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ORIGINAL RESEARCH ARTICLE

Macular function measured by binocular mfERG and compared with macular structure in healthy children

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Abstract
Purpose To create normative data in children from binocular multifocal ERG (mfERG) recordings and compare results with the macular thickness.
Methods Forty-nine 5- to 15-year-old healthy, full-term children were examined with Espion Multifocal System, using DTL electrodes. The stimulus matrix consisted of 37 hexagonal elements. Amplitudes, implicit times and response densities (presented in three rings) of the first-order component P1 were analyzed. Measurements of macular thickness were performed with spectral-domain Cirrus OCT.
Results There were no significant differences between right and left eyes regarding mfERG recordings. Median P1 implicit times of Rings 1–3 of the 46 right eyes were 30.0, 30.0 and 30.8 ms and response densities 20.5, 10.9 and 7.6 nV/deg^2, respectively. Implicit time was longer in boys than in girls ($p = 0.009$, 0.039, 0.005 in Rings 1–3) and was correlated with age ($r_s = 0.417$, 0.316, 0.274 in Rings 1–3). Implicit time in Ring 1 correlated significantly with the inner circle of the OCT measurements ($p = 0.014$).
Conclusion Binocular mfERG with DTL electrodes is a reliable test of the central macular function in children and correlates with macular structure. As previously not shown, there was a significant difference in implicit time between boys and girls.

Keywords Binocular · Multifocal electroretinogram · DTL electrodes · Healthy children · Optic coherence tomography

Introduction

Early and proper diagnosis is essential in children with visual impairment, which emphasizes the importance of evaluation of the prognosis, the habilitation, and current and subsequent treatment. Electrophysiological examinations have been shown to be of great significance in the investigation of reduced visual acuity of unknown origin [1]. Since introduction of the multifocal retinogram (mfERG) in 1992 by Sutter and Tran [2], it has been possible to objectively evaluate the function of the macular area, i.e., photoreceptors, predominantly the cones, and bipolar cell function [3, 4]. The mfERG has been shown to be a valuable tool in the diagnosis of macular disease at an early stage, in particular when appearance of the fundus is normal or pathological findings are subtle [5].

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The full-field electroretinogram (ffERG), which reflects the total retinal function, can be normal, whereas the mfERG may detect reduced local cone function in the macular region in patients with Stargardt disease, even in the absence of major fundus abnormalities [5, 6]. Further, because the mfERG mainly reflects macular cone function, it could enhance our possibilities to differentiate between optic nerve disorder and retinal disorder in patients with visual loss of unknown origin [7]. Finally, examination with mfERG makes it possible to monitor the course of a macular/retinal disease [8], and it can be useful when evaluating macular function after possible gene therapy in the future.

Examination in children requires methods that are painless, fast, and at the same time accurate, in providing necessary diagnostic information. We have recently reported normative data regarding optical coherence tomography (OCT) in children [9]. The primary aim of the present study was to create normative data from binocular mfERG recordings in children with the help of a clinically applicable protocol. A second aim was to relate the findings to age and gender. A third aim was to correlate the mfERG recordings with macular morphology measured with OCT.

Materials and methods

A number of 200 study participants aged 5–15 years were randomly chosen from the birth register of the Swedish National Board of Health and Welfare, living in Uppsala County. A letter for recruitment to the study was sent out to their parents. A written consent was obtained from the parents of the participating children and oral consent from children. Ethical approval for the study was obtained from the Ethics Committee of Uppsala University. Altogether, forty-nine children accepted both examinations with mfERG and OCT and were examined from December 2012 until September 2014. Inclusion criteria were having been born at term ($\geq$37 weeks of gestation), normal birth weight ($\geq$2500 g), normal health, no eye disease, manifest strabismus, refraction with a spherical equivalent between +3 and −3 and cylinder strength >-2 and a visual acuity $\leq$0.1 logMar.

Monocular visual acuity (VA) was obtained with a linear LogMar chart. Pupils were fully dilated with cyclopentolate 0.85 % and phenylephrine 1.5 % eye-drops. Cycloplegic autorefraction and fundus examination were performed.

The mfERG signals were recorded using the Espion Multifocal System (Diagnosys, Lowell, MA, USA version 6.2012.1211.52), and accorded to ISCEV recommendations [10] except for the stimulus matrix, which consisted of 37 hexagonal elements corresponding to 20° from the center of the fovea, Fig 1. This made the examination suitable for children. The stimulus was presented on a liquid crystal display (LCD) screen. The patch sizes of the hexagons were scaled for cone density, with larger hexagons in the periphery. The stimulus had a maximal luminance of 200 cd/m^2, and the stimulation rate of the black and white hexagons was 75 Hz. The signals were recorded under room lighting.

The mfERG was performed binocularly. Retinal activity was measured with DTL electrodes [11] through fully dilated pupils. The eyes were anesthetized with tetracaine 1 % drops before electrode placement over the lower eyelid on the conjunctiva. A ground electrode was placed on the back of one hand, and reference electrodes were placed on the skin over the zygomatic bone. An impedance of the electrodes of less than 10 kΩ was accepted. Before the recordings, it was ensured that the patients were seated in a relaxed position and that their eyes were at the right height in relation to the stimulus target. The fixed viewing distance was 330 mm. The fixation target was

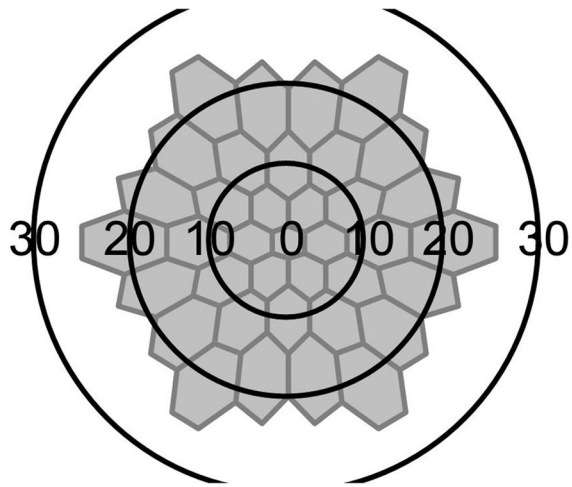

Fig. 1 Illustration of the stimulus matrix with 37 hexagons and the retinal areas (Rings 1–3) measured in degrees from the fovea

a central red cross. During the whole test period, fixation was monitored with the help of a camera. Examination time was 2 min if the test was performed without pauses or blinks. Throughout the test, the examiner encouraged the child to fixate on the target. If blinks occurred during the measurements, the signals were rejected by the artifact rejector and the measurements restarted. The mfERG signals were filtered through a 10- to 100-Hz band-pass filter and amplified with 32-bit amplifiers. Further, as in other published mfERG systems, spatial averaging of 25 % was used.

The electrical potential measurements (nanovolts) were cross-correlated with the pseudorandom binary m-sequence responses producing the focal macular responses [2]. Implicit times and amplitudes of the first-order component P1 (first positive peak) were summarized and analyzed, Fig. 2.

The hexagons were divided into three areas, Rings 1–3 (Fig. 3), of which Rings 1 and 2 measure the macular area. The measurements of the response density were also investigated using the formula nanovolts per square degree (nV/deg^2), i.e., the amplitudes in a ring are divided by the area of the hexagons in the same ring.

The results of the mfERG measurements were presented as a trace array, see Fig. 4. The majority of the examinations were performed by the first author.

Measurements of the macular thickness were obtained with spectral-domain Cirrus, version 6.0.2.81 (Carl Zeiss Meditec, Dublin, CA, USA), using the macular cube protocol 512 × 128. The OCT measurements were performed by an experienced research nurse (E.N). Three examinations of each eye were done, and inclusion criteria were: a signal strength >7, no large movements with the scanning beam, and no blinks over the measured area. The mean values of the three measurements were calculated. The OCT values were presented in nine ETDRS areas

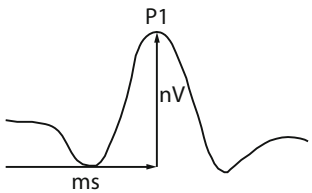

Fig. 2 The waveform of the multifocal electroretinogram (mfERG)

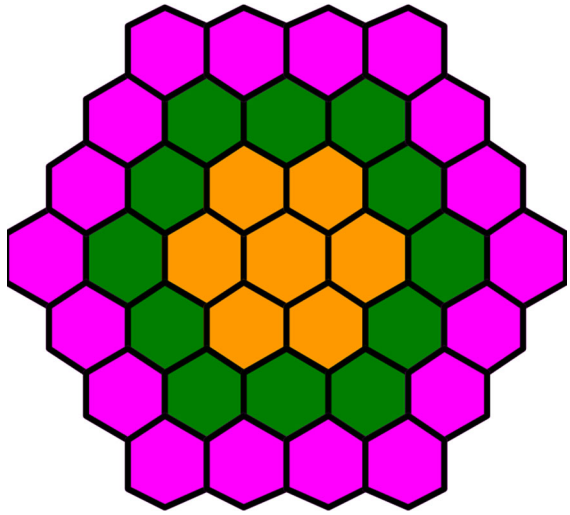

Fig. 3 Schematic illustration of the three mfERG rings (Ring 1: *orange*, Ring 2: *green*, Ring 3: *lilac*). In this figure, there is no scaling for photoreceptor density

established by the Early Treatment Diabetic Retinopathy Study Research Group [12]. The central retinal area (A1) has a diameter of 1 mm, the inner circle (A2–A5) together with A1 has a diameter of 3 mm, and the outer circle (A6–A9) together with A1 and the inner circle has a total diameter of 6 mm [12]. According to Holm and Lövestam Adrian [13], 1 mm of the OCT macular map corresponds to 4° of the mfERG rings. Hence, Ring 1, with a diameter of 20°, was chosen when comparing the mfERG recordings with the OCT values.

Statistical methods

According to recommendations regarding analysis of mfERG [10], nonparametric tests were used throughout the analyses. The Wilcoxon signed rank test was used for comparison of right and left eyes, the Friedman rank sum test for comparison between Rings 1 and 3, Mann–Whitney analysis for comparison of girls and boys, and Spearman's test for correlation (r_s) between mfERG responses and age, as well as between mfERG responses and OCT measurements.

Multivariate analysis of covariance (ANCOVA) was performed in order to explore the effects of age and gender on implicit time. Each analysis was performed in two steps. In the first step, the model included the interaction term of age and gender. In the

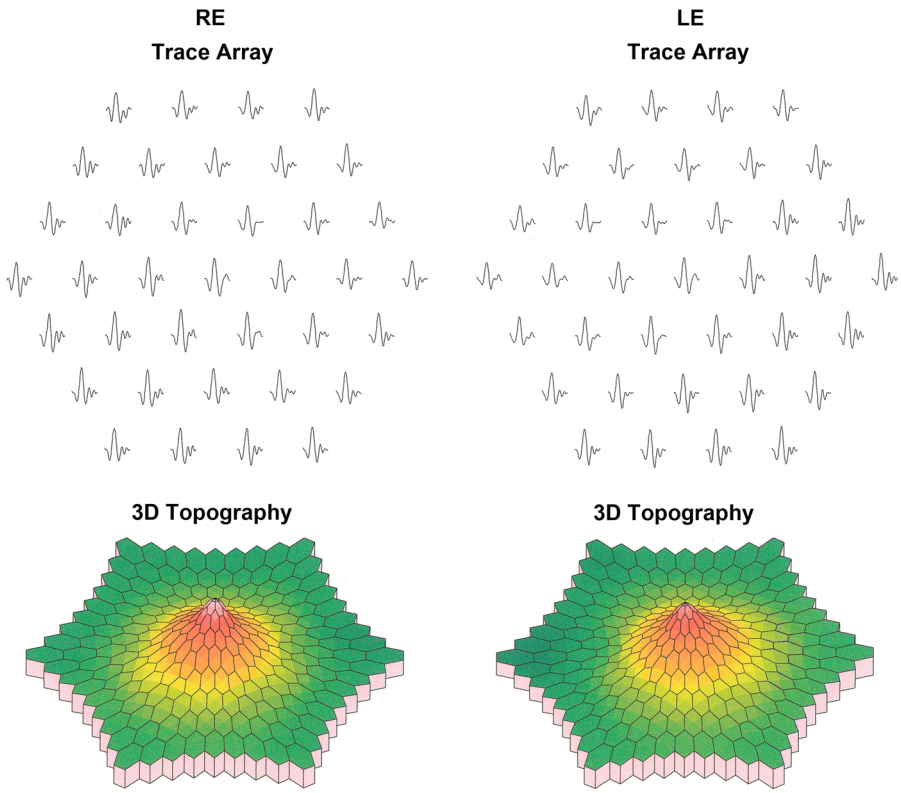

Fig. 4 The mfERG recordings from one of the children in the study group. *RE*: right eye and *LE*: left eye

second step, the interaction term was excluded (if not significant), and the final model contained the main effects of age and gender. Throughout the analyses, $p < 0.05$ was regarded as significant, but since no adjustment for multiplicity was performed, the p values should be interpreted as descriptive.

Statistical analyses were performed with SPSS 21 [14] and R version 3.1.1.

Results

Forty-nine children participated in the study. One child was excluded due to poor cooperation during the mfERG recordings. The mfERG measurements of two right and two left eyes were excluded due to alternating current disturbances. Hence, 46 right eyes and 46 left eyes were included in the study.

Mean age of the 48 children was 10.9 years (range 5–15). There were 24 girls and 24 boys. Mean age of the girls and boys was 10.2 years and 11.7 years, respectively. Mean visual acuity in the right and left eyes was −0.054 LogMar (range −2 to 0.1) and −0.057 LogMar (range −2 to 0.0), respectively. Mean spherical equivalent in the right and left eyes was +0.95 (−0.38 to +2.5) and +0.91 (0.0 to +3.0), respectively.

Regarding the OCT measurements, both eyes of one 7-year-old girl were excluded due to large eye movements with the scanning beam.

There were no major significant differences between right and left eyes. Hence, the results of the 46 right eyes will be presented. Median values, interquartile ranges (IQR) and ranges of the mfERG responses of P1 in Rings 1–3 in the 46 right eyes are presented in Table 1.

Comparisons of implicit time, amplitude and response density in Rings 1–3, respectively, revealed a difference regarding all measurements, most pronounced regarding response density, see box plots Fig. 5a–c.

There was a difference between girls and boys regarding implicit times where the boys had longer implicit times in Ring 1 (girls 30.0 ms vs. boys

Table 1 Median values, interquartile range (IQR) and range of the mfERG responses of P1 in 46 right eyes; implicit time (ms), amplitude (nV) and response density (nV/deg^2)

Area	Implicit time (ms) Median IQR (range)	Amplitude (nV) Median IQR (range)	Response density (nV/deg^2) Median IQR (range)
Ring 1	30.0	583.9	20.45
	30.0–31.0	454.8–651.1	15.9–22.8
	(28.3–33.3)	(337.3–975.6)	(11.8–34.2)
Ring 2	30.0	533.3	10.85
	30.0–30.8	403.9–584.2	8.2–11.9
	(28.3–32.4)	(283.7–970.2)	(5.8–19.7)
Ring 3	30.8	521.2	7.6
	30.0–31.6	414.5–587.5	6.0–8.5
	(29.1–32.4)	(233.8–986.3)	(3.4–14.3)

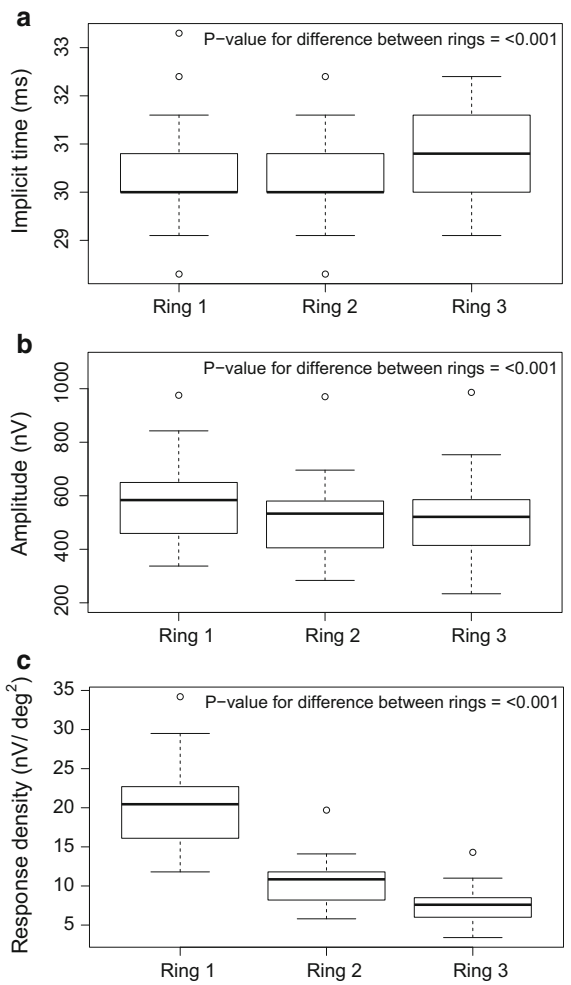

Fig. 5 **a** Comparison of implicit time (ms) in Rings 1–3. **b** Comparison of amplitude (nV) in Rings 1–3. **c** Comparison of response density (nV/deg^2) in Rings 1–3

30.8 ms, $p = 0.009$), Ring 2 (girls 30.0 ms vs. boys 30.8 ms, $p = 0.039$) and Ring 3 (girls 30.0 ms vs. boys 30.8 ms, $p = 0.005$). There were no differences regarding amplitudes or response densities and gender.

There was a significant correlation between age and implicit time in Ring 1 and Ring 2 and a borderline correlation in Ring 3, see Table 2.

In multivariate analysis of Rings 1–3, the effect of both age and gender remained similar to that in the univariate analyses, where implicit time increased with age and was slightly longer in boys. The results for Ring 1 are illustrated in Fig. 6. In the figure, the predicted values for boys and girls at different ages are illustrated along with 95 % prediction intervals.

Correlations between implicit time in Ring 1 and the different OCT variables are illustrated in Table 3. Regarding amplitude and response density, no significant correlations were found with any of the OCT variables.

Discussion

In the present population-based study, 49 healthy, full-term children were examined with mfERG and Cirrus OCT. Implicit time in the mfERG recordings increased with age and was longer in boys than in girls. There was also a correlation between implicit time in Ring 1 and the inner circle of the OCT measurements.

The mfERG method used in this study has several strengths. It is well tolerated in children, and all except one child were able to cooperate. It is painless, quick

Table 2 Correlations between age and implicit time, amplitude and response density in Rings 1–3 in 46 right eyes

	Age (years)					
	Ring 1		Ring 2		Ring 3	
	Correlation coefficient	*p* value	Correlation coefficient	*p* value	Correlation coefficient	*p* value
Implicit time (ms)	0.417	0.004*	0.316	0.032*	0.274	0.065
Amplitude (nV)	−0.064	0.682	−0.057	0.714	0.097	0.532
Response density (nV/deg^2)	−0.069	0.657	0.091	0.556	−0.052	0.736

* p value < 0.05

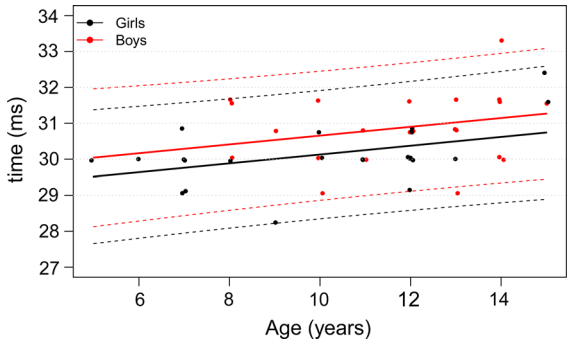

Fig. 6 Scatter plot of implicit time in Ring 1. *Solid lines* illustrate predicted values for boys and girls, respectively, and *dashed lines* illustrate the 95 % prediction intervals

and can be performed without general anesthesia in children as young as 5 years of age. DTL electrodes are easily accepted by children, and previous studies have reported repeatability and reliability with such electrodes [15–17]. Binocular recordings and a stimulus of 37 hexagons limit the examination time and provide information of the total macular function. The similarities between the mfERG values of the right and the left eyes point toward adequate recordings of the two eyes in the study group of healthy children. Further, the increased response density in the central ring of the mfERG recordings, as compared to the more peripheral rings in the present study, indicates a good fixation of the eyes. This finding is in line with the fact that the density of the cone photoreceptors is highest in the most central area of the macula [18]. Our data are in accord with previous mfERG studies showing highest response densities in the central rings and decreasing densities in more peripheral recordings [19–21]. Regarding implicit time, differences between Rings 1–3 were small, in accordance with Seeliger et al. [22].

