halle	0	1	0	0
Hamburg	0	22	0	5
Heidelberg	0	25	0	14
Homburg/Saar	0	3	0	38
Köln	0	6	0	3
München TU	0	5	0	0
München Uni	0	17	0	3
Regensburg Uni	0	14	0	2
	28	**164**	**29**	**126**
F – France				
Lyon	20	0	10	0
GB – Great Britain				
Dundee	1	0	0	0
Liverpool	1	0	1	0
London H. F. Sick Children	1	0	0	0
	3	**0**	**1**	**0**
I – Italy				
Firenze	0	3	0	9
Sassari	0	2	0	0
	0	**5**	**0**	**9**
N – Norway				
Aalesund	0	0	0	1
Bergen	13	0	1	0
Forde Sentralsjukehuset	0	3	0	1

Table 2 continued p. 104.

TABLE 2, *continued*

Clinic	*Entered early surgery*	*Entered late surgery*	*Excluded early surgery*	*Excluded late surgery*
Haugesund	5	0	2	0
Lillehammer	0	2	0	0
Tonsberg	0	5	0	10
	18	**10**	**3**	**12**
NL–Netherlands				
Amsterdam	3	0	1	0
Goes	2	0	1	0
Rotterdam Akademisch Z.	0	4	0	10
Rotterdam Oogziekenhuis	0	0	22	0
	5	**4**	**24**	**10**
S–Sweden				
Boras	0	0	0	4
Danderyd	0	8	0	0
Eskilstuna	2	0	1	0
Huddinge	0	1	0	0
Jönköping	11	0	5	0
Linköping	7	0	3	0
Sundsvall	0	5	0	1
Umeå	5	0	0	0
Vaexjö	0	4	0	0
	25	**18**	**9**	**5**
T–Turkey				
Adana	0	1	0	1
Ankara Hacettepe Univ.	1	0	5	0
Ankara Saglik Bakanligi	2	0	0	0
Ankara Univ. Tup Fakultesi	6	0	7	0
Edirne Trakya Univ.	0	8	0	19
Istanbul Beyoglu	0	0	0	2
Izmir 9 Eyuel Univ.	4	0	2	0
	13	**9**	**14**	**22**
All Clinics	**186**	**277**	**160**	**243**

TABLE 3. Listing of exclusion criteria employed.

Reason	*Frequency*
Age limit	21
Onset of strabismus after the age of 4 months	111
Prematurity	27
Congenital nystagmus	46
Cerebral palsy or other neurological deficit	86
Angle of strabismus <50	24
Angle of strabismus >300	58
Divergent strabismus	10
No exclusion criteria apply but parents declined to participate	6
Other medical reasons (e.g. tachycardia)	13
Organisational reasons (e.g. language problems)	6
Formal reasons (e.g. application after surgery)	93

3 Quality of the documentation Tables 4 and 5 summarise the completeness of the documentation forms and of the data for all entered patients. The plausibility is permanently monitored by the study centre. Table 4 lists all documentation forms into one of five categories. 'Complete' means that the forms are without error. 'Due' means that the forms should become available to the study centre shortly. There can be various reasons for this to happen, for instance a delay in the examination procedure or an internal organisational problem. 'Returned' means that the forms have been returned for completion or for correction of plausibility errors. The number of forms per clinic in each category is listed in the table.

TABLE 4. State of documentation forms per clinic.

Country and Clinic	*omplete*	*Returned for <= 4 weeks*	*Due for <= 4 weeks*	*Returned for > 4 weeks*	*Due for > 4 weeks*
AU–Austria					
Graz	32		1	3	5
Linz	10				1
Salzburg	11	1		1	1
St. Pölten	85	2	2		1
Wien Hanusch-Krh.	55		5	1	7
Wien II. Uni-Augenklinik	61	3	2	1	3
Wien Wilhelminenspital	72		3	2	7
Wiener Neustadt	83	2	4		
	409	8	17	8	25
B–Belgium					
Bruxelles	144				9
Edegem	6	1		2	1
	150	1	0	2	10
CH–Switzerland					
Lausanne	82		3	1	3
Zürich	11				1
	93	0	3	1	4
D–Germany					
Berlin Charité	58		1		7
Berlin Steglitz	6				2
Dresden	44				2
Erlangen	86		3		37
Frankfurt/M. Uni	81		1	2	3
Freiburg Uni	151		1		3
Halle	3				
Hamburg	71	3	1	3	
Heidelberg	102		3	2	17
Homburg/Saar	12				
Köln	13		3	1	6
München Tu	19				1
München Uni	78			1	7
Regensburg Uni	61		1		11
	785	3	14	9	96

Table 4 continued p. 106.

TABLE 4, *continued*

Country and Clinic	*Complete*	*Returned for <= 4 weeks*	*Due for <= 4 weeks*	*Returned for > 4 weeks*	*Due for > 4 weeks*
F – France					
Lyon	100				6
GB – Great Britain					
Dundee	3				1
Liverpool		2			1
London H. F. Sick Children			1		5
	3	2	1	0	7
I – Italy					
Firenze	2			4	12
Sassari	5			1	
	7	0	0	5	12
N – Norway					
Bergen	56	2	1	2	24
Forde Sentralsjukehuset	11			1	4
Haugesund	31			3	2
Lillehammer	3			1	5
Tonsberg	23	3	1	1	2
	124	5	2	8	37
NL – Netherlands					
Amsterdam	6			1	5
Goes	14	1	1		1
Rotterdam Akademisch Z.	22		1		
	42	1	2	1	6
S – Sweden					
Danderyd	30	1		2	5
Eskilstuna	10				2
Huddinge	5		1		
Jönköping	57				1
Linköping	45	1	1	1	2
Sundsvall	23			1	3
Umeå	29				
Vaexjö	18		3	2	3
	217	2	5	6	16
T – Turkey					
Adana				2	3
Ankara Hacettepe Univ.	1			1	
Ankara Saglik Bakanligi	7				1
Ankara Univ.	13				1
Edirne	24	1	2		6
Izmir 9 Eyuel Univ.	6			3	11
	51	1	2	6	22
All Clinics	**1981**	**23**	**46**	**46**	**241**

TABLE 5. Percentage of completeness of required data per clinic.

Country and Clinic	*Entry Examination Form*	*Examination Form*	*Surgery Form*
AU–Austria			
Graz	100	100	100
Linz	100	100	
Salzburg	100	98	
St. Pölten	100	100	94
Wien Hanusch-Krh.	100	98	
Wien II. Uni-Augenklinik	100	97	100
Wien Wilhelminenspital	100	96	100
Wiener Neustadt	100	100	88
B–Belgium			
Bruxelles	100	99	97
Edegem	100	96	91
CH–Switzerland			
Lausanne	99	95	100
Zürich	100	100	100
D–Germany			
Berlin Charité	99	98	100
Berlin Steglitz	100	100	
Dresden	100	100	100
Erlangen	100	100	
Frankfurt/M. Uni	100	98	95
Freiburg Uni	99	99	100
Halle	100	100	
Hamburg	99	99	
Heidelberg	100	100	
Homburg/Saar	100	99	
Köln	98	99	
München Tu	100	98	100
München Uni	100	100	100
Regensburg Uni	99	100	
F–France			
Lyon	100	98	98
GB–England			
Dundee	100	93	86
Liverpool	78	93	
I–Italy			
Firenze	92	89	
Sassari	100	100	
N–Norway			
Bergen	100	96	100
Forde Sentralsjukehuset	100	99	
Haugesund	100	98	100
Lillehammer	100	98	
Tonsberg	97	96	

TABLE 5 *continued p. 108.*

TABLE 5. *continued*

Country and Clinic	*Entry Examination Form*	*Examination Form*	*Surgery Form*
NL–Netherlands			
Amsterdam	100	90	
Goes	95	92	100
Rotterdam Akademisch Z.	100	96	96
S–Sweden			
Danderyd	99	99	
Eskilstuna	100	98	100
Huddinge	100	96	
Jönköping	99	99	98
Linköping	94	93	96
Sundsvall	100	94	
Umeå	100	98	100
Vaexjö	97	89	
T–Turkey			
Adana	91	64	
Ankara Hacettepe Univ.	88	100	
Ankara Saglik Bakanligi	100	97	92
Ankara Univ.	100	99	
Edirne	100	97	
Izmir 9 Eyuel Univ.	97	100	100
All Clinics	**99**	**98**	**98**

The completeness rates of the forms are still good. The proportion of forms due for more than 4 weeks has increased from 10%, last year, to 12% however.

Table 5 shows the percentage of completeness of the required data among all documentation forms of entered patients. All forms that are available to the study centre were included in this part of the analysis, regardless of whether they were 'complete' or 'returned'. Interdependencies in the data are taken into account. For instance, patterns of previous occlusion therapy can only be mentioned when the question 'previous occlusion therapy?' has been answered affirmatively.

4 Dropouts and deviations of therapy

4.1 DROPOUTS In total, 25 children have been lost to follow-up, 13 in the early and 12 in the late operating group. In 6 cases the child and parents had moved, in 10 cases the parents were no longer compliant, in one case the treatment had to be continued in another clinic because of a health insurance problem. In 8 cases the parents were not contacted and the reason for the dropout remains unknown.

4.2 SURGERY SCHEDULE Surgery should be performed before the child's second birthday in the early operating group, and after its 32nd month in the late group.

In the early group, 106 children have been operated in accordance with the study protocol (The Early vs. Late Infantile Strabismus Surgery Study Group, 1993). For 26 children, no surgery has been documented although they are already two years old. Seven children have definitively been operated too late. Among these, in total, 33 children, 3 cases could not be operated as scheduled because the child was ill, in 4 other cases the childrens' parents opted for late surgery. For 3 patients surgery was canceled because of a small angle of strabismus, and 9 children were dropouts. In 14 cases the reason is not known to the study centre.
In the late group, 12 children have been operated up to now. Three of them had not completed their 32nd month of life at the time of surgery. In one case the reason is known to the study centre: the patient suffered from pronounced torticollis and A-pattern and only in 30 degrees downgaze, binocular vision was present.

4.3 EXAMINATION INTERVALS Intermediate examinations should be performed every 6 months with a maximum delay of 4 weeks. 786 out of 866 documented examinations have been performed accordingly. The two longest examination intervals were 15 and 17 months. Intermediate examinations should also be performed within 2 weeks after surgery, with a tolerance of two weeks. This has been achieved in 107 of 137 cases of surgery (including 12 cases of re-operation). Furthermore, 12 examinations were done within the 2nd month after surgery. Eight cases with a delay of 3 to 9 months after surgery are considered as regular intermediate examinations instead of postoperative examinations. In 10 cases, no examination is documented at the study centre since surgery.

5 Prognostic factors To ensure the internal validity of the study's results, prognostic factors should be distributed homogeneously in the early and late surgery groups. With respect to external validity, it is also desirable that the distribution of the samples (entered children) is the same as in the population. Therefore, excluded children are also documented. Details about important prognostic factors are reported below.

5.1 RETINOSCOPY VALUES The spherical equivalents of the worse eye in the early and the late group followed a unimodal distribution, both with a median of Sph. +2. Values ranged from −1.5 to +10 in the early group and from −1.5 to +7.5 in the late group. Excluded children also have a unimodal distribution with the same median of Sph. +2, but with values ranging from −11 to +30.

5.2 HORIZONTAL ANGLE OF SQUINT The range is limited by the exclusion criteria from 5 to 30 degrees. The median values were 22 degrees in the early and 20 degrees in the late surgery group. Excluded children had a median of 17 degrees with extreme values of −25 and +50 degrees.

5.3 DEGREE OF AMBLYOPIA OF THE WORSE EYE The distributions were similar for all groups. The most frequent category was 2 (alternating but preference of fixation). Forty percent of the early surgery and 48% of late surgery children, as well as 37% of excluded children fell into this category. The proportion of children within categories 1 to 3 was 94% in the early and

TABLE 6. Summary of variables.

Variable	*Early surgery*	*Late surgery*
Mean of occlusion pretreatment in months	1.5	1.4
Median of occlusion pretreatment in months	1	1
Third quartile of occlusion pretreatment	2	2
Mean age in days at the entry examination	343	330
Rate of previously prescribed glasses	20%	25%
Rate of previously prescribed atropine	3%	2%
Rate of permanent occlusion tolerance	81%	80%
Rate of vertical deviation in primary position	6%	14%
Rate of vertical deviation in left or right gaze	20%	33%
Rate of V-pattern >5 degrees	3%	9%
Rate of A-pattern	1%	2%
Rate of latent nystagmus	16%	33%
Rate of torticollis	10%	20%
Rate of DVD	6%	15%

96% in the late group as compared to 84% in the excluded group (categories 1 to 3 are prognostically better than 4 and 5).

5.4 RESTRICTION OF ABDUCTION OF THE WORSE EYE Distributions were similar. The most frequent category was 1 (free, using pursuit movements), the second was 3 (passing midline but not free, using any method). Categories 1 and 2 applied to 63%, 58% and 61% for early, late and excluded children, respectively.

A summary of the distribution of other variables is presented in Table 6.

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