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DONATA MONTVILAITĖ

ANALYSIS OF ASSOCIATIONS AMONG VISUAL SYSTEM AND AUXOLOGICAL CHARACTERISTICS IN PRESCHOOL CHILDREN WITH RETINOPATHY OF PREMATURITY

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VILNIAUS UNIVERSITETAS

DONATA MONTVILAITĖ

PRIEŠMOKYKLINIO AMŽIAUS VAIKŲ, KURIE SIRGO NEIŠNEŠIOTŲ NAUJAGIMIŲ RETINOPATIJA, REGOS SISTEMOS IR AUKSOLOGINIŲ CHARAKTERISTIKŲ SĄSAJŲ ANALIZĖ

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Abbreviations

ACD – Anterior chamber depth

AL – Axial length

BCVA – Best corrected visual acuity

BW – Birth weight

BMI – Body mass index

CR – Corneal radius

ETDRS – Early Treatment of Diabetic Retinopathy Study

ELBW – Extremely low birth weight

GA – Gestational age

LT – Lens thickness

LBW – Low birth weight

Max – Maximum

M – Mean

Min – Minimum

NCVA – Not corrected visual acuity

OCT – Optical Coherent Tomography

PC – Perinatology Centre

ROP – Retinopathy of prematurity

SN – Standard deviation

TMV – Total macular volume

VEGF – Vascular endothelial growth factor

VUHSK – Vilnius University Hospital Santariškių Klinikos

VA – Visual acuity

VLBW – Very low birth weight

1. **INTRODUCTION**

New medical technologies and improving medical doctor qualification allow for high-quality perinatal and neonatal care, which is the reason for a growing survival rate for preterm newborns with increasingly lower birth weight [1], [2], [3]. In 2013, the world's infant mortality caused by premature birth complications accounted for 15% of total deaths among children under the age of 5 years. Prematurity poses a huge problem, as a result of which approximately 1 million children died in 2013 (data for 2014-2015 is not available). It is considered that the death rate could be reduced to 3.4% by 2030 [4]. An international study of 184 countries revealed that 11% of the world's children, i.e. 15 million babies, are born prematurely every year [5]. The more premature a newborn is, the higher the risk to his/her life and health is [6]. Hence, premature birth remains a serious problem that should to be handled by joint and concerted actions at a global level [7].

More than twenty years ago (after the restoration of independence), Lithuania started using the most recent neonatal intensive care methodologies and establishing new neonatal units for preterm newborns [8]. Improvement was observed in terms of both neonatal assistance and care of preterm newborns, and the survival rate [9]. Throughout the last decade, there was a minor fluctuation in the number of preterm newborns in Lithuania, which approximated to 5.3-5.4%, while in 2015 the number remained stable (5.4%), with the most significant variations being observed with regard to the number of the 32-36 week newborns of gestational age. Immaturity of organs and their systems in newborns results manifests itself as the failure of a variety of functions, while immaturity of retina leads to visual system disorders, which commonly result in blindness [6]. Even in the case o f recovery of a newborn, the consequences of diseases might have an adverse effect on subsequent growth and motor and neuropsychological development [10], [11], [12].

The studies of the physical development of preterm children carried out back in the mid 20th century demonstrated that, as compared to term children, after birth they developed differently, falling behind in terms of height, weight and skeletal size [13]. A great deal of studies carried out thereafter showed that preterm children, even newborns with particularly low birth weight, are able to make up and catch up with their peers [14], [15], [16]. Unfortunately, authors of the most recent studies claim that, as compared with term newborns, the growth of children with low birth weight differs not only quantitatively, but also qualitatively, the latter being characterised by very early or delayed puberty, central adipose tissue accumulation, susceptibility to cardiovascular diseases, Type 2 diabetes, other diseases relating to metabolic syndrome [17], [18]. On the other hand, it is still discussed which care, feeding and treatment tactics should be used for preterm newborns, especially those with very low birth weight, immediately after birth and in subsequent periods of growth in order to avoid, as much as possible, growth unfavourable to health and health risks encountered as an adult [19], [20], [21], [22]. Individual growth trajectories of such children are not clear either.

The growth of preterm newborns with very low birth weight until the age of five years was explored in Lithuania in 2001-2002, and it was established that physical development indices for born preterm children aged between 1 and 5 still lagged behind as compared to children with regular birth weight [18], [23], [24]. Growth and development characteristics of preterm children were considered at a global level also in the context of impairment of different systems in the postnatal period: it is agreed that the more

immature a baby is born and the more affected he/she is during the first weeks following the birth, the poorer his/her development will be afterwards and the greater health concerns he/she will have [10], [12], [25].

The development and growth of preterm newborns who suffered from retinopathy in later ontogenetic periods have not received much attention not only in Lithuania, but also worldwide.

Retinopathy of prematurity (ROP) is a disease of a premature and underdeveloped retina, which may lead to blindness. Retinal blood vessels of such newborn are not fully developed, and the degree of immaturity of the retina depends on the immaturity of the newborn at birth [26]. It is assumed that the major ROP factors are very low birth weight and gestational age [27], it is also established that the risk of ROP is particularly increased as a result of oxygen therapy [28], [29], [30], [31].

The degree of ROP prevalence differs among developed and developing countries, accordingly accounting for 5-8% in developed countries and even 30% in developing countries [32], [33]. Notwithstanding improving medicine and new treatment options, in certain parts of the world ROP comes first among the causes of childhood blindness. This disease is responsible for 3-11% of all cases of sight loss in developed countries and 11-60% in third world countries [34].

In Lithuania, no information was available about the disease for a long time, no newborn physical examination was performed or treatment offered. After restoration of Lithuania's independence, with the rise of the survival rates among preterm newborns and improvement of ROP diagnostics, an increasing number of cases were recorded with regard to this disease. According to Vilnius Perinatology Centre (PC), in 1998 ROP was found in 48.3% of preterm newborns, including nearly 14%, which received treatment [35]. In 2005, the Premature Newborn Department of the Neonatology Centre, the Affiliate of Vilnius University Hospital Santariškių Klinikos (VUHSK), diagnosed 15.8% of preterm newborns with ROP, 8.0% of which were treated. Recently, ROP has been diagnosed less often. In 2015, the Premature Newborn Department treated 289 newborns, out of which 9.3% were diagnosed with ROP and only 1.7% were given medical treatment (according to the data of annual performance reports of the Premature Newborn Department). Although more than 70 years have lapsed since ROP was described for the first time, today there still are factors causing the disease and delayed outcomes of the disease that yet remain unidentified. Even though the disease is getting less spread in Lithuania, nearly one in ten preterm infants are affected by it.

There are not many studies on the change of eye condition in children born prematurely and affected by ROP in the period of their growth [36], [37], [38], [39], [40], and as regards works discussing, in an integrated manner, the dynamics of retinopathy of prematurity in connection with other auxological indices, nearly none were found [41], [42]. According to general principles of growth and studies carried out in the last decades, the physical condition of preterm newborns is closest to the growth indices of term children in the preschool period [43]. However, the development and condition of preterm newborns affected by ROP immediately before school, also individual variety in growth of such children, maturation of their visual system and physical condition, links between these indices and readiness for school in terms of the latter biological parameters remain unclear.

Children born premature and affected by ROP fall within a high-risk group (considering their visual system). Ophthalmologists should follow-up these children more often than

children born on time and not affected by the disease. In the world, there is little awareness of further eye and vision development of those children and the consequences of treatment by using certain therapies. Quite a number of these children are myopic, suffer from astigmatism, strabismus or degenerative retinal disorders [44]. Nevertheless, authors of various studies commonly explore individual indices on a case-by-case basis without reference to visual and physical condition at birth. Visual impairment impedes proper children's understanding of the surrounding world, they cannot easily read and write, orient themselves in the environment and find it more difficult to communicate or fulfil routine tasks. This is a matter of great concern not only for patients' parents, but also for the staff of health care and education institutions.

In Lithuania, at the age of 6 to 7 years, just before commencing primary education, children are examined with regard to their physical and psychosocial maturation, preparedness for education and the condition of the visual system. No exceptions are made to postpone primary education, and in this regard the administrative liability rests with parents. The question is when preterm children with very low birth weight affected by ROP are sufficiently physically mature to go to school. The aforementioned studies carried out in other countries provide data about peculiarities of growth of preterm children aged between 5 to 7, while in Lithuania the growth of children with very low birth weight was thoroughly investigated only in respect of children under the age of 6 years [18, 23, 24]. Both at a global level and in Lithuania until now there have been no integrated studies focusing on the specific visual and physical condition of preterm newborns, delayed outcomes of ROP after birth or any links between the visual system of children affected by ROP and auxological indices in the preschool period at the age of 5 to 7 years.

1.1. Relevance and scientific novelty of the research

Every year, approximately 15 million babies are born prematurely, and the preterm birth rate remains stable in many countries. On the other hand, high-quality perinatal and neonatal care has a positive effect on the survival rate among very low birth weight newborns. However, it is also true that the more immature a newborn is born, the more common irregularities in the development of various organs and systems are, and their treatment and care poses a serious challenge even for modern medicine. Disorders of the visual system in preterm newborns stemming from the immature retina often continue to persist and might eventually lead to blindness. Extremely early birth today remains a particularly pressing problem, while the number of studies on the link between the visual condition in children affected by ROP and the growth period is modest. No integrated research dealing with the dynamics of preterm newborns in relation with other indices of growth have been carried out in Lithuania, neither did we find any studies of the kind done on a global scale. So far we have never had an answer to the question how children born in the period when diagnostics and treatment of ROP was mastered in Lithuania are growing. This is important taking into consideration the fact that growth of children in different regions and populations of the world varies considerably in the case of both the norm and pathology.

As regards children affected by ROP, this thesis for the first time identifies late peculiarities of the visual system and physical condition in the preschool period at the age between 5 and 7 years taking account of the child's condition at birth and severity of

retinopathy (based on retrospective data of the same children collected from their medical records of 2006-2008). One of the most state-of-the-art methods for retina and choroid examination – Optical Coherent Tomography (OCT) – was used to examine the visual condition of preterm children aged between 5 and 7 years who were affected by ROP. Risk factors of further visual system development and individual variety in growth of such children were clarified. The link between different previous phases of ROP and the condition of the child's visual system in the preschool period was explored. For the first time an integrated multi-dimensional analysis focused on the relationship between the visual system and physical condition of preterm children affected by ROP was carried out and, as a result, provided new knowledge about ontogeny of preterm newborns in terms of similarities and differences in the development of a visual organ immature at the time of birth and of the whole body.

In a general biological sense and clinically the findings of the research are significant to general medical practitioners, paediatricians and ophthalmologists, who assess the condition of the visual system and auxological parameters of children affected by ROP (body size, shape, composition and the topography of the subcutaneous adipose tissue), identify health problems and control the efficiency of treatment and preventive measures in order to eliminate health risks at adult age.

1.2. Theoretical and applied implications of the research

This research is first in Lithuania to identify peculiarities of the visual system and physical condition of children affected by ROP in the preschool period at the age between 5 and 7 years considering their condition at birth and severity of ROP (based on retrospective data of the same children collected from their medical records of 2006-2008). What is also new is that risk factors of further visual system development and the individual variety of growth of such children are determined in Lithuania for the first time. An analysis is carried out in respect of the relationship between minor and acute ROP phases after birth and a child's visual system in the preschool period. The thesis provides an integrated multi-dimensional analysis of the interrelations between the visual system and physical condition of children affected by ROP, which broadens knowledge about the ontogeny of preterm newborns.

The significance of the research in terms of its application is that such children should not enter school under the age of 7, and some of them should be even recommended starting their schooling at a later time. We believe that continuous ophthalmological and paediatric care of those children should be provided more often than recommended for term children according to Annex 3 to Order No 301 of the Ministry of Health of the Republic of Lithuania of 31 May 2000 [45]. Given that such children are prone to a number of health problems, continuous and regular consultations of not only an ophthalmologist, but also a cardiologist and endocrinologist could be recommended.

2. THE GOAL OF THE THESIS

This thesis aims are evaluating, from the point of view of a child's development, the relationship between late visual system and anthropometric indices for preterm children with ROP in the preschool period taking into consideration these indices at birth and severity of ROP.

3. OBJECTIVES OF THE THESIS

1. Retrospective evaluation of the visual system of preterm newborns who received treatment in 2006-2008 at the Children's Hospital, Affiliate of Vilnius University Hospital Santariškių Klinikos, in terms of the frequency, severity of ROP and treatment tactics.
2. Retrospective assessment of the key anthropometric indices of preterm newborns with ROP and their comparison with the corresponding indices of preterm newborns not affected by ROP.
3. Analysis of the main functional and biometric indices of the visual system in children with ROP of the preschool age in view of previous severity of ROP and birth weight and comparison of the data obtained with the data of preterm children not affected by ROP and children born in due time.
4. Analysis of indices of the physical condition in children with ROP of the preschool age considering their eye condition and birth weight and comparison of the findings with the data of preterm children not affected by ROP and children born in due time.
5. Integrated evaluation of the relationship between prematurity, ROP, visual system and anthropometric indices in the preschool period.

4. MATERIALS AND METHODS

The research was carried out at the Clinic of Childrens' Diseases of the Faculty of Medicine of Vilnius University, Paediatric Ophthalmology Department of the Children's Hospital, Affiliate of Vilnius University Hospital Santariškių Klinikos (VUHSK), and VULSK Centre of Eye Diseases in 2011-2015. To that end, permit No 158200-12-565-165 was obtained from the Lithuanian Bioethics Committee.

The subjects were selected after having reviewed the medical records of preterm newborns treated at the Preterm Newborns Unit and Neonatal Intensive Care Unit in 2006-2008, accessed in the archive of the Children's Hospital, Affiliate of Vilnius University Hospital Santariškių Klinikos (VUHSK). There were totally 150 medical documents of premature newborns diagnosed with ROP found. The group of subjects was comprised of 103 children born prematurely in 2006-2008 and treated at the Children's Hospital. In total, 81 children were diagnosed with ROP, including 40 children (49.4%) with severe ROP and 41 children (50.6%) with mild ROP. The research also concerns 22 children who have not shown any signs of ROP. The latter, being diagnosed with not fully mature retina, fell within the group of preterm newborns not affected by ROP. In this study, the control group consisted of 40 children with regular

birth weight, who were born prematurely in 2006-2008 and were not diagnosed with any congenital and chronic systematic conditions and eye pathology at the preschool age.
ROP stages I and II were identified as a minor form of ROP, while stages III to V refer to sever ROP condition. No child diagnosed with mild ROP required treatment, whereas in the case of severe ROP 38 preterm newborns were given treatment.
The review of medical records allowed for collecting data about the physical status of children at birth (gestational age (GA), birth weight (BW), height, head and chest circumference), ophthalmological characteristics (ROP diagnosis, ROP zone, ROP stage or immature retina condition and treatment provided), also recording the neurological pathology anamnesis and significant complications that occurred in the neonatal period.
The control group consisted of 40 children with normal birth weight, who were born prematurely in 2006-2008 and were not diagnosed with any congenital or chronic systematic conditions and eye pathology at the preschool age.
Grouping criteria for the subjects.

Criteria for including preterm children affected by ROP in the study are as follows:

- Children born in 2006-2008;
- Children born prematurely, i.e. in pregnancy week 22-36;
- Children diagnosed with ROP;
- Children without any eye injury and other chronic eye diseases (except for ROP);
- Parents or guardians of the children signed their consent for participation in the study.

Criteria for including preterm children not affected by ROP in the study are as follows:

- Children born in 2006-2008;
- Children born prematurely, i.e. in pregnancy week 22-36;
- Children who were not diagnosed with retinal prematurity;
- Children without any eye injury and other chronic eye diseases (except for ROP);
- Parents or guardians of the children signed their consent for participation in the study.

Criteria for excluding preterm children from the study are as follows:

- Children under the age of 5 and above the age of 7;
- Children suffering from chronic eye diseases (uveitus, chronic conjunctivitis, glaucoma, etc.) or had an injury of the globe of the eye (eye injury);
- No parents' or guardians' consent was obtained for the child's participation in the study.