Implicit time of P1 was correlated with age in the present study, while there were no significant correlations between amplitude or response density and age. Hansen et al. [23] have previously shown that in infants (age range 61–77 days), mfERG amplitudes of P1 were smaller and implicit times longer than in adults (age range 22–51 years), which probably reflects the immaturity of the macula as described by Hendrikson et al. [24]. In adults, however, it has been shown that the amplitude and response density of P1 decrease significantly and implicit time increases slowly as a function of age [21, 25, 26]. Whether the small increase in implicit time with age in the present study mirrors an "aging" process in the central macula is a matter of speculation.

In the univariate analyses in the present study, boys had longer implicit times than girls in all rings of the mfERG. The mean age of the boys was, however, slightly higher (11.7 years) than that of the girls (10.2 years). Nevertheless, even when adjusting for age, implicit times remained longer in boys. A recent study [27] in healthy subjects younger than 50 years ($n = 24$) revealed that the average implicit time of mfERG recordings was significantly shorter in females than in males in this age group. The authors speculated on the influence of estradiol on neuroretinal function. Further, the presence of sex hormone receptors in the retinal pigment epithelium has been reported [28, 29]. Whether hormone factors have an influence on the shorter implicit time in the present study can only be hypothesized. Interestingly, Dion et al. [30] reported gender differences regarding VEP response and speculated on differences in brain organization between boys and girls as an explanation.

The present study provides normative mfERG data in children aged 5–15 years. Normal values of mfERG

Table 3 Correlations between implicit time, amplitude and response density in Ring 1 and OCT parameters in 46 right eyes

OCT parameters	Ring 1 Implicit time (ms)		Ring 1 Amplitude (nV)		Ring 1 Response density (nV/deg^2)	
	Correlation coefficient	p value	Correlation coefficient	p value	Correlation coefficient	p value
Central area	0.192	0.211	0.171	0.266	0.171	0.267
Inner circle	0.368	0.014*	0.132	0.394	0.129	0.405
Outer circle	0.153	0.321	0.074	0.634	0.072	0.642
CV	0.243	0.111	0.109	0.482	0.107	0.490
CAT	0.240	0.117	0.104	0.500	0.102	0.508

CV cube volume (mm^3), *CAT* cube average thickness (μm)

* p value <0.05

recordings in adults have been reported [19, 25, 31], but to our knowledge, there are no previous studies regarding normative data in children. Our normal values may be of help to other electrophysiological departments. The number of children in the present study was too small for creating normal values with respect to age and gender. However, based on a model, predictive values for boys and girls of different ages were calculated (Fig. 6) and may be of value in the clinical situation.

The mfERG recordings were finally compared with OCT measurements of the macular area, and this pointed to a correlation between structure and function of the central retina. The implicit time of Ring 1 became longer with increasing thickness of the inner circle of the OCT measurements. Fovea is an interesting region histologically. Previous studies have shown that implicit time is prolonged with increasing macular thickness, for example macular edema in diabetic retinopathy [32]. Interestingly, the present study shows a positive correlation between implicit time and macular thickness also in healthy eyes.

Function and structure of the central macula are affected in various diseases in childhood such as Stargardt disease, achromatopsia and x-linked juvenile retinoschisis [33–35]. Although not always in agreement, a combination of mfERG and OCT provides important and complementary information about the central retina [36]. Early diagnosis is crucial in order to facilitate early habilitation, information to families and schools, genetic counseling and possibly future gene therapy. The present study shows that mfERG is a useful and objective test of the central macular function also in children. The method is well tolerated, seems to provide reliable results and can be recommended, together with OCT, in the investigation of reduced visual function of unknown origin in children.

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Compliance with ethical standards

Conflict of interest All authors certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Statements of human rights The tenets of the Declaration of Helsinki were strictly adhered to during the course of the study.

Informed consent Written consent was obtained from the parents of the participating children and oral consent from children. Ethical approval for the study was obtained from the Ethics Committee of Uppsala University.

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