4.1. Ophthalmologic analysis

All children underwent a complete ophthalmic examination, by the same physician, including best-corrected distance and near visual acuity (VA), each eye separately was evaluated according to the Monoyer system at a 6 meters distance with a Snellen E chat, and near BCVA at a distance of 0.4m. Snellen VA was converted to the logarithm of the minimum angle of resolution VA (logMAR) for statistical analysis. Automatic cycloplegic refraction was followed by manual streak cycloplegic retinoscopy after

dilating the pupils with cyclopentolate 1%, twice at a 10 min interval, 30 min before examination (spherical equivalent was calculated). Astigmatism was recorded as a negative cylinder and defined as significant (when ≥1D) and high (when ≥2d). Children were considered to have a significant refractive error if they had hypermetropia >/= 2.0 diopters (D), myopia >/=-0.50 D. Anisometropia was defined as significant when the difference in spherical equivalent between the eyes was >/= 1D, and high, if >/= 2D. Amblyopia was defined as a 2-line logMAR difference between the two eyes in the presence of an amblyogenic factor.

Examination of ocular movement and cover test for distance and near were performed. Stereopsis was assessed by using the Stereo Fly test (standard stereo testing) and the Lang Stereo test 'I and II'. Stereoscopic vision and depth perception testing was important in identifying a defect in binocular vision and higher risk of amblyopia, strabismus, severe anisometropia, or extremely poor vision caused by retinal or optic disease. Cover and cover-uncover tests for distance and near were performed to detect strabismus. Strabismus was defined as all types of intermittent and manifest strabismus, and microtropia was determined as well. A prism bar was used for measuring the angle of deviation. All patients were assessed for ocular motility by letting the child fixate an object on the Lang fixation stick, which was moved to different positions of gaze. Anterior segment examination with a slit lamp and indirect fundoscopy were performed in all children. Ophthalmoscopy was performed through dilated pupils. The peripheral fundus was examined with an indirect ophthalmoscope and type of peripheral ablative procedure, such as laser therapy or cryotherapy, was recorded.

All children underwent the measurement of optical components. The corneal radius (CR) and refractive status were measured with autokeratorefraktometer (ACUREF-K 9001, SHIN-NIPPON, Japan). Including anterior chamber depth (ACD), lens thickness (LT) and axial length (AL) were obtained by contact A-scan ocular ultrasound device (A-scan ultrasound biometry) (UltraScan Imaging System, Alcon, USA). The scan was taken on to the centre of the cornea perpendicularly, and the child was asked to fixate the internal target. The automatic biometry program calculated the mean of ten measurements.

The OCT measurements (Heidelberg Engineering Spectralis OCT, Serial #:HRA2-KT-02897, Version 6.0.11.0. Heidelberg Engineering GmbH, 69121 Heidelberg, Germany) were performed in a room after pupil dilatation. The pupils were dilated to at least 5 mm diameter before the measurements. Macular measurements were performed with Early Treatment of Diabetic Retinopathy Study (ETDRS) macular mapping protocol. An internal fixation target was used in all scans, with the location of each scan on the retina monitored using an infrared sensitive video camera. All children were asked to fixate an internal target and the examiner centered the macular scan on the fovea pit. Retina thickness was automatically determined by the instrument software as the distance between the internal limiting membarane and retinal pigment epitelium. Total area measurements were divided into three concentric regions. The central disc (foveal region) and the inner and outer circles were divided into four quadrants. Average retinal thickness was provided for each of the nine regions, and total macular volume (TMV) was calculated by the software automatically from these data. The average retinal thicknesses of the four inner and the four outer segments were also calculated.

The choroid was imaged in the 'choroidal mode' and measured manually. Its thickness was defined as the distance between the outer border of the retinal pigment epitelium to hyperrefractive line behind the large vessel layer of the choroid, it was presumed to be

the choroid – scleral interface. The choroidal thickness was measured under the fovea, at 1000μm intervals from the fovea. The average of the choroidal thickness readings was recorded as the macular choroidal thickness. Choroidal thickness was defined as the choroidal thickness measured at the center of the foveola.

4.2. Anthropometric analysis

In order to evaluate the body composition, size and proportions of children participating in the study, all indices of the physical status of children such as standing and sitting height, weight, various body circumferences (head, chest, waist, hip, thigh, calf, arm, forearm), body segment breadths (shoulder and chest, chest depth, hip breadth) and limb diameters (arm, forearm, thigh, tibia distal epiphysis breadth, hereinafter referred to as elbow, wrist, knee, ankle widths), skinfold thickness in different body areas (subscapular, suprailiac, abdominal, triceps, front thigh, medial calf) were measured in accordance with the standard anthropometric methodology [46].
The right part of the body was measured for all subjects. When measured, children wore underwear only.

The standard anthropometric instruments and standard anthropometric methods were used [46]. The possible bias due to interobserver error could be excluded as the author performed the measurements.

The wide anthropometrical programme of the study included the following measured and computed indices:

1. Body height, body weight and body mass index (BMI = weight kg/ height $(m)^2$), sitting height (leg length = body height – sitting height).
2. Skeletal dimensions: shoulder breadth, chest breadth and depth, hip breadth, distal widths of elbow, wrist, knee and ankle.
3. Circumferences: head, chest, waist, hip, arm, thigh (max), calf (max).
4. Indices of amount and topography of the subcutaneous fat: abdominal, suprailiac, subscapular, triceps, front thigh and medial calf skinfolds; sum of skinfolds and subscapular/triceps skinfolds ratio (index of fat centralisation).
5. Relative body fat mass was calculated using M.H. Slaughter formula [47].

4.3. Grouping

In terms of their eye condition immediately after birth, children were grouped as follows: children with ROP (severe and mild) and without ROP (Table 1).

Table 1. Distribution of the subjects in groups by eye condition in the neonatal period

Children groups by eye condition	Total	Boys/girls	Aged 5/6/7 years
Born prematurely with ROP:	81	39/42	33/27/21
severe ROP	40	21/19	17/12/10
mild ROP	41	19/22	16/15/11
Born prematurely without ROP	22	12/10	13/5/4
Healthy full term children	40	23/17	13/15/12
Total	143	74/69	59/47/37

ROP – Retinopathy of prematurity

Given that there was no statistically significant difference identified between the right and left eye indices ($p>0,05$), further analysis of ophthalmological morphometric indices included only the results of the right eye condition. In addition, no current differences in the eye condition were found between girls and boys and among groups of ages 5 to 7 years, hence, the ophthalmological analysis did not take account of gender and age.
Current indices of the eye condition were compared among preterm newborn subgroups and the control group.
As current anthropometric indices did not significantly differ among children with severe and minor ROP, the two groups were joined into one group of children with ROP (81 children). This study excludes gender differences of the anthropometric indices on account of a small number of subjects and in order to align children groups from the ophthalmological and anthropometric dimension of the study (indices of the eye condition were analysed regardless of gender and age).
Also, children were grouped by birth weight: extremely low birth weight (<1,000 g), very low birth weight (<1,500 g, but >1,000 g) and low birth weight (>1,500 g) (Table 2).

Table 2. Distribution of preterm newborns among subgroups by birth weight in the neonatal period

Children groups by birth weight	Preterm children subgroups: mild ROP/severe ROP/no ROP	Total	Boys/girls	Age of 5/6/7 years
Extremely low BW (<1000 g)	13/10/0	23	10/13	11/6/6
Very low BW (1000–1500 g)	20/18/7	45	23/22	20/13/12
Low BW (>1500 g)	6/14/15	35	16/19	15/13/7

ROP – Retinopathy of prematurity

Present eye condition and anthropometric indices were compared among the groups and with the control group in connection with birth weight.

4.4. Statistical analysis methods

Descriptive index statistics – mean, arithmetic average (M), standard deviation (SN), minimum (min) and maximum (max) values – were used to systematise the research results.

Distribution normality of quantitative indices was verified by calculating the asymmetry coefficient and the excess coefficient in relation to their standard errors, by carrying out the Kolmogorov-Smirnov test and evaluating the histogram. Where distributions of certain anthropometric indices (weight, BMI, skinfold, etc.) were asymmetrical, the nonparametric Mann-Whitney-Wilcoxon test (two independent samples) or Kruskal-Wallis test (more than two independent samples) was used to verify the hypotheses concerning intergroup differences among variables.

Differences among indices of the two compared groups were evaluated by using the Student's t test. Where the test results in $p<0.05$, differences between the two groups are statistically significant. When comparing a few groups, the dispersion analysis (ANOVA) was carried out in respect of one factor. Where $p<0.05$, differences between at least two groups are statistically significant.

The χ^2 test was used to compare proportions among several groups. The significance level is $p<0.05$. The relative standard deviation method or the standard Z scores (*Z-score*, *SD-score*) were employed to compare an individual anthropometric index with the population's mean and to determine the deviation of a number of indices from the average indices of the population and their distribution level. In this regard, data of preschool children from Vilnius of 2003-2007 were selected; the study also considered healthy children aged between 5 and 7 and born in 1996-1999. [48]. The standard scores are obtained through the linear transformation of data, where the mean equals 0 and the

standard deviation is 1, in accordance with the formula: (index of a concrete individual M_1 – the mean of the population M) / standard deviation of the population (SD). A positive standard score signals that the index is higher than the mean, and the negative score means that the index is lower [49]. All standard Z scores were computed taking into account age and gender. The linear regression and the logistic regression were also used in order to define dependence of individual indices and predict the indices at issue. The linear regression determines the link between two interval variables. The logistic regression is used in the case of the binary categorical dependent variable. The dependent variable can have two values: 0 or 1. When determining the reliability of the logistic model a variety of criteria are considered: the Hosmer-Lemeshow test demonstrates whether the model is aligned with the data (if $p>0.05$, aligned); the Cox-Snell R^2 and Nagelkerke's R^2 show the variation percentage explained by the given model; it is also analysed which percentage of values the model classifies correctly. The logistic model is used to compute the likelihood ratio $exp\{B\}$, which indicates how the likelihood of Y to reach 1 varies. For the purpose of grouping of the given variables in respect of their correlations, the factor analysis was made. In the case of the factor analysis, it is stated that variables from individual groups correlate in terms of an unobserved latent factor. Individual variable groups are distinguished from the rotated component matrix.

The statistical analysis was performed using MS Excel and IBM SPSS Statistics 23.0 programs [49].

5. RESULTS

5.1. General characteristics of the subjects and the retrospective analysis of condition after birth

The final research analysis includes 103 preterm children (the subject group comprised of 49.5% boys and 50.5% girls) and 40 full term children (the control group consisting of 57.5% boys and 42.5% girls). In terms of age, children are distributed as follows: in the group of preterm children there were 46 five-year-olds, 32 six-year-olds and 25 seven-year-olds (the average age is 5.8 years); in the group of full term children there were accordingly 13 five-year-olds, 15 six-year-olds and 12 seven-year-olds (the average age is 5.97 years), which gives no significant difference between the two groups. The stage and severity of ROP was classified according to the international Classification of ROP (ICROP) [50]. All eyes fulfilling our criterion for treatment had been treated. The criterion for treatment was ROP stage 3, extraretinal neovascularization in at least 5 contiguous or 8 cumulative clock hours, even in the absence of 'plus' disease within zones I or II [26], [51].

24 (61,5 %) had been cryotreated, 14 (35,9 %) had been treated using combination of laser therapy and cryotherapy (cryopexy), and 1 (2,6 %) had been treated using only laser therapy. There were no treated patients with intravitreal bevacizumab (Avastin, Genentech, USA), a vascular endothelial growth factor (VEGF) antibody injection.

There were too small sample groups to compare the results of different treatment. According to the eyes condition, all children were divided into groups: those who had ROP (severe and mild ROP) and non-ROP group. 81 children had ROP (39 had been

treated, 42 did not receive any treatment, cause ROP regressed) and 22 had no history of ROP. Including 103 prematurely born infants a mean gestation age (GA) was 29,4 weeks, and mean birth weight (BW) was 1343,5 g. There was a significant difference between preterm children according to the eyes condition: children who had severe and mild ROP had smallest GA and BW. The proportion of boys and girls were similar. So, we didn't find statistical difference between boys and girls in the analysis comparing children with different eyes condition. Therefore the gender we didn't take into account, in the analysis of other indicators at birth.

A more detailed retrospective analysis of the anthropometric indices in the subjects at birth reveals that not only birth weight, but also BMI of children with severe ROP was reliably lower than that of children with minor ROP and without ROP ($p<0.05$ and $p<0.005$). Children with ROP were reliably shorter than those without ROP ($p<0.001$), however, no significant difference between the groups of children with severe and minor ROP was find in terms of birth height ($p>0.05$). As compared with children from other subgroups, children with severe ROP had significantly smaller head and chest circumferences at birth ($p<0.05$).

5.2. Results of ophthalmologic analysis in the preschool period

There was a statistically significant difference between prematurely born children and control group as regards visual acuity (VA). Distance and near VA significantly better was in full term children than in prematurely born children: in the distribution of not corrected visual acuity (NCVA) ($p<0,001$) and best corrected visual acuity (BCVA) ($p<0,001$). The analysis of VA (logMAR) according to the eyes conditions at birth revealed that prematurely born children with severe ROP had worse NCVA and worse BCVA (8 table, distance BCVA $p<0,05$; near BCVA $p<0,005$; 9 table, distance NCVA $p<0,05$, near NCVA $p<0,05$).

We didn't find significant differences between VA in prematurely born children without ROP and control group ($p>0,05$), but children with severe ROP (distance and near NCVA and BCVA) significantly differed from children with mild ROP ($p<0,05$).

Table 3. Mean values of BCVA in prematurely born children subgroups and control group (logMAR)

BCVA	Severe ROP (39)	Mild ROP (42)	No ROP (22)	Control group (40)
Distance BCVA (logMar)	0,11 (0,16)	0,00 (0,03)	0,00 (0,00)	−0,01 (0,03)
Near BCVA (logMar)	0,12 (014)	0,03 (0,02)	0,00 (0,00)	−0,04 (0,03)

BCVA – Best corrected visual acuity, ROP – Retinopathy of prematurity

Table 4. Mean values of NCVA in prematurely born children subgroups and control group (logMar)

NCVA	Severe ROP (39)	Mild ROP (42)	No ROP (22)	Control group (40)
Distance NCVA (logMAR)	0,39 (0,30)	0,05 (0,03)	0,10 (0,20)	0,05 (0,19)
Near NCVA (logMAR)	0,28 (0,20)	0,08 (0,02)	0,10 (0,18)	0,03 (0,10)

NCVA – Not corrected visual acuity, ROP – Retinopathy of prematurity

The results of BCVA (Decimal) we've divided into three groups (BCVA <0,3; between 0,3 - <0,7; and ≥ 0,7). This analysis showed that 3 children with severe ROP were visually impaired (BCVA <0,3) in the better eye (WHO's criteria) [52]. 6 children in severe ROP group and 1 child in mild ROP group BCVA was 0,3 - <0,7. However 76,9 % children with severe ROP, in the better eye had BCVA ≥ 0,7, but it was significantly less than in control group, no ROP group and mild ROP group (P=0,001). In the analysis of refractive errors, the prevalence of hypermetropia (≥2D) was higher in the premature group, irrespective of ROP stage. The frequency of hypermetropia was detected lower in the control group and no-ROP group, in comparison with ROP group, though there was no statistically significant difference (p>0,05). Significant myopia was measured from ≤− 0,5D. We found significant difference between prematurely born children and full term children. The highest prevalence of myopia (p<0,001) was in severe ROP group, but no-ROP group children also had significantly more myopia than full term children (p=0,05) (Table 5).

Table 5. Distribution of refractive errors in all subgroups

Refractive errors	Severe ROP (39)	Mild ROP (42)	No-ROP (22)	Control group (40)
Hypermetropia (≥2D) N (%)	12 (30,8)	13 (31)	5 (22,7)	6 (15)
Myipia (≤−0,5D) N (%)	14 (35,9)	6 (14,4)	5 (22,7)	3 (7,5)

ROP – Retinopathy of prematurity

When we evaluated astigmatism, we found that the control group had less total astigmatism (mean value) than the preterm group (p=0,03). Astigmatism more than 2D was more dominant in the severe ROP group (p<0,005), though half of no-ROP group had smaller but significant astigmatism (≥1 - <2,0 D) (Table 6).

Table 6. Distribution of astigmatism in all subgroups

Astigmatism	Severe ROP (39)	Mild ROP (42)	No-ROP (22)	Control group (40)
Significant astigmatism (≥1D ir <2D) N (%)	13 (33,3)	22 (52,4)	15 (68)	11 (27,5)
High astigmatism (≥2D) N (%)	24 (61,5)	4 (9,5)	2 (9)	0 (0)
Total astigmatism N (%)	37 (94,8)	26 (61,9)	17 (77)	11 (27,5)

ROP – Retinopathy of prematurity

The results of our study showed the frequency of astigmatism as well as of anisometropia in preterm children group. There were 65% (n=15) significant anisometropia (≥1D - <2D) and 35% (n=8) high anisometropia (≥2D) in the preterm group and only 5% (n=2) significant anisometropia in control group (p=0,014). Within the severe ROP group, children had the highest frequency of significant and high anisometropia (p<0,05).

Ambliopia (0,2 and >) was significantly greater in the premature group than in the control group in preschool period. Moreover, amblyopia was more common in severe ROP group (p<0,0005). Our results detected that especially in severe ROP group strabismus had significant prevalence (p<0,001) in preschool age children. Absent stereopsis was most common in severe ROP group (p<0,001).

Although our analysis didn't find statistically significant corneal radius (CR) differences between all subgroups (p>0,05), but preterm severe ROP group had steeper mean corneal curvature. The biometric optic components in preterm children with mild and severe ROP appeared to have shallower anterior chamber depth (ACD) (p<0,01) and greater lens thickness (LT) (p<0,001) than in other groups. A comparison of axial length showed significant difference: mild and severe ROP group children had shorter axial length (AL) (p<0,005) than full term children.

Both eyes in every child were examined by OCT. In the OCT analysis, we found significant differences in retina and choroidal thickness when we compared mild and severe ROP group with no-ROP group and control group. The mean values of foveal thickness and central retinal thickness were found to be greatest in severe ROP group children (p<0,01) in preschool age (Table 7). Either the mean values of total macular volume were significant different in comparison severe ROP group and control group (p<0,01). Moreover, there were seen statistically significant differences between mild and severe ROP groups and no-ROP and full term children (p<0,01). There was no difference between parafoveal and perifoveal circles in all subgroups (p>0,05). Furthermore choroidal thickness was significantly lower in severe ROP group in preschool age (p<0,05) and mild ROP group, respectively.

Table 7. The mean values of OCT parameters

OCT indices	Severe ROP M (SN)	Mild ROP M (SN)	No-ROP M (SN)	Control group M (SN)
Central retinal thickness (A1), μm	290,1 (24)	271,2 (18,0)	260,3 (9,7)	249,1 (18,5)
Foveal thickness, μm	275,4 (25,8)	244,1 (21,8)	235,4 (9,5)	226,9 (16,7)
Central retinal volume, mm^3	0,24 (0,02)	0,23 (0,01)	0,22 (0,01)	0,21 (0,01)
Parafoveal thickness, μm	320,3 (20,5)	314 (13,2)	310,5 (12,7)	320 (10,3)
Perifoveal thickness, μm	301,2 (19,5)	293,1 (14,2)	290,0 (14,7)	298,8 (10,9)
Central choroidal thickness, μm	203,7 (29,8)	215,4 (28,7)	236,2 (11,4)	288,6 (19,4)

OCT – Optical coherent tomography, ROP – Retinopathy of prematurity

5.3. Vision system connection with birth weight and ROP in the preschool period

The detail analysis of visual system at preschool age, according to birth weight showed differences in both functional and biometric parameters. In connection with birth weight the anterior chamber depth was significantly shallower, lens thickness was significantly thicker ($p<0,05$). But there was no difference in axial length in connection with birth weight ($p>0,05$). A very significant difference of foveal thickness ($p<0,001$) was found between extremely low birth weight group and very low birth weight group. The incidence of refractive errors (myopia, hypermetropia, astigmatism) and amblyopia significantly differed at preschool age - extremely low birth weight group and very low birth weight group children had significantly higher risk than low birth weigh group ($p<0,05$). There were no significant differences in the incidence of anisometropia and strabismus according to birth weight ($p>0,05$).

5.4. Results of anthropometric analyses in the preschool period

In the first place, the descriptive statistics of all anthropometric indices was computed, the resulting means were compared among the subgroups of preterm children in terms of their eye condition only and then in connection with birth weight. The standard scores were calculated for all indices in the context of the data of the wide-scope study of preschool children [48]. The analysis of standard scores revealed that the majority of anthropometric indices in children within the control group were significantly larger than the mean of the population (Figure 1 and 2). As compared to the mean of the population, there was a minor difference observed with regard to BMI of the five-year-olds and six-year-olds in the control group, subcutaneous limb fat in the five-year-olds, head circumference and certain limb circumferences in the six-year-olds and seven-year-olds. It was established that the comparison of the anthropometric data of the preterm children

and children within the control group was not appropriate, as the results distort the conclusions. For this reason, the summary excludes the descriptive statistics of anthropometric data for the control group and the comparison of preterm children and the control group in terms of the anthropometric indices.

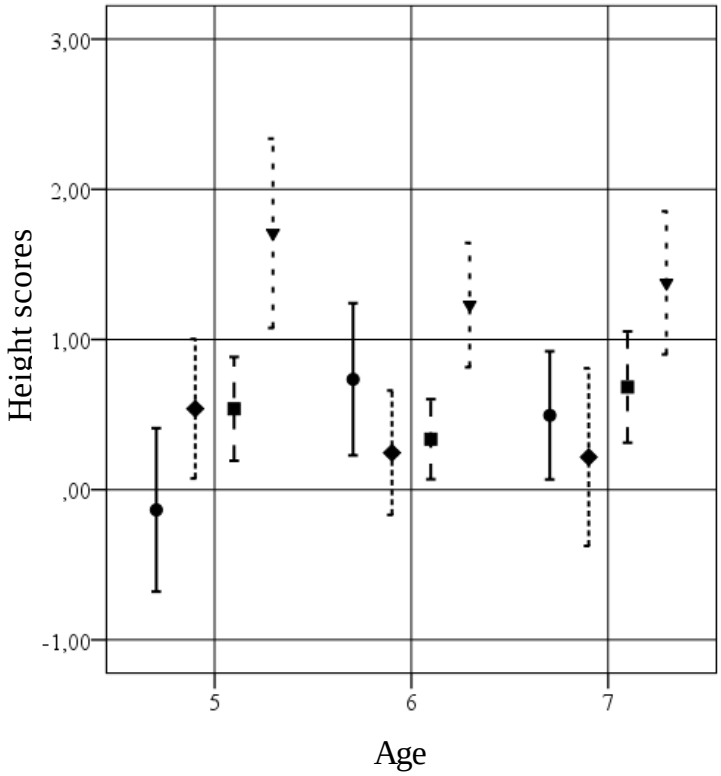


Figure 1.Comparison of different eye condition and standard height scores in the control group by age.

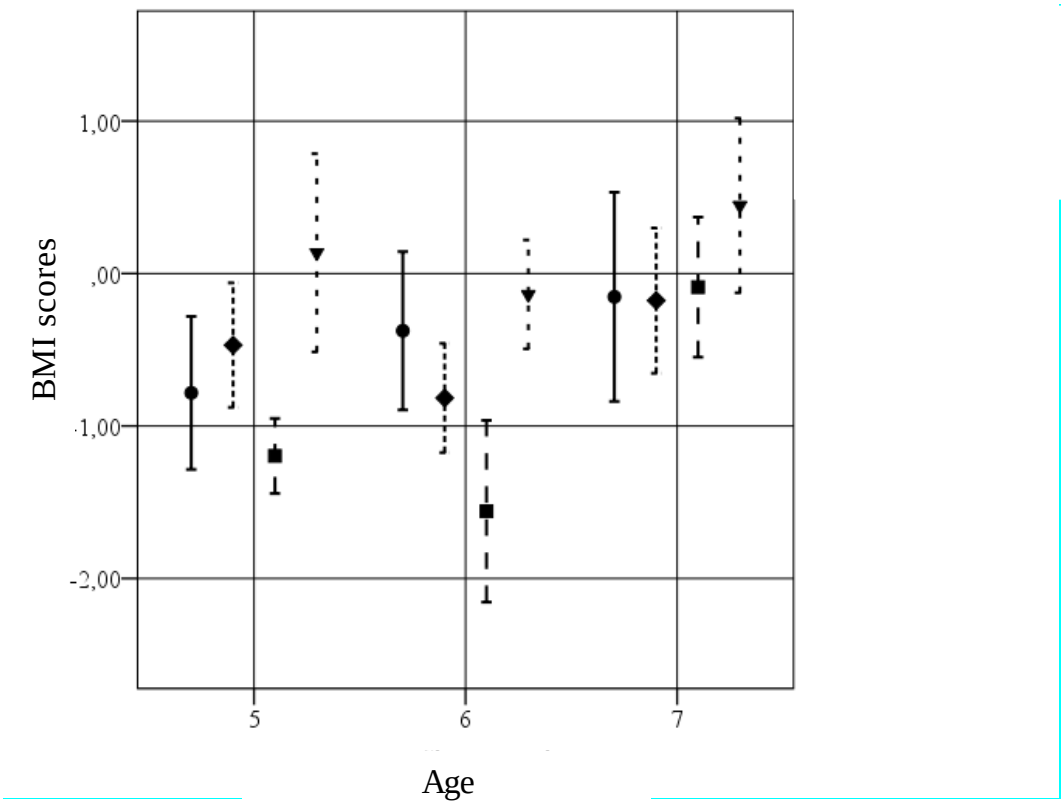


Figure 2.Comparison of different eye condition and standard BMI scores in the control group by age.

5.4.1. Main body size indices

First, we compared the main body size indices for preterm children aged between 5 and 7 years in relation to their eye condition. We did not find any statistically significant differences between preterm children with ROP and without ROP in terms of their height and other longitudinal indices, except that the seven-year-olds with ROP had shorter legs (Table 8). We established that the six-year-olds without ROP had a significantly lower weight, and BMI of the five-year-olds and six-year-olds without ROP was also significantly lower. It is apparent that BMI of children with ROP increased at the age of 5-7 years, i.e. their adiposity rebound occurred earlier (at the age of 5) than in the case of children without ROP (they had adiposity rebound at the age of 6).

We have also compared the same indices for the preterm children with ROP taking into account their weight. ANOVA revealed a significant delay in height and other longitudinal indices of the five-year-olds with extremely low birth weight as compared to the five-year-olds with higher birth weight, while there were no significant differences observed among the indices of the six-year-olds and seven-year-olds with different birth weight (Table 9). The weight of children with extremely low birth weight also fell behind the weight of children with higher birth weight; however, a significant difference was determined only among the five-year-olds.

Table 8. Average main body size indices of preterm children with ROP and without ROP and their comparison (t test).

Age	with ROP (all)	without ROP	P value
Height, cm M (SN)			
5 years	112.6 (4.9)	114.3 (2.7)	0.1387
6 years	120.6 (4.2)	119.8 (1.5)	0.4599
7 years	125.2 (4.1)	127.0 (1.5)	0.1447
Sitting height, cm M (SN)			
5 years	62.2 (1.9)	62.9 (1.3)	0.1792
6 years	65.2 (2.1)	64.4 (0.9)	0.1773
7 years	67.9 (2.1)	67.4 (0.8)	0.3877
Leg length, cm M (SN)			
5 years	50.4 (3.3)	51.4 (1.52)	0.1464
6 years	55.4 (2.6)	55.4 (0.93)	0.9973
7 years	57.3 (2.4)	59.6 (1.11)	0.0130
Body weight, kg M (SN)			
5 years	19.0 (2.1)	18.4 (1.5)	0.3069
6 years	21.9 (2.6)	19.5 (1.4)	0.0143
7 years	24.9 (2.7)	25.6 (1.5)	0.5000
BMI, kg/m^2 M (SN)			
5 years	14.94 (1.22)	14.04 (0.62)	0.0021
6 years	15.01 (1.14)	13.58 (0.71)	0.0054
7 years	15.78 (1.43)	15.88 (0.56)	0.8209

ROP – Retinopathy of prematurity

Table 9. Average main anthropometric indices of preterm ROP children with different birth weight and their comparison (ANOVA).

Age	BW<1kg	BW=1-1.5 kg	BW>1.5 kg	P value
Height, cm M(SN)				
5 years	110.0 (5.3)	112.9 (4.3)	115.6 (2.1)	0.004
6 years	118.6 (2.7)	120.2 (4.3)	121.6 (3.8)	0.295
7 years	123.2 (2.6)	126.5 (3.9)	125.9 (4.2)	0.223
Sitting height, cm M(SN)				
5 years	61.2 (2.2)	62.3 (1.7)	63.4 (0.9)	0.005
6 years	64.5 (1.4)	65.1 (2.1)	65.4 (2.2)	0.674
7 years	66.9 (1.7)	68.1 (2.2)	68.1 (1.7)	0.449
Leg length, cm m(SN)				
5 years	48.8 (3.6)	50.6 (2.8)	52.2 (1.7)	0.011
6 years	54.1 (2.2)	55.1 (2.5)	56.2 (2.1)	0.184
7 years	56.3 (1.4)	58.3 (2.2)	57.8 (3.0)	0.215
Body weight, kg M(SN)				
5 years	17.8 (2.8)	18.7 (1.6)	19.7 (1.3)	0.040
6 years	20.7 (1.2)	21.6 (2.9)	21.8 (2.9)	0.683
7 years	23.2 (1.2)	25.6 (4.2)	25.5 (2.9)	0.333
BMI, kg/m^2 M(SN)				
5 years	14.65 (1.67)	14.67 (1.11)	14.74 (0.76)	0.976
6 years	14.70 (1.06)	14.93 (1.32)	14.67 (1.20)	0.855
7 years	15.25 (0.31)	15.91 (1.75)	16.06 (0.96)	0.522

BW – Birth weight; BMI – Body mass index

Further, we compared standard height scores in relation to eye condition (Figure 1) and birth weight (Figure 3). It is clear that, in terms of eye condition only, height in all subgroups of preterm children approximated the mean or was even higher (in older age groups). Standard height scores in the control group manifestly exceeded the average height of both preterm children and the population to a significant degree.

The comparison of children with different birth weight demonstrated that the height of the five-year-olds with extremely low birth weight was the most lagging behind the mean (the highest negative values of standard indices), but at the age of six years it caught up with the average values. The height of children with higher birth weight was close to or higher than the average.

The comparison of BMI in terms of eye condition only showed that the values did not significantly depart from the mean, and more valuable information was acquired from birth weight-based comparison (Figure 2 and 4). It is evident that all preterm ROP five-year-olds and six-year-olds as well as the seven-year-olds with extremely low birth weight did not reach the mean.

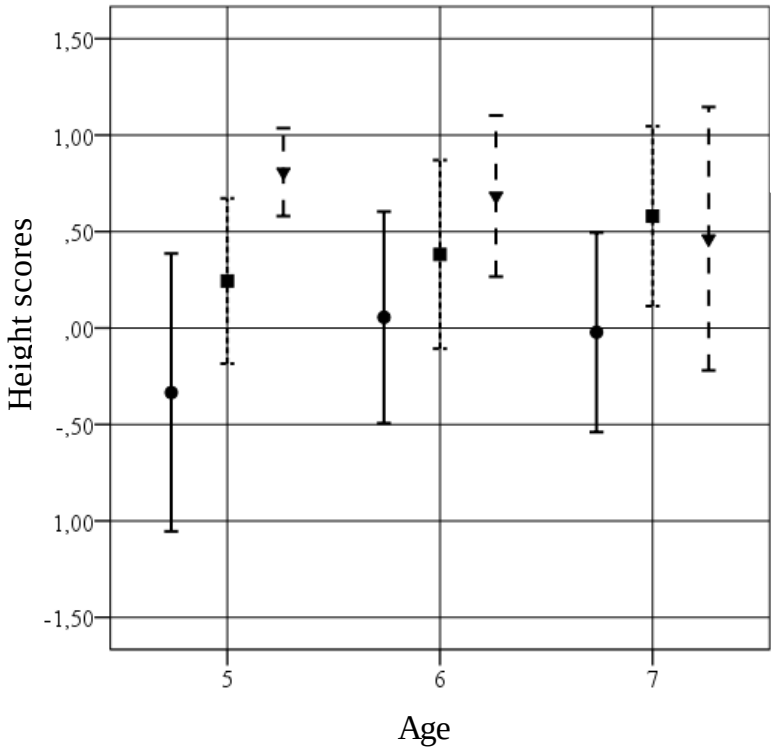


Figure 3.Comparison of standard height scores of preterm ROP newborns with different birth weight in terms of age.

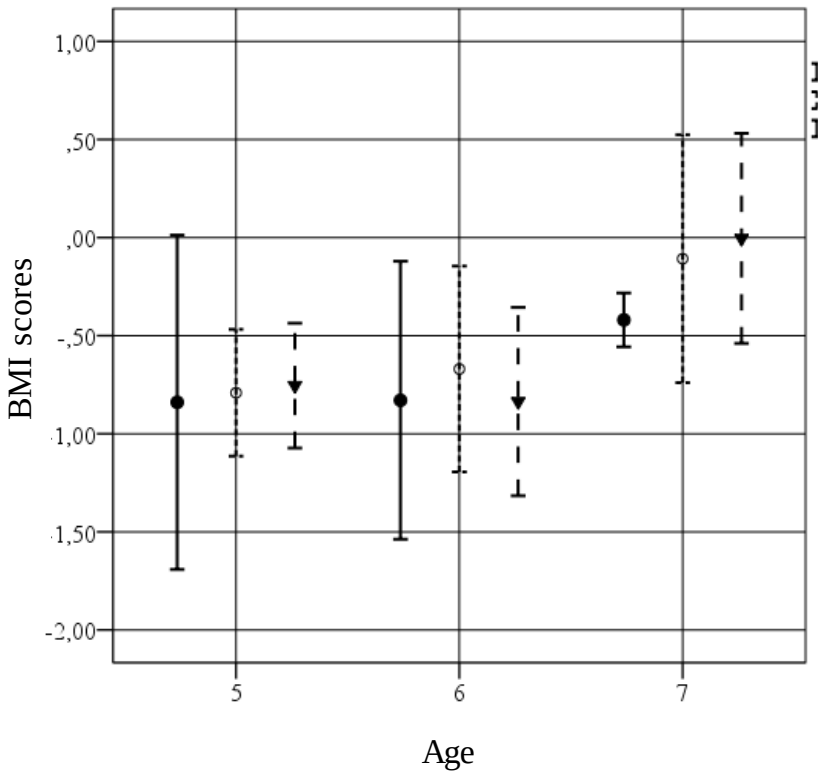


Figure 4.Comparison of standard BMI scores of preterm ROP newborns with different birth weight in terms of age.

5.4.2. Skeletal size indices

Firstly, we compared skeletal size indices for preterm children aged between 5 and 7 in respect of their eye condition. As a result, we obtained statistically significant differences among certain indices, but the tendencies remained unclear: in some age groups lower indices were found for ROP children, while in other groups the same were identified with preterm children without ROP (Table 10). The comparison in respect of birth weight was more successful: the majority of skeletal size indices for the five-year-olds with extremely low birth weight were lower than those of children with higher birth weight, though, in fact, not all differences were statistically significant (Table 11).
The comparison of standard scores revealed that shoulder breadth indices in preterm five-year-olds with ROP were lower than the mean of the population, and the less was birth weight, the more they fell behind the average (Fig. 5). The six-year-old index approached the mean irrespective of birth weight, while shoulders of the seven-year-olds with higher birth weight were broader than the mean of the population.

Table 10. Average skeletal size indices of preterm children with ROP and without ROP and their comparison (t test).

Age	with ROP (all)	without ROP	P value
Shoulder breadth, cm M(SN)			
5 years	23.7 (1.2)	23.5 (0.5)	0.3846
6 years	25.8 (1.2)	24.8 (0.3)	0.0012
7 years	26.9 (1.8)	28.6 (0.8)	0.0095
Chest breadth, cm M(SN)			
5 years	17.8 (0.8)	16.8 (0.5)	0.0000
6 years	18.7 (1.1)	17.4 (0.4)	0.0003
7 years	19.0 (1.7)	19.6 (0.8)	0.2414
Chest depth, cm M(SN)			
5 years	13.1 (0.7)	13.6 (0.5)	0.0042
6 years	13.4 (0.8)	13.9 (0.5)	0.1291
7 years	13.9 (0.8)	14.6 (0.5)	0.0373
Hip breadth, cm M(SN)			
5 years	17.9 (0.9)	17.5 (0.8)	0.0948
6 years	19.2 (1.1)	18.4 (0.5)	0.0238
7 years	20.4 (1.4)	20.1 (0.6)	0.6038
Elbow width, cm M(SN)			
5 years	5.2 (0.3)	5.3 (0.2)	0.2615
6 years	5.6 (0.3)	5.4 (0.0)	0.0295
7 years	5.9 (0.4)	6.1 (0.1)	0.0256
Wrist width, cm M(SN)			
5 years	4.0 (0.2)	4.0 (0.2)	0.6190
6 years	4.2 (0.2)	4.1 (0.1)	0.1578
7 years	4.2 (0.2)	4.2 (0.1)	0.9071
Knee width, cm M(SN)			
5 years	7.3 (0.3)	7.2 (0.3)	0.1771
6 years	7.6 (0.4)	7.5 (0.1)	0.1390
7 years	8.1 (0.5)	7.8 (0.1)	0.0063
Ankle width, cm M(SN)			
5 years	5.2 (0.2)	5.2 (0.3)	0.9731
6 years	5.6 (0.3)	5.4 (0.0)	0.0103
7 years	5.8 (0.3)	5.8 (0.2)	0.9551

ROP – Retinopathy of prematurity

Table 11. Average skeletal size indices of preterm ROP children with different birth weight and their comparison (ANOVA).

Age	BW<1kg	BW=1-1.5 kg	BW>1.5 kg	P value
Shoulder breadth, cm M (SN)				
5 years	23.3 (1.5)	23.6 (0.8)	24.0 (0.8)	0.284
6 years	25.4 (1.0)	25.7 (1.5)	25.6 (1.0)	0.901
7 years	26.0 (0.7)	27.2 (1.9)	28.2 (1.6)	0.076
Chest breadth, cm M (SN)				
5 years	17.4 (0.6)	17.7 (0.9)	17.4 (1.0)	0.668
6 years	18.5 (0.8)	18.7 (1.4)	18.3 (1.0)	0.648
7 years	18.3 (1.6)	19.3 (1.7)	19.3 (1.1)	0.418
Chest depth, cm M (SN)				
5 years	13.0 (0.8)	13.1 (0.7)	13.6 (0.5)	0.011
6 years	13.3 (0.6)	13.6 (0.9)	13.4 (0.8)	0.184
7 years	13.3 (0.6)	13.9 (0.8)	14.6 (0.5)	0.215
Hip breadth, cm M (SN)				
5 years	17.9 (0.9)	17.5 (0.8)	19.0 (1.0)	0.937
6 years	19.2 (1.1)	18.4 (0.5)	19.8 (0.7)	0.687
7 years	20.4 (1.4)	20.1 (0.6)	20.9 (1.4)	0.353
Elbow width, cm M (SN)				
5 years	5.0 (0.3)	5.3 (0.3)	5.4 (0.2)	0.001
6 years	5.5 (0.3)	5.6 (0.2)	5.5 (0.3)	0.599
7 years	5.6 (0.2)	6.0 (0.4)	6.1 (0.2)	0.039
Wrist width, cm M (SN)				
5 years	3.9 (0.2)	4.0 (0.2)	4.1 (0.1)	0.030
6 years	4.1 (0.2)	4.2 (0.2)	4.1 (0.2)	0.550
7 years	4.2 (0.1)	4.2 (0.3)	4.3 (0.1)	0.821
Knee width, cm M (SN)				
5 years	7.1 (0.3)	7.3 (0.3)	7.4 (0.3)	0.167
6 years	7.6 (0.2)	7.6 (0.3)	7.6 (0.4)	0.872
7 years	7.9 (0.3)	8.1 (0.5)	8.1 (0.5)	0.562
Ankle width, cm M (SN)				
5 years	5.0 (0.2)	5.2 (0.3)	5.3 (0.3)	0.017
6 years	5.6 (0.3)	5.7 (0.4)	5.5 (0.2)	0.396
7 years	5.6 (0.2)	5.8 (0.3)	5.9 (0.2)	0.094

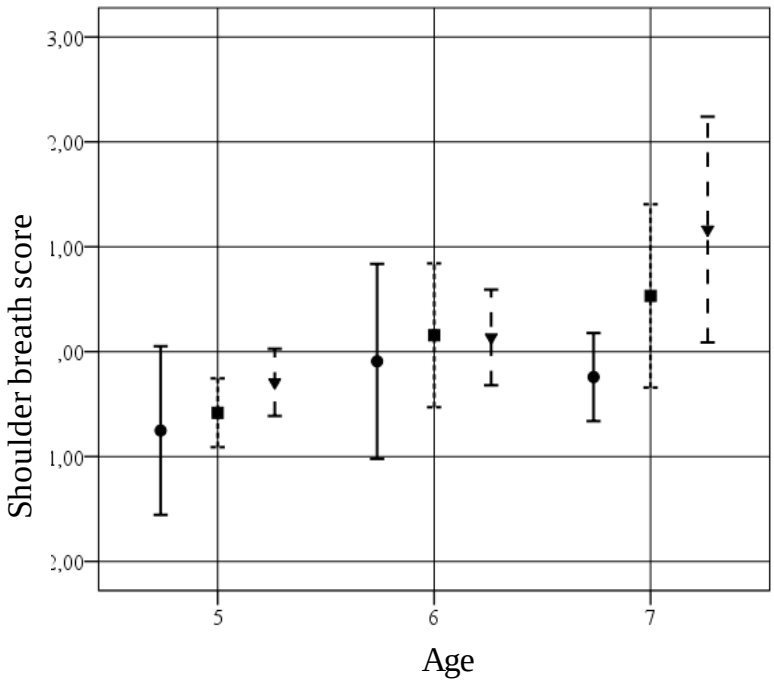


Figure 5. Comparison of standard shoulder breadth scores of preterm newborns with different birth weight in terms of age.

Standard scores of chest breadth and depth did not reliably depart from the average, however, it is clear that values are widely distributed and differently departed from the mean value, which indicates variations in the thoracic shape (Fig.6 and 7). Greater chest depth index in preterm ROP five-year-olds and six-year-olds suddenly dropped at the age of 7, which signifies more intense flattening of thorax in that period. More rounded thorax that remains longer than in the case of full term children should be regarded as a sign of immaturity.

Growth imbalances are also observed when analysing size indices of limb bones (Fig. 8 and 9): elbow width reached the mean of the population sooner than knee width. It results that the arm skeleton of preterm children grew faster than that of legs, while differences were observed in all birth weight groups.

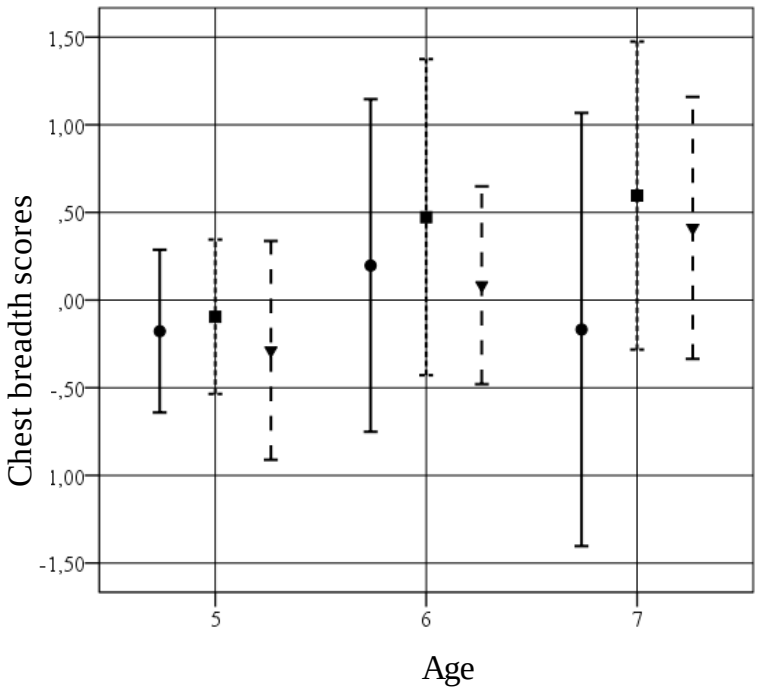


Figure 6. Comparison of standard chest breadth scores of preterm newborns with different birth weight in terms of age.

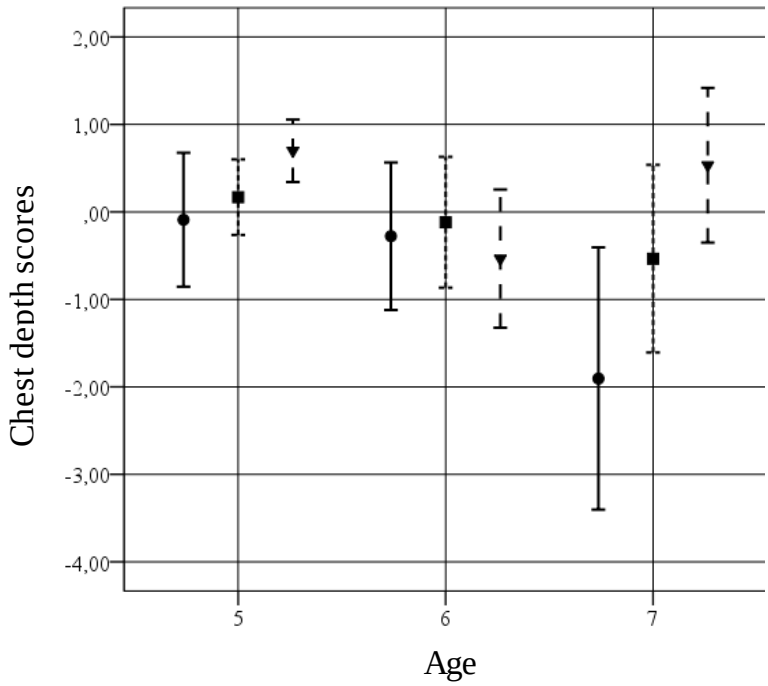


Figure 7. Comparison of standard chest depth scores of preterm newborns with different birth weight in terms of age.

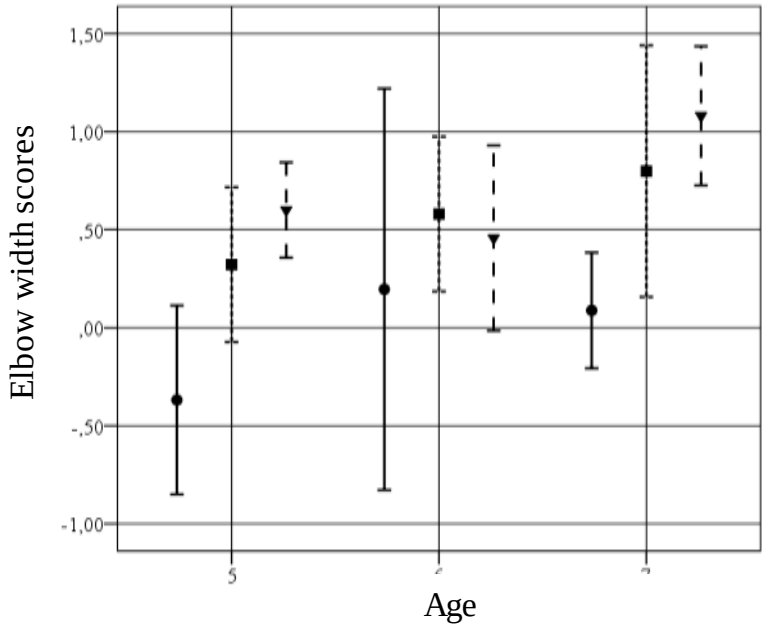


Figure 8. Comparison of standard elbow width scores of preterm newborns with different birth weight in terms of age.

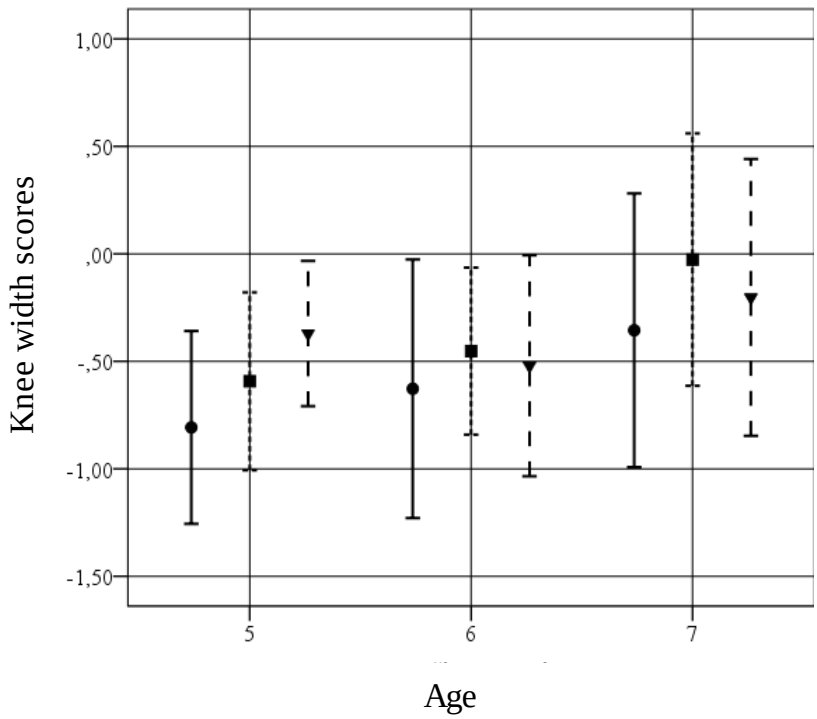


Figure 9. Comparison of standard knee width scores of preterm newborns with different birth weight in terms of age.

5.4.3. Head, body and limb circumferences

In the first place, we compared circumference indices for preterm children aged between 5 and 7 with regard to their eye condition only. As a result, we obtained statistically significant differences among certain indices, but the tendencies again were unclear: in some age groups lower indices were identified with ROP children, while in other groups they were found in preterm children without ROP (Table 12). The comparison of circumferences by birth weight revealed that the majority of circumferences in the five-year-olds with extremely low birth weight were statistically least significant. In groups of older children differences became statistically insignificant (Table 13).

Table 12. Average circumferences of preterm children with ROP and without ROP and their comparison (t test).

Age	with ROP (all)	without ROP	P value
Head circumference, cm M (SN)			
5 years	50.6 (1.1)	50.5 (0.5)	0.4483
6 years	51.9 (1.0)	51.3 (0.4)	0.0679
7 years	51.8 (1.2)	52.5 (0.7)	0.1761
Chest circumference, cm M (SN)			
5 years	54.9 (2.3)	56.3 (1.5)	0.0150
6 years	57.3 (2.5)	57.5 (1.1)	0.7335
7 years	58.9 (2.4)	62.3 (0.5)	0.0000
Waist circumference, cm M (SN)			
5 years	51.9 (2.4)	52.1 (1.8)	0.8069
6 years	53.9 (2.7)	53.9 (0.5)	0.9847
7 years	54.9 (2.3)	56.0 (1.7)	0.2947
Hip circumference, cm M (SN)			
5 years	57.8 (2.5)	58.9 (1.4)	0.0774
6 years	61.8 (3.1)	60.4 (0.5)	0.0399
7 years	64.6 (3.5)	64.0 (1.5)	0.5851
Arm circumference, cm M (SN)			
5 years	16.7 (1.4)	17.5 (1.4)	0.1076
6 years	17.7 (1.6)	17.8 (0.3)	0.8563
7 years	19.0 (1.4)	20.8 (1.0)	0.0225
Thigh circumference, cm M (SN)			
5 years	32.3 (2.2)	31.5 (2.0)	0.2433
6 years	34.3 (2.7)	34.0 (0.4)	0.5239
7 years	38.0 (2.2)	36.3 (1.0)	0.0289
Calf circumference, cm M (SN)			
5 years	22.7 (1.7)	22.1 (1.3)	0.2404
6 years	24.2 (1.7)	23.5 (0.5)	0.0985
7 years	26.0 (1.9)	25.9 (0.3)	0.7607

ROP – Retinopathy of prematurity

Table 13. Average circumferences of preterm ROP children with different birth weight and their comparison (ANOVA).

Age	BW<1kg	BW<1-1.5 kg	BW>1.5 kg	P value
Head circumference, cm M (SN)				
5 years	50.1 (1.3)	50.5 (0.7)	51.0 (0.8)	0.060
6 years	51.3 (1.0)	51.9 (1.0)	51.7 (0.9)	0.850
7 years	51.7 (1.2)	52.0 (1.2)	52.3 (1.1)	0.331
Chest circumference, cm M (SN)				
5 years	53.8 (3.0)	55.1 (1.8)	56.6 (1.2)	0.003
6 years	56.6 (2.0)	57.8 (2.2)	57.2 (2.6)	0.575
7 years	57.3 (2.5)	59.8 (2.4)	60.8 (1.7)	0.029
Waist circumference, cm M (SN)				
5 years	51.0 (3.1)	51.5 (1.9)	53.2 (1.3)	0.019
6 years	52.5 (1.8)	54.7 (2.3)	53.7 (2.8)	0.180
7 years	53.3 (0.5)	55.7 (2.6)	55.4 (1.5)	0.072
Hip circumference, cm m (SN)				
5 years	56.6 (2.9)	58.2 (1.9)	59.3 (1.6)	0.010
6 years	60.6 (1.8)	62.2 (3.1)	61.4 (3.4)	0.568
7 years	63.3 (2.1)	65.3 (3.8)	64.2 (2.9)	0.452
Arm circumference, cm M (SN)				
5 years	16.2 (1.7)	16.8 (1.2)	17.7 (1.0)	0.020
6 years	17.2 (1.2)	18.2 (1.1)	17.6 (1.8)	0.354
7 years	18.2 (0.7)	19.4 (1.7)	20.1 (1.2)	0.066
Thigh circumference, cm M (SN)				
5 years	31.5 (2.7)	31.8 (2.3)	32.7 (1.4)	0.286
6 years	33.5 (2.8)	34.2 (2.1)	34.7 (2.6)	0.632
7 years	37.9 (0.8)	38.0 (2.7)	37.0 (2.2)	0.624
Calf circumference, cm M (SN)				
5 years	21.8 (1.7)	22.4 (1.7)	23.2 (1.1)	0.076
6 years	22.9 (1.4)	24.2 (1.7)	24.5 (1.5)	0.129
7 years	25.1 (0.8)	26.3 (2.1)	26.3 (1.6)	0.364

ROP – Retinopathy of prematurity; BW – Birth weight.

The comparison of standard scores showed that in all age groups head circumference of preterm children with ROP and without ROP was significantly smaller than the mean of the population, and the less was birth weight, the more they fell behind the average (Fig. 10 and 11).

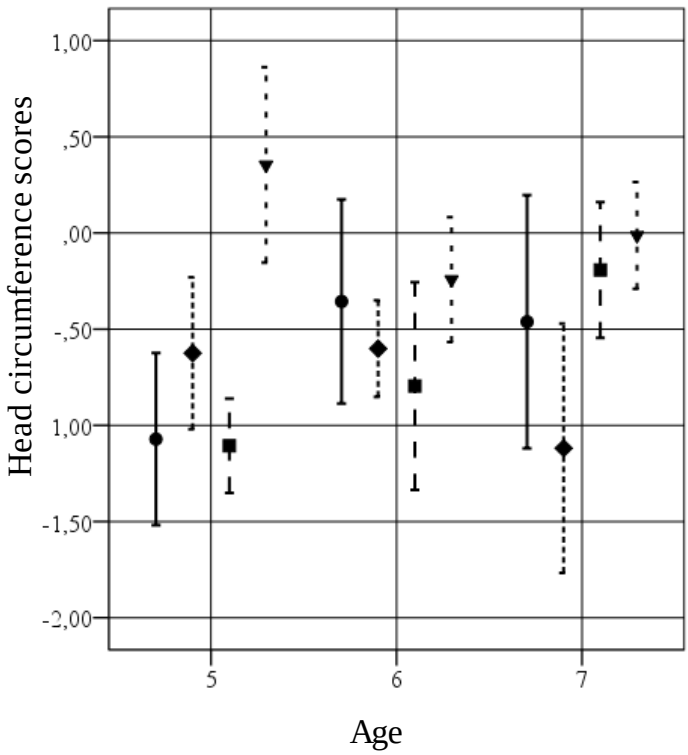


Figure 10. Comparison of standard head circumference scores among the groups with different eye condition and the control group in terms of age.

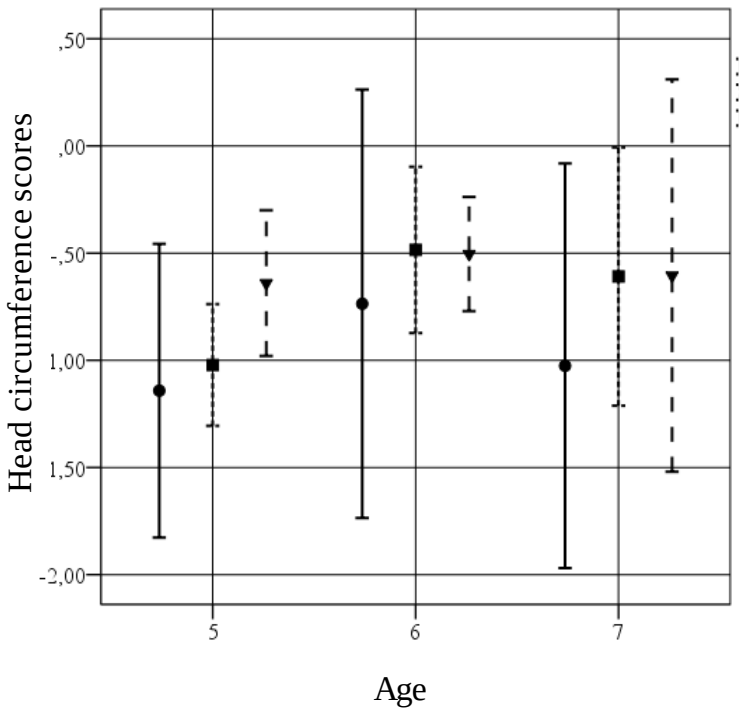


Figure11. Comparison of standard head circumference scores of preterm newborns with different birth weight in terms of age.

Also, we found that waist circumference scores in all age groups were lower than the mean of the population, however, with age disparities decreased (Fig.13-14). Lowest indices were identified with the five-year-olds with extremely low birth weight. Circumferences were moving towards the average indices unevenly – the increase in chest circumference was fastest, and that in hip circumference, by contrast, was slowest, which indicates slower hip growth in preterm children characteristic of all preterm preschool children regardless of their birth weight, though variation is not as vivid among children with higher birth weight.

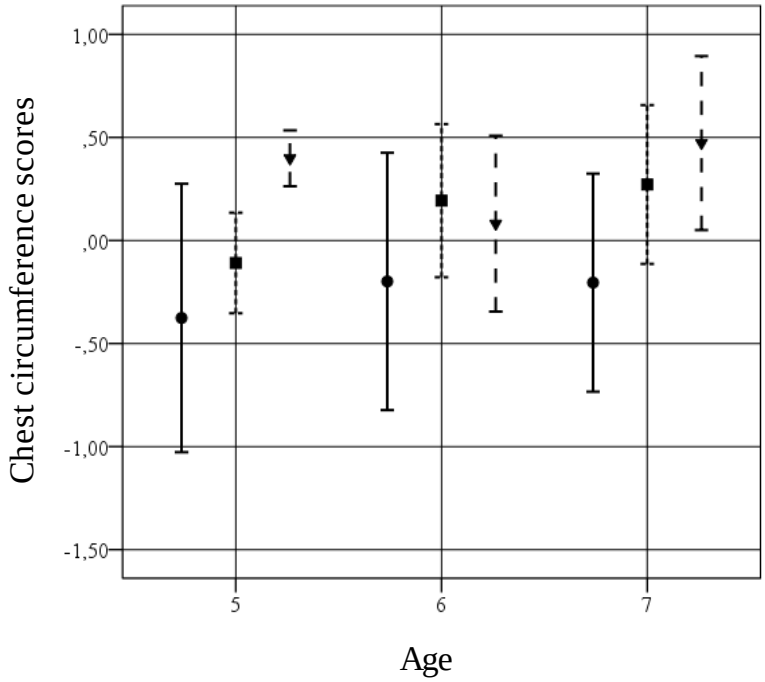


Figure12. Comparison of standard chest circumference scores of preterm newborns with different birth weight in terms of age.

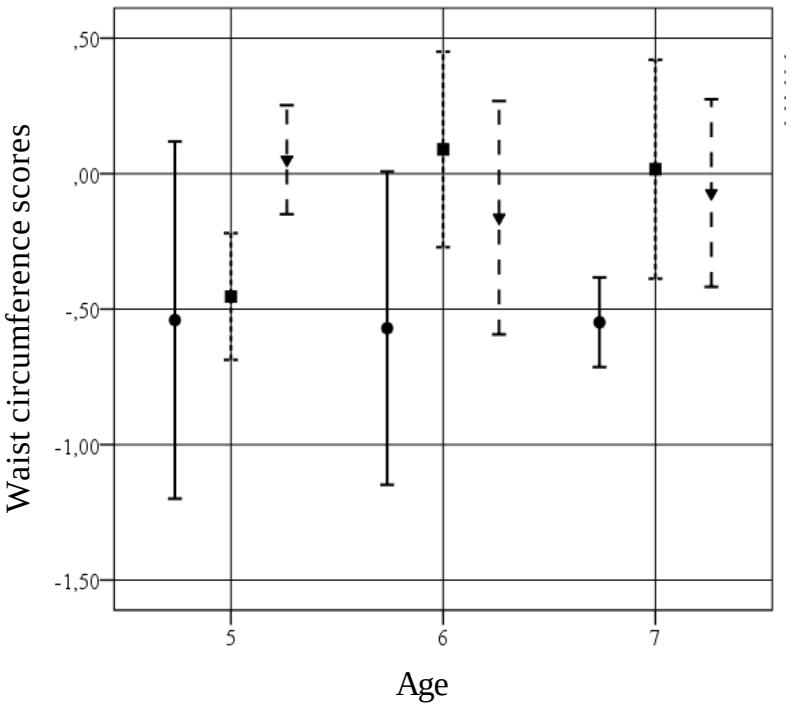


Figure13. Comparison of standard waist circumference scores of preterm newborns with different birth weight in terms of age.

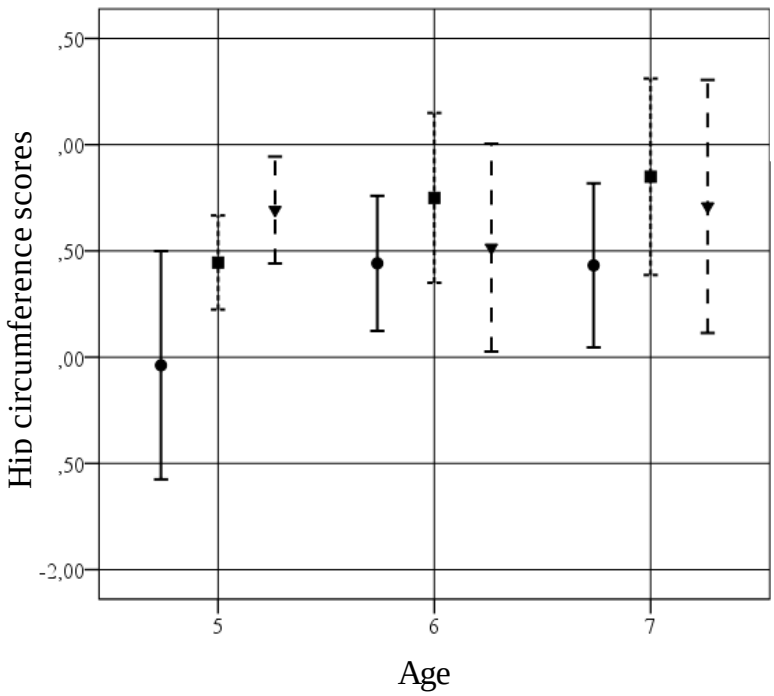


Figure14. Comparison of standard hip circumference scores of preterm newborns with different birth weight in terms of age.

The analysis of standard limb circumference indices demonstrated that arm circumferences practically did not differ from average indices, but the less was birth weight, the lower leg circumferences were and the more they lagged behind. This signifies the slowdown in the growth of the lower part of the body.

5.4.4. Skindfolds and other indices of body fat mass

Firstly, we compared subcutaneous fat and topography indices in preterm children of the age of 5 to 7 years considering their eye condition only (Table 14). It is established that the five-year-olds with ROP had significantly thinner limb skinfolds (triceps and medial calf), whereas at the age of seven years (after adiposity rebound) their mid-axillar skinfolds were significantly larger. Taking into account birth weight, it appeared that the five-year-olds with extremely low birth weight had thinnest skinfolds and the smallest amount of skinfolds, while the seven-year-olds with very low birth weight had the thickest skinfolds and the amount of skinfolds was the largest. The five-year-olds with extremely low birth weight and very low birth weight had significantly smaller relative amount of fat as compared to children born with weight above 1.5 kg. However, at the age of seven years the relative fat mass in both groups was remarkably larger, although we were unable to identify any statistically significant difference. The comparison of the fat centralisation index, though in many cases unreliable, revealed the fat centralisation tendency in preterm children with extremely low birth weight: the seven-year-olds with extremely low birth weight had the highest index.

Table 14. Average skinfolds, skinfold amount and derivative body composition indices of preterm children with ROP and without ROP and their comparison (t test).

Age	with ROP (all)	without ROP	P value
Abdominal skinfold, mm M(SN)			
5 years	7.3 (0.9)	7.2 (0.5)	0.8376
6 years	8.0 (1.2)	8.4 (0.7)	0.3368
7 years	11.1 (3.3)	8.7 (0.3)	0.0034
Suprailiac skinfold, mm M(SN)			
5 years	6.2 (0.8)	6.3 (0.5)	0.3403
6 years	7.2 (1.2)	7.1 (0.4)	0.7341
7 years	9.1 (2.5)	7.4 (0.3)	0.0064
Subcapular skinfold, mm M(SN)			
5 years	5.4 (0.8)	5.6 (0.3)	0.1552
6 years	6.0 (0.8)	6.4 (0.4)	0.1086
7 years	7.6 (1.5)	6.5 (0.3)	0.0075
Triceps skinfold, mm M(SN)			
5 years	8.9 (1.3)	9.5 (0.6)	0.0334
6 years	9.8 (1.5)	9.3 (1.0)	0.3138
7 years	12.6 (3.4)	10.8 (0.7)	0.0397
Front thigh skinfold, mm M(SN)			
5 years	12.1 (1.4)	12.0 (0.9)	0.8031
6 years	14.2 (1.9)	14.5 (0.9)	0.5170
7 years	16.3 (3.1)	16.1 (0.9)	0.8540
Medial calf skinfold, mm M(SN)			
5 years	7.6 (0.8)	8.2 (0.5)	0.0087
6 years	8.5 (1.0)	8.4 (0.6)	0.7791
7 years	10.2 (2.0)	9.0 (0.3)	0.0134
Amount of skinfolds, mm M(SN)			
5 years	47.4 (5.5)	48.9 (2.69)	0.2307
6 years	53.7 (6.6)	54.1 (3.54)	0.8475
7 years	66.8 (15.3)	58.4 (1.91)	0.0238
Relative body fat mass, % M(SN)			
5 years	14.1 (1.8)	14.6 (1.3)	0.3244
6 years	15.3 (2.2)	15.1 (1.8)	0.8241
7 years	18.5 (3.7)	16.7 (1.0)	0.0891
Fat centralisation index M(SN)			
5 years	0.61 (0.06)	0.59 (0.04)	0.3581
6 years	0.61 (0.07)	0.69 (0.06)	0.0297
7 years	0.62 (0.09)	0.60 (0.05)	0.6620

ROP – Retinopathy of prematurity

Table 15. Average skinfolds, skinfold amount and derivative body composition indices of preterm ROP children with different birth weight and their comparison (ANOVA).

Age	BW<1kg	BW=1-1.5 kg	BW>1.5 kg	P value
Andominal skinfold, mm M(SN)				
5 years	6.8 (0.8)	7.3 (0.8)	7.5 (0.5)	0.06
6 years	7.5 (1.5)	8.0 (0.6)	8.5 (1.2)	0.19
7 years	9.8 (3.3)	11.5 (3.3)	10.1 (3.1)	0.49
Suprailiac skinfold, mm M(SN)				
5 years	5.7 (0.9)	6.2 (0.7)	6.6 (0.5)	0.01
6 years	6.8 (0.8)	7.3 (1.3)	7.3 (1.1)	0.62
7 years	8.6 (2.4)	9.3 (2.5)	8.4 (2.4)	0.68
Subscapular skinfold, mm M(SN)				
5 years	4.9 (0.8)	5.6 (0.7)	5.7 (0.4)	0.01
6 years	5.5 (0.9)	6.1 (0.6)	6.2 (0.8)	0.13
7 years	7.3 (1.5)	7.7 (1.4)	7.1 (1.5)	0.64
Triceps skinfold, mm M(SN)				
5 years	8.3 (1.5)	9.0 (0.9)	9.8 (0.7)	0.00
6 years	9.7 (2.1)	9.5 (1.1)	10.0 (1.5)	0.75
7 years	11.7 (3.7)	12.8 (3.4)	11.9 (2.7)	0.75
Front thigh skinfold, mm M(SN)				
5 years	11.7 (1.6)	11.9 (1.1)	12.6 (1.1)	0.14
6 years	13.8 (2.1)	14.2 (1.7)	14.4 (1.9)	0.82
7 years	15.1 (3.0)	16.7 (3.1)	16.4 (2.4)	0.55
Medial calf skinfold, mm M(SN)				
5 years	7.3 (0.8)	7.6 (0.7)	8.4 (0.6)	0.00
6 years	8.5 (1.5)	8.4 (0.9)	8.5 (0.7)	0.95
7 years	9.9 (2.4)	10.4 (1.7)	9.4 (1.8)	0.57
Amount of skinfolds, mm M(SN)				
5 years	44.7 (6.1)	47.6 (4.3)	50.5 (3.2)	0.08
6 years	51.8 (8.6)	53.5 (4.6)	54.9 (6.5)	0.11
7 years	62.4 (16.0)	68.4 (14.6)	63.2 (13.4)	0.75
Relative body fat mass, % M(SN)				
5 years	13.9 (1.7)	13.9 (1.6)	15.1 (1.4)	0.01
6 years	14.9 (3.2)	15.0 (2.0)	15.7 (1.7)	0.61
7 years	18.0 (4.1)	18.8 (3.5)	17.4 (3.1)	0.64
Fat centralisation index M(SN)				
5 years	0.59 (0.05)	0.63 (0.07)	0.58 (0.04)	0.07
6 years	0.57 (0.05)	0.65 (0.07)	0.63 (0.07)	0.63
7 years	0.64 (0.09)	0.62 (0.10)	0.60 (0.07)	0.69

BW – birth weight

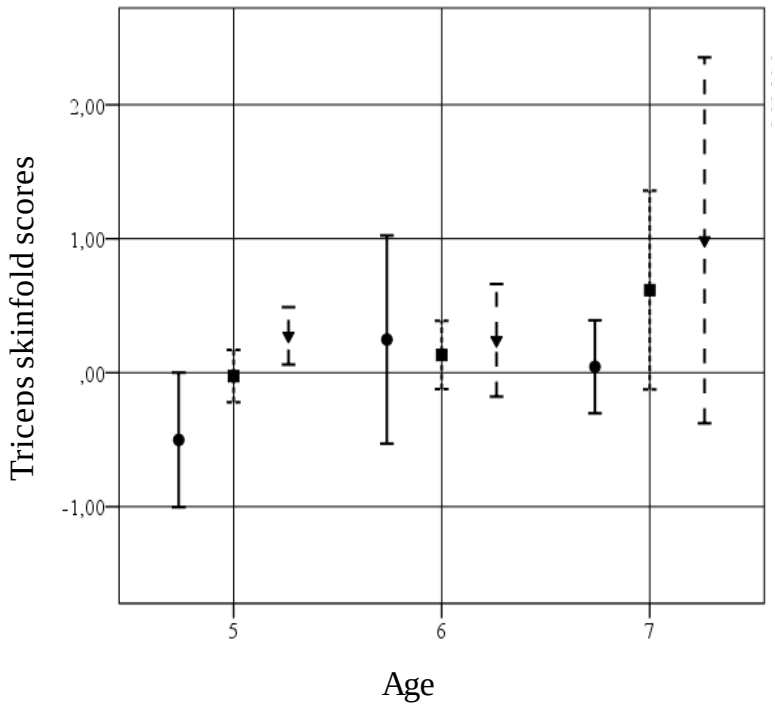


Figure15. Comparison of standard triceps skinfold scores of preterm newborns with different birth weight in terms of age.

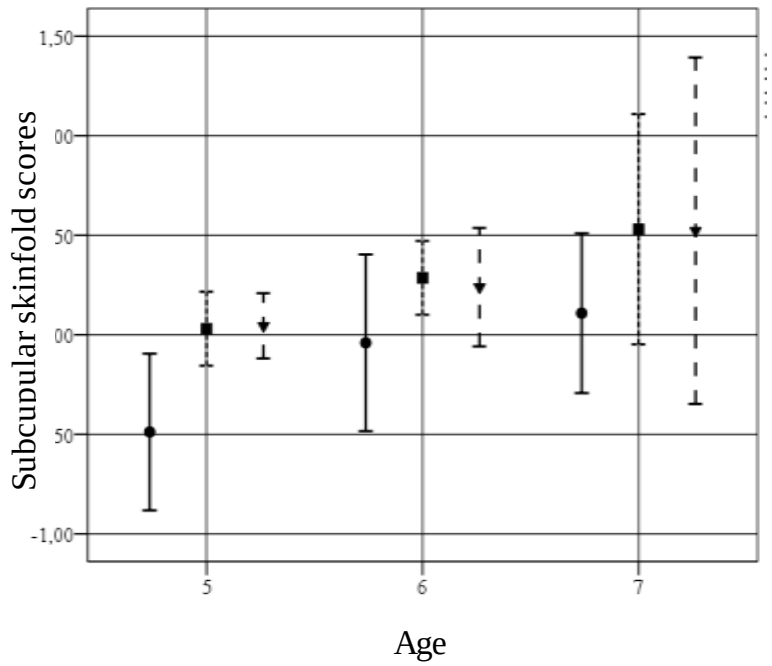


Figure16. Comparison of standard subcupular skinfold scores of preterm newborns with different birth weight in terms of age.

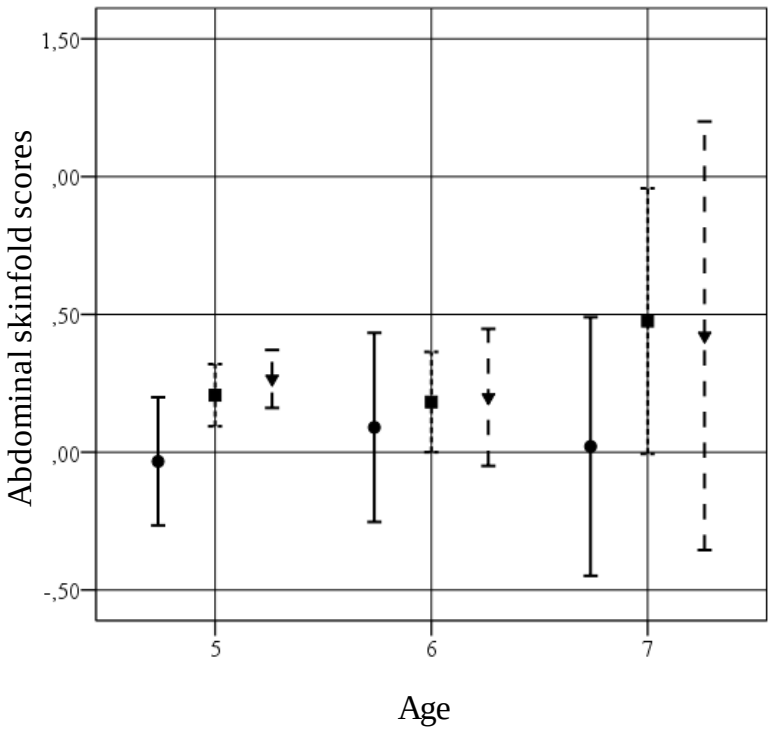


Figure17. Comparison of standard abdominal skinfold scores of preterm newborns with different birth weight in terms of age.

Standard skinfold scores were significantly negative only in ROP five-year-olds with extremely low birth weight, while in other age groups they approached the average or was higher irrespective of birth weight (Figures 15-17). The comparison of standard skinfold scores showed that preterm children, as compared to full term children, have a very similar amount of adipose tissue, and given that their body weight and BMI are lower, the relative fat amount is even greater. Differences between individual skinfolds and the average indicate that the topography of peripheral fat also varies: less fat is found on limbs (lower triceps skinfold values), and more fat is accumulated on the waist (higher abdominal and subscapular skinfold values).

To sum up the physical status of preterm ROP children with extremely low birth weight in the preschool period, it can be stated that the majority of indices of the five-year-olds with extremely low birth weight were significantly lower than the average. Height of children with extremely low birth weight reached the average at the age of six years, yet their weight and BMI remained lower, and adiposity rebound in children with extremely low birth weight and very low birth weight occurred earlier than in the case of children with low birth weight and full term children. Delay in other dimensions varied and demonstrated uneven growth; there was a particular backwardness as regards the skeletal size and indices of the lower part of the body. Head circumference in all preterm children was significantly lower than the average, independent of birth weight and did not approach the average of peers over the entire period in question. Fat amount in children with extremely low birth weight and low birth weight was comparable to that of full term peers, and at the age of seven years it accumulated rather centrally.

5.5 Multi-dimensional analyses

5.5.1. Regression analysis of the moment of birth, visual system and physical status of ROP children in the preschool period

Logistic regression was performed in order to evaluate the risk factors for impaired visual acuity. First, the uncorrected distance visual acuity model was analysed. Prior to that, the values for uncorrected distance visual acuity had been re-coded as follows: 1, when visual acuity (VA) exceeded 0.5, and 0, when VA was less or equal to 0.5.
For the analysis of distance visual acuity, we chose spherical equivalent, corneal astigmatism, depth of the anterior chamber, and thicknesses of the lens, retinal macula and central fovea as the independent variables. The analysis showed that only corneal astigmatism appeared to be a statistically significant independent variable (). The model explained 27-40% of total variation (the values of Cox-Snell R^2 and Nagelkerke R^2 were 0.271 and 0.404, respectively). The logistic regression model classified 84.5% of values correctly.
Statistical conclusion: if corneal astigmatism increases by 1 unit, then the probability for the uncorrected distance visual acuity to exceed 0.5 increases by 3.8 (the output value Exp(B)=3.817).
For the analysis of near visual acuity, we chose spherical equivalent, corneal astigmatism, depth of the anterior chamber, and thicknesses of the lens, retinal macula and central fovea as the independent variables. The analysis showed that once again only corneal astigmatism appeared to be a statistically significant independent variable ($p<0.05$). Therefore, the other variables were excluded from further analysis. The value of the Hosmer-Lemeshow test was $0.428>\alpha$, therefore this model matched our data and explained up to 35.7% of total variation (the values of Cox-Snell R^2 and Nagelkerke R^2 were 0.211 and 0.357, respectively).
We have later included several birth parameters in the analysis. It seemed that some of them (gestational age and head circumference at birth) were statistically significant ($p<0.05$). However, the applied model explained only 12% of total variation (based on evaluation of Cox-Snell R^2 and Nagelkerke R^2 values), thus the aforementioned model should not be applied. The anthropometric variables were statistically insignificant.
After spherical equivalent was added to multiple regression model as the main variable, it seemed that it was mainly influenced by corneal astigmatism, optical axis length and depth of the anterior chamber. All three variables were statistically significant ($p<0.05$). Other variables (thicknesses of the lens, retinal macula, central fovea and choroid) appeared to be statistically insignificant; therefore they were excluded from further analysis). The model explained 40% of total variation.

5.5.2. Analysis of the visual system and physical status factors (main components) in preschool children with ROP

Seven factors (principal components) that were able to explain more than 80% of total variation in ROP children's indices in the preschool period were found performing factorial analysis.

λ values of the variables in the matrix showed dependence between indices and corresponding components. The aforementioned dependence was considered significant if λ value exceeded 0.22; otherwise, we considered that there was no dependence between the variable and the factor. Five principal components seemed to determine the most of variation.

The first component determined the most of anthropometric indices; therefore it might be called the body size and active mass factor at preschool age. The second, or the adiposity factor, determined by the amount of fat tissue, was mostly associated with central fat at the age of 5-7 years. The third component, associated with children's optic system at the age of 5-7 years, determined both distance and near visual acuity and ocular parameters (thicknesses of the lens and central retina were negatively associated with visual acuity, while depth of the anterior chamber and corneal astigmatism – positively). The fourth, newborn maturity factor included gestational age and body size indices at birth; remarkably, there was a significant negative association between the component and thicknesses of retinal macula and central fovea at preschool age (the lower the gestational age was, the thicker the aforementioned parameters were at the age of 5-7 years). The fifth component supplemented the third one (the component associated with children's optic system at preschool age); it was associated with the length of optical axis at the age of 5-7 years (negatively), spherical equivalent (positively) and thicknesses of retinal macula and central fovea (a weak positive association was found). The sixth component in preschool period mainly determined central choroidal thickness and positively associated with other parameters of the body size, such as body height and other longitudinal dimentions. But it was associated negatively with BMI. It means the higher the BMI, the thinner central choroid. We consider that the seventh component is accidental. There was a positive association with ankle width and negative association with corneal astigmatism and central retina and fovea thickness.

Summing up the results of factorial analysis, it is possible to state that visual acuity in preschool children with ROP was mainly determined by the separate third factor that was associated with the ocular parameters. The latter was also partly associated with the variables of the fourth factor (newborn maturity factor). The ocular parameters such as thicknesses of central retina and central fovea and length of optical axis were associated with 3rd, 4th and 5th factors, spherical equivalent – with 3rd and 5th ones, corneal astigmatism – with 3rd and 7th factors. As it was stated previously, the thickness of central choroid was mostly (compared to all the other ocular parameters at preschool age) associated with physical indices. The factors that determined indices of body size and proportions were not much associated with the variables of the other factors.

In order to compare multiple associations between ocular and auxological parameters of preschool children with ROP and their healthy peers, we performed factorial analyses of the aforementioned variables without regard to data at birth. The analysis of the rotation matrices' principle components revealed that all tested ocular and physical variables in the control group were determined by more factors (8) compared to children with ROP at preschool age (6 factors); furthermore, visual acuity and other ocular indices in the control group were associated with 6 factors, while only 3 factors were associated with the aforementioned factors in children with ROP. In means that normal variety is determined by more factors; meanwhile in a case of pathology the body mainly concentrates on solving of a problem.

6. DISCUSSION OF THE RESULTS

Today preterm newborns with increasingly lower birth weight survive worldwide, but they are exposed to increased risk of developing certain chronic diseases in the future [2], [3]. Previous or current diseases and their lifelong effects have a dramatic impact on the child's further development, unbalanced growth and quality of life [53].
The world's literature provides little data about the peculiarities of physical development of preterm children of the preschool age and general connections with their visual system [41], [42]. This study looked into the present condition of children's visual system and its development and compared the findings with the data of their growth and physical status. We have carried out an integrated analysis of the physical status and condition of the visual system in preschool children.
The analysis revealed that in 2006-2008 the Children's Hospital diagnosed 150 newborns with ROP, including 26.5% treated both with cryotherapy and photocoagulation.

6.1. Eye condition and anthropometric indices of preterm children in the neonatal period

After grouping preterm children by eye pathology in the neonatal period, the retrospective analysis of anthropometric indices at birth showed that not only birth weight, but also BMI of children with severe ROP after birth was reliably lower than those of children with minor ROP or without ROP. Our study indicated that in Lithuania preterm newborns with not only extremely low birth weight, but also with very low birth weight can develop ROP, while the incidence was much lower among children with the weight above 1.5 kg. With regard to birth weight, we noted that ROP children, as compared to children without ROP, had reliably lower weight, however, no significant difference in birth height was observed among the groups with minor ROP and severe ROP. Head and chest circumferences in children with severe ROP at birth were also significantly lower than those in other subgroups. This retrospective analysis of anthropometric indices suggests that, in comparison with children without ROP, the most vulnerable children with severe or minor ROP had the shortest gestation and the lowest weight.

6.2. Visual system analysis in preschool period

Retinopathy of prematurity in its severe forms can cause visual impairment or can lead to blindness. It is one of the complications for the preterm birth, which affect visual system [34]. However, there are not enough studies about the visual system development and visual outcomes of prematurely born children after ROP at preschool age.
Few studies have shown that children born prematurely have an increased risk of visual impairment, higher incidences of low vision, strabismus, visual field defects and contrast sensitivity [38], [54], [55], [56], [57]. Those studies analyse visual functions of children at different ages. It is known that these children are more likely to have difficulties at school, they require significantly more educational assistance because they usually have lower

intelligence quotients and academic achievements scores [58]. Still there are discussions how often and how long these children should be on an ophthalmologist follow up and what are the risk factors for the visual system development [59].

In our study we found the difference between control group children and preterm group in the ophthalmological results in preschool period. Highest differences were in severe ROP group and the lowest birth weight children group. It means, that both lower birth weight and severity of ROP influence visual system and ophthalmological parameters at preschool age.

This study had proved that prematurely born children had poorer VAs than children born at term, especially severe ROP group had worst NCVA and BCVA for distance and near. In this group 3 (7,7%) children were visually impaired, but none was blind. All three children belonged to different group of birth weight (LBW, VLBW and ELBW). Therefore, we can conclude, that in Lithuania children even born at low birth weight can be visually impaired.

According to Larsson et al [39] in their study, where they investigated 10 years old preterm children, visual impairment was found in 4 (1,8%) of premature born children of whom 1 (0,4%) was blind [2]. Other authors concluded in their study greater visual impairment and blindness due to prevalence of ROP. In the study by Fledelius [60] from 411 preterm children there were 13 (3,2%) visual impaired, Darlow et al [61] in their study confirmed that from 337 preterm children group, 7% were visual impaired. There were various prevalences of visual impairment in different studies [60], [61], most of these children were blind due to ROP. Whereas none of these children was cryotreated, cause they had been born prior to recommendations of 'threshold disease' treatment was proposed.

Though VA for distance and near was poorer in preterm children than in children born at term, overall visual acuity outcome in our study of preterm children were good. Even 76.9% severe ROP group children had VA between 0.7 – 1.2. It is well known that VA reduction can be due not only to ROP, but preterm birth *per se*, the neonatal environment and neurological damage.

Fledelius [62] in his study has noted that children with neurologic complications had poorer VA, than those without. In accord with Darlow et al [63] and O'Connor et al [64] we didn't associate VA results to neurologic findings.

Nevertheless we didn't find any difference in BCVA in distance and near between children with mild ROP and children without ROP. Our VA findings are very similar with Swedish Population-based Study in prematurely born children at 10 years of age [39] where they noted that children who had received cryotherapy had the highest risk of a reduced VA. In present study, of ROP treated group 24 (61.5%) had been cryotreated, 14 (35.9%) – got both laser and cryotherapy, and 1 (2.6%) had been treated using only laser therapy. Therefore we couldn't exclude cryotherapy as separate treatment from other options, and can't compare results of different treatment groups.

Severe ROP group had worst NCVA and BCVA; likewise this group had a lower spherical equivalence (SE) mean value. This explains why in severe ROP group the prevalence of myopia and high astigmatism (≥2D) was significantly greatest. However, even no-ROP group had significantly more myopia than full term children at preschool age. This confirms the theory, that there are different patterns of myopia and it varies in onset, severity and features: myopia secondary to severe ROP, myopia of prematurity irrespective of ROP, and myopia as the result of arrested development of the anterior segment. The preterm born children had a higher prevalence of hypermetropia (>/=2D),

regardless of the severity of ROP. But it didn't reach statistically significant difference when we compared with control group. The analysis of our study revealed that significant astigmatism (≥1D - <2D) and anisometropia were more frequent and greater in all premature groups than in the control group, even in no-ROP group. But severe ROP group had the highest prevalence of high astigmatism (>/= 2) and anisometropia. It would be possible to discuss whether high astigmatism was determined by advanced ROP stage or cryotreatment per se. Unfortunately, we are unable to answer this question in our analysis, cause all children who needed the treatment, matched the criteria underwent cryotreatment. Swedish population-based study [65], [39], [66], [67] had confirmed that the stage of ROP and cryotreatment per se were identified as risk factors for astigmatism of 1D. In Quinn et al [68] study the results showed a tendency for a higher frequency of astigmatism of 1D or more in treated eyes than untreated.

Strabismus, anisometropia and amblyopia make a huge influence on visual system development. In our study mostly of these changes were seen in severe ROP group, less in mild ROP group. We agree with other studies [36] [69] and conclude that in the severe ROP group amblyopia was found very often ($p<0,0005$), as well as strabismus ($p<0,001$). In preterm children group high prevalence of strabismus may be associated with poor muscular system – it is confirmed by the results of anthropometric analyses. Evaluation of optical components in prematurely born children at preschool age showed a steeper corneal curvature in severe ROP group. In severe and mild ROP groups' children had shallower anterior chamber depth (ACD) and greater LT ($p<0,01$). Same variations of optical components were found in the group of the smallest birth weight children. Other authors in their studies found similar changes of anterior segment, although the different children age [70]. We found that severe and mild ROP groups had shortest ALs, but there was no birth weight influence on AL. There were given different results from the researches that evaluated AL in preterm children with and without ROP. Chang-Sue Yang et al. [70] didn't find the difference in axial length between the two groups. In the study of preterm children aged 7 to 9 years Ta-Ching Chen [71] found insignificant difference in AL from the control group, but ALs were much more variable in the preterm group.

Our study provided analysis and unique findings about refractive errors development on premature children with ROP. It demonstrated significant refractive errors in preterm ROP group children. It is well known that myopia associates with ROP. But the main mechanism is still not well understood. Some studies have found that high refractive errors are not due to increased axial length, rather it might be related to changes in the anterior segment [71], [72]. However, prematurity per se, may affect ocular development and influence the emmetropization process. Even our study confirms it. Secondary, because of the arrested development of anterior segment, we observed steeper corneal curvature, shallow anterior chamber and greater lens thickness in children with advanced ROP. It is anterior segment changes, not AL elongation. Our and others researchers' studies agree that premature characteristics of anterior segment components may persist until school age [73], [71]. All these changes in the anterior segment can influence future developments of glaucoma, cataracta or other ocular diseases [74], [75], [76].

There are studies that showed the affects of prematurity not only for anterior segment, but also for the retina [70], [77] optic nerve [78], [79] and visual cortex [80]. In our study we evaluated the central retina thickness, foveal thickness and choroidal thickness using Heidelberg Engineering Spectralis OCT. Our results revealed that central retina

thickness and foveal thickness were significantly thicker in prematurely born children than control group, especially thick retina was found in severe ROP group. OCT imaging showed quantitative modifications in the macular structure – foveal depression became smooth. These changes could reflect mainly the interrupted development of the eye. Moreover, the results showed that even no-ROP group had significantly thicker retina than control group. But there were no differences between the parafoveal and perifoveal circles in all groups. Our results coincide with the Swedish study [81], although their results showed thinner retina in comparison with our results. It might be because of different OCT devices; different children age or even these differences could be caused by distinct development of the retina after previous different treatments.
In preterm children we found significantly thinner choroid than in full term children, especially in severe ROP group. We agree with Vrabec et al [82] that choroidal atrophy could be due to cryotherapy, but mild ROP group had thinner choroid as well. Choroidal involution in ROP remains under investigation. There is a theory that the cause could be vaso-obliteration, affecting choroidal thickness [83].

6.3. Analysis of anthropometric indices in the preschool period

The comparison of anthropometric indices among groups with different eye condition gave no clear results, as the groups consisted of children with varied birth weight: newborns with extremely low birth weight, very low birth weight and low birth weight suffered from both severe and minor ROP. When comparing indices among subgroups with different eye condition, differences were less noticeable and often insignificant, though children aged between 5 and 6 years both with ROP and without ROP remained behind the average population in terms of certain indices. More distinct differences in anthropometric indices were established among the groups of preterm newborns with varied birth weight: children with extremely low birth weight stayed behind most and longest, whereas those with birth weight of 1.5 kg and more lagged behind insignificantly.
It also appeared that it was inappropriate to compare anthropometric indices of preterm children with the control group, as those in the control group did not reflect the average of the population and the majority of the indices were much higher. Such results could be determined by too low a sample of the control group, which included only children higher than the average of the population; the ongoing acceleration of height in preschool children, which is as well recorded in other studies of researchers from the Department of Anatomy, Histology and Anthropology of the Faculty of Medicine of Vilnius University [84], could also have influence of the results.
Nevertheless, it can be said that there should be no major differences between the control group and the average population with regard to eye condition indices. When comparing various eye parameters by age and gender of the subjects, also morphometric indices of the left eye and the right eye, our study did not identify any remarkable variations. The statement is also supported by the results of the multi-dimensional analysis, which revealed that eye condition and body parameters practically have no interconnection. To conclude the analysis of the standard Z scores for the anthropometric indices of preterm children, it is clear that differences between anthropometric indices of preterm children and average indices of healthy children between 5 to 7 years of age are gradually decreasing: the most of significant differences were found among the five-year-olds and

the least were observed among the seven-year-olds. Indices do not change in the same way – the majority of children catch up the average height, but still have lower weight and BMI and smaller bones, and most of them have average or larger amount of fat, especially central fat.

Such results indicate that at the age of 5 to 7 years preterm children are still in late growth, which is also supported by the results of longitudinal studies: the standard scores for height and weight of American preterm children with very low birth weight at the age of eight years were –0.5 (boys) and –0.2 (girls) and approached the mean of the population as compared to the same indices at the age of 20 months [85]; in Sweden the standard scores for height and weight of very premature children (born before gestation week 26) at the age of ten years were –0.7 and –0.2 (boys) and –0.4 and –0.2 (girls) and moved towards the mean of the population as compared with the indices at the age of two years [85]. It should be noted that BMI (and accordingly weight) indices of preterm children of the preschool age fall significantly behind the average, except for the seven-year-olds born heavier than 1.5 kg. It is also important that adiposity rebound in preterm children, save for those with birth weight above 1.5 kg, was earlier than that of full term children and children with higher birth weight. This signals faster accumulation of fat, which is also confirmed by the dynamics of individual skinfolds, amount of fat and relative body fat mass. The results showing that skinfolds grow faster in preterm children than body weight were also published by other groups of researchers [86]. It also appeared that preterm children are prone to accumulate central fat. Departing of the majority of measured body and limb circumferences from the average population, where the amount of fat is much the same, indicates that preschool children born prematurely have less lean body mass, especially muscles. Smaller lean body mass of preterm children at an older age and in their adulthood was also determined by researchers with the help of more complex research methods [16], [87], [88]. Particularly distinct differences were identified in all age groups of children with extremely low birth weight, for this reason, the seven-year-olds with extremely low birth weight may demonstrate worse functional muscle indices that might cause delay in both gross motor and fine motor skills and interfere with the child education process at school. Delay in head circumference of preterm children as compared to the average population is also evident: head circumference was heavily influenced by birth weight and practically did not change with age; similar delay was observed in all age groups.

On the other hands, eye condition indices significantly depended on whether a newborn suffered from ROP and its severity degree. Such results suggest that body growth and the development of the visual system are affected not only by the same, but also some other factors, a more intense growth of eyes is observed earlier, just as the growth of CNS [32]. At the preschool age the condition of the visual system is most influenced by previous pathology, and the worst outcomes are for children who suffered from more acute disease and received treatment. Those children generally had extremely low birth weight or very low birth weight.

6.4. Multi-dimensional analysis of the moment of birth, visual system and physical status in preterm children with ROP

The factor analysis revealed that visual acuity in preterm children with ROP at preschool age was mostly determined by the separate third factor and to a certain extent by the fifth factor of some other eye parameters, which only partly related to the maturation of a newborn. Interestingly, out of all eye parameters at the preschool age, the central choroidal thickness was most linked to the key indices of the physical status and had most commonalities with other variables of the visual system and maturation of a newborn, therefore, this parameter could be interpreted as the most multi-dimensional and multi-functional (its development relies on a number of complementary factors). Not all visual system and eye parameters were closely related within a single component: visual acuity and such eye parameters as central foveal thickness, central retina thickness and axial length were largely associated with three factors, while lens thickness, anterior chamber depth, corneal astigmatism and spherical equivalent correlated to two factors. On the other hand, body size and proportions were basically influenced by two separate factors – first and second – which have little to do with the indices of the visual system in the preschool period.

It can be assumed that in the ontogenic process in premature children the organism invested maximum resources to safeguard optimal development of the visual system (the three generally unrelated factors determined visual system parameters at the preschool age), but sacrificed come other less vitally important indices of the physical status. This hypothesis was also partially complemented by the comparison of the main components of rotated matrices, made as part of the factor analysis of preterm and full term children of the preschool age, irrespective of birth data of the subjects.

Unfortunately, our results are not comparable with the data obtained by other authors, as we did not come across any similar studies in the literature concerned. However, our research verifies the conclusions of several studies on the growth of preterm newborns suggesting that children with very low birth weight are susceptible to metabolic syndrome and central obesity [17], [18], [89].

This research for the first time revealed the specific characteristics of the visual system and physical status of the preschool children prematurely born and affected by ROP: it is evident that such children should not enter school under the age of 7 (on a case-by-case basis, some of those could be recommended even a later start of schooling). We can see that scientific literature and described studies dealing with further development of children with ROP and their certain systems do not offer any solution as to how often and which medical specialists should pay a greater attention to those children. To sum up the study, it can be concluded that ophthalmological and paediatric care of those children should be provided more often than recommended for full term children according to Annex 3 to Order No 301 of the Ministry of Health of the Republic of Lithuania of 31 May 2000 [45]. Given that such children are prone to a number of health problems, continuous and regular consultations of not only an ophthalmologist, but also a cardiologist and endocrinologist could be recommended.

6.5. Strengths and weaknesses of the study

The major strength of this study is the in-depth ophthalmological and anthropometric study on preterm children with ROP at the preschool age, which relates the current condition of the visual system and physical status of each child with his eye and body size indices at birth. The most important finding is that this study identified interconnections between different body parameters and indices of the visual system on the basis of the factor analysis.

Unfortunately, we were unable to examine a sufficiently numerous group of premature children without ROP, which would correspond to the sample of children with ROP by birth parameters, thus it was hard to compare the body size of preterm children with ROP and without ROP at the preschool age in connection with their birth weight. For the purpose of the comparative analysis of ophthalmological indices, the group of preterm children without ROP was sufficient, as there was no need to group them by age. However, the analysis of anthropometric indices is not feasible without taking into account age – at this point age dynamics is particularly important given that the growth continues at the preschool age and, moreover, rapidly catches up in preterm children.

Considering that certain problems with the visual system are also caused by premature birth, it would be appropriate to conduct a detailed study on the parameters of the visual system and body growth in preterm children without ROP and to compare the results with the data of full term children.

7. CONCLUSIONS

1. In 2006-2008, the Children's Hospital treated 876 preterm newborns, including 150 (17%) newborns diagnosed with ROP, 78 (52%) newborns with acute ROP and 77 treated by surgery.

2. Newborns with both acute and minor ROP had shorter gestation and lower weight as compared to babies not affected by ROP. The birth weight, BMI, chest and head circumference of newborns with acute ROP were significantly lower than those in the case of minor ROP or absence of ROP.

3. Given the eye condition alone, the functional and biometric indices of the eye condition of children at preschool age with ROP remarkably varied as compared to those in the case of children not affected by ROP and maturely born children: within the group of children with severe ROP the uncorrected and the best corrected visual acuity appeared to be worst, and SE was lowest; the majority of children had myopia, high astigmatism (≥2D), amblyopia and strabismus. In the groups of both forms of ROP the depth of the anterior chamber was substantially shallower, while the lens was thicker. The retina of those children was remarkably thicker and the choroid was thinner.
   With regard to the birth weight of children with ROP, it was established that in the case of children with extremely low and very low birth weight refractive errors and amblyopia were significantly more prevalent. The retina in these children groups was remarkably thicker, and choroid was thinner than that in the group of children with low birth weight.

4. a. With mere regard to the eye condition, no significant differences between preterm children with ROP and unaffected by ROP in connection to their anthropometric indices; a number of indices of those children (except for head circumference and some other circumference values) did not differ reliably from the average of the population, whereas the indices of the preterm five-year-olds, by contrast, fell behind.
   b. As regards the birth weight of children with ROP, it was established that the height of children with very low and low birth weight in all age groups approximated or even exceeded the average of their Lithuanian healthy peers, the weight and BMI caught up with the indices of healthy peers at the age of 7 years, adiposity rebound of children with very low birth weight remained the same, while in the case of children with low birth weight it coincided with adiposity rebound for healthy children.
   c. The head circumference among all groups of birth weight of children with ROP was significantly smaller than the average of the population in all age groups. The hip and lower limb indices for all children with ROP (diameters and circumference values) increased slower than those of the upper torso and upper limbs.
   d. The majority of anthropometric indices of five-year-olds with extremely low birth weight significantly lagged behind the average of the population; with the age the differences decreased in an uneven pattern: the average of height of six-

year-olds with extremely low birth weight caught up with the average of the population, but those children still had lower weight and BMI, their body circumference values and some indices of the skeletal size were lower, and skinfolds were relatively larger in all age groups. Children with extremely low birth weight had less lean body mass, but earlier adiposity rebound, and there was relatively more centralisation of the adipose tissue. Hence, the body size, composition and proportions of children with extremely low birth weight in the preschool period were rather associated with properties typical of metabolic syndrome and the so-called sparing phenotype.

5. The physical condition of preterm children with ROP at birth, body size, central adiposity and eye condition in the preschool period were influenced by a variety of factors (relationships determined by different factors were identified):
    - According to logistic regression, visual acuity in the preschool period was largely dependent on the corneal astigmatism.
    - According to the factor analysis:
        a. The indices of the body size, proportions and central adiposity of children with ROP in the preschool period were determined by factors loosely related to the variables of other factors; in addition, the first two factors of the physical condition clarified almost 50% of the total variation of the indices in question;
        b. Visual acuity on the preschool period was largely determined by a separate factor which was only partly related to the maturation variables of a newborn and explained nearly 12% of the total variation of the indices in question;
        c. Out of all eye parameters, the central choroidal thickness in the preschool period was most associated with the indices of the physical condition;
        d. The visual system and the body are developed in parallel, however specific mechanisms exist to ensure proper and efficient development of the said systems, focusing primarily on the correction of the system, which is functionally more important (vision).

Table 38: Rotated component matrix of the physical status and visual system factors in preterm newborns with ROP at birth and 5 to 7-year-olds. Rotation method: Varimax with Kaiser Normalisation.
The closest "weight" values determined by one factor are highlighted.

Characteristics features	The main components (factors)						
	1	2	3	4	5	6	7
Weight (now)	,909	,300					
Elbow width	,902						
Chest circumference(now)	,901						
Waist circumference	,870						
Shoulder breadth	,855					,265	
Hip circumference	,852	,368					
Knee width	,850	,277					
Wrist width	,844						
Hip breadth	,836					,282	
Arm circumference	,812	,378					
Calf circumference	,804	,319					
Chest breadth	,794						
Thigh circumference	,789	,453					
BMI (body mass index)	,759					-,455	
Height (now)	,741	,268				,527	
Head circumference (now)	,733						
Chest depth	,727						
Front thigh skinfold	,690	,668					
Leg lenght	,640	,263				,606	
Abdominal skinfold	,573	,783					
Medial calf skinfold	,568	,770					
Sum of skinfolds	,645	,757					
Triceps skinfold	,590	,751					
Subscapular skinfold	,636	,700					
Suprailiac skinfold	,636	,670					
BCVA (distance)			,881				
BCVA (near)			,827				
Lens thickness			-,821				
Anterior chamber depth			,813				
Astigmatism			,792				-,366
Central retinal thickness			-,671	-,407	,283		-,230
Foveal thickness			-,541	-,440	,384		-,258
Birth weight				,917			
Head circumference(birth)				,835			
Height (birth)				,816			
Gestational age			,275	,807			
Chest circumference (birth)	,266			,754			
Spherical equivalent			,407		,788		
Axial length			,270	,302	-,748		
Choroidal thickness					,227	,478	
Ankle width							,809
Variations %	**36,47**	**12,44**	**11,52**	**10,24**	**4,15**	**3,75**	**3,08**
Total variantion %	**36,47**	**48,91**	**60,43**	**70,67**	**74,82**	**78,57**	**81,65**

Table 39: Rotated component matrix of the physical status and visual system factors in preterm 5- to 7-year-olds with ROP. Rotation method: Varimax with Kaiser Normalisation.
The closest "weight" values determined by one factor are highlighted.

Characteristics features	The main components (factors)					
	1	2	3	4	5	6
Chest circumference (now)	,876	,296				
Elbow width	,872	,282				
Wrist width	,858					
Weight (now)	,843	,449				
Waist circumference	,842	,305				
Shoulder breadth	,800	,337			,311	
Knee width	,788	,419				
Hip breadth	,773	,294			,320	
Chest breadth	,772	,249				
Hip circumference	,766	,515				
Calf circumference	,740	,456				
Arm circumference	,739	,520				
BMI (body mass index)	,723	,348			-,449	
Head circumference (now)	,713	,295				
Chest depth	,685	,345				
Thigh circumference	,682	,593				
Height (now)	,677	,366			,590	
Leg lenght	,577	,343			,664	
Medial calf skinfold	,410	,869				
Sum of skinfolds	,495	,863				
Triceps skinfold	,446	,850				
Subscapular skinfold	,503	,802				
Front thigh skinfold	,555	,782				
Suprailiac skinfold	,499	,774				
BCVA (distance)			,908			
BCVA (near)			,854			
Lens thickness			-,811			
Anterior chamber depth			,801			
Astigmatism			,781			-,370
Central retinal thickness			-,684	,516		-,239
Axial length			,233	-,763		-,240
Spherical equivalent			,482	,736		
Foveal thickness			-,550	,627		-,255
Ankle width			-,204			,714
Choroidal thickness		-,206	,213		,409	,436
Variations %	**34,18**	**20,996**	**13,212**	**5,393**	**4,531**	**3,447**
Total variantion %	**34,18**	**55,178**	**68,390**	**73,782**	**78,31**	**81,761**

Table 40: Rotated component matrix of the physical status and visual system factors in full term 5- to 7-year-olds (control group). Rotation method: Varimax with Kaiser Normalisation. The closest "weight" values determined by one factor are highlighted.

Characteristics features	The main components (factors)							
	1	2	3	4	5	6	7	8
Shoulder breadth	,925	,217						
Chest circumference (now)	,898							,221
Weight (now)	,893	,270				,267		
Height (now)	,884						-,247	
Waist circumference	,876							
Hip breadth	,834	,268						
Elbow width	,818	,254						
Leg lenght	,814						-,325	
Knee width	,806						,417	
Chest breadth	,798							,368
Calf circumference	,780	,230				,233		
Thigh circumference	,778	,443						
Hip circumference	,764	,501						
Wrist width	,763	,359						
Ankle width	,749							
Arm circumference	,749	,319					,317	,242
BMI (body mass index)	,660	,323				,375	,327	
Chest depth	,624	,322	,270			,296		,249
Triceps skinfold	,389	,841						
Abdominal skinfold	,374	,840						
Front thigh skinfold	,441	,755					-,287	
Medial calf skinfold	,384	,754						
Subscapular skinfold	,628	,660						
Antrerior chamber depth			,805				,222	
Axial length	,370	-,283	,769					
Spherical equivalent			-,745				,336	
BCVA (distance)	,235		-,694			-,292		,423
Suprailiac skinfold				,929				
Sum of skinfolds	,257	,479		,785				
Lens thickness	-,245		-,354	,556			,220	
Foveal thickness					,951			
Central retinal thickness					,914			
Astigmatism	-,247					-,774		
Head circumference (now)	,487					,521		,385
Choroidal thickness							-,643	
BCVA (near)			,292	-,271			-,276	,739
Variations %	**37,18**	**13,01**	**7,8**	**5,76**	**5,71**	**4,55**	**4,49**	**4,36**
Total variantion %	**3,18**	**50,19**	**57,99**	**63,75**	**69,46**	**74,01**	**78,49**	**82,85**

8. SUMMARY IN LITHUANIAN

Įvadas

Naujos medicinos technologijos ir gerėjanti gydytojų kvalifikacija lemia aukštos kokybės perinatalinę ir neonatologinę priežiūrą, dėl kurios pastaruoju metu didėja vis mažesnio svorio neišnešiotų naujagimių išgyvenamumas. Pasaulyje naujagimių mirtingumas dėl neišnešiotumo komplikacijų 2013 metais sudarė 15 proc. visų iki 5 metų amžiaus vaikų mirčių. Neišnešiotumas – didžiulė problema, dėl kurios 2013 m. mirė apie 1 milijonas vaikų (2014–2015 metų duomenys dar nėra skelbiami). Manoma, kad iki 2030 metų jį pavyktų sumažinti iki 3,4 proc. Tarptautinis 184 šalių tyrimas atskleidė, kad per anksti pasaulį išvysta 11 proc. pasaulio vaikų, tai yra kasmet 15 milijonų kūdikių gimsta neišnešioti. Kuo nebrandesnis gimsta naujagimis, tuo didesnis pavojus gresia jo gyvybei ir sveikatai. Tad priešlaikinis gimimas išlieka didelė problema, kuri spręstina bendrais ir suderintais veiksmais pasaulio mastu.

Daugiau nei prieš dvidešimt metų (atkūrus nepriklausomybę), Lietuvoje buvo pradėtos taikyti naujausios naujagimių intensyviosios terapijos metodikos ir steigiami nauji neišnešiotų naujagimių skyriai. Pradėjo gerėti neonatologinė pagalba ir neišnešiotų naujagimių priežiūra bei išgyvenamumas. Lietuvoje neišnešiotų naujagimių skaičius pastarąjį dešimtmetį svyravo mažai ir buvo ~5,3–5,4 proc., 2015 metais šis skaičius išliko stabilus, 5,4 proc., labiausiai kito 32–36 savaičių gestacinio amžiaus naujagimių skaičius. Dėl nebrandžių naujagimių organų ir jų sistemų pasireiškia įvairių funkcijų nepakankamumas, o dėl nebrandžios tinklainės – regos sistemos sutrikimai, dažnai lemiantys ir aklumą. Net ir naujagimiui pasveikus, persirgtų ligų pasekmės gali neigiamai veikti tolesnį augimą, motorinę ir psichoneurologinę raidą. Neišnešiotiems vaikams augant ilgainiui gali išryškėti įvairios sveikatos problemos, kurios trikdo vystymąsi ir blogina gyvenimo kokybę, apsunkina mokymąsi ir adaptaciją visuomenėje. Tačiau neišnešiotiems naujagimiams būdingi ir tokie sutrikimai, kurie netrukdo jų išgyvenamumui, nesunkina būklės pirmosiomis savaitėmis, bet jų pasekmės gali labai bloginti gyvenimo kokybę. Viena iš tokių ligų yra neišnešiotų naujagimių retinopatija. Neišnešiotų naujagimių retinopatija (NNR) – tai nesubrendusios, neišsivysčiusios tinklainės liga, kurios nedidelė, bet reikšminga baigčių dalis gali lemti aklumą. Neišnešiotų naujagimių tinklainė nėra iki galo vaskuliarizuota, ir tinklainės nesubrendimo laipsnis priklauso nuo naujagimio nebrandumo gimimo metu. Šiandien yra manoma, kad pagrindiniai veiksniai, nulemiantys NNR atsiradimą, yra mažas gimimo svoris ir mažas gestacinis amžius, taip pat NNR atsiradimo riziką labai padidina deguonies terapija. NNR paplitimas labai skiriasi išsivysčiusiose ir besivystančiose šalyse: išsivysčiusiose šalyse siekia 5–8 %, o besivystančiose – net 30 %. Nežiūrint tobulėjančios medicinos ir atsirandančių naujų gydymo galimybių, NNR tam tikrose pasaulio šalyse užima pirmą vietą vaikų aklumo priežasčių tarpe. Ši liga lemia 3–11 % regėjimo praradimo išsivysčiusiose šalyse ir net 11–60 % – trečio pasaulio šalyse [34]. Neišnešiotų naujagimių retinopatija pradėta diagnozuoti ir gydyti Vilniaus universitetinėje vaikų ligoninėje 1994 m. Vėlesniu dešimtmečiu, išgyvenant vis didesniam skaičiui neišnešiotų naujagimių ir gerėjant NNR diagnostikai, šios ligos paplitimas labai išaugo. Pastaruoju metu NNR diagnozuojama rečiau, bet ši liga nėra išnykusi.

Neišnešiotų naujagimių, sirgusių retinopatija, raida ir augimas vėlesniais ontogenezės laikotarpiais mažai tyrinėtas ne tik Lietuvoje, bet ir pasauliniu mastu. Vaikų, kurie gimė neišnešioti ir sirgo NNR, akių būklės kitimo augimo laikotarpiu studijų yra nedaug, o darbų, kurie kompleksiškai nagrinėtų neišnešiotų naujagimių retinopatijos dinamiką siejant ją su kitais auksologiniais rodikliais, beveik neaptikome. Pagal bendruosius augimo dėsnius ir pastaraisiais dešimtmečiais atliktas studijas, neišnešiotų naujagimių fizinė būklė labiausiai priartėja prie išnešiotų vaikų augimo rodiklių priešmokykliniu laikotarpiu. Tačiau lieka neaiški sirgusių NNR neišnešiotų naujagimių raida ir būklė prieš pat mokyklą, taip pat individuali tokių vaikų augimo įvairovė, jų regos sistemos ir fizinės būklės branda, sąsajos tarp šių rodiklių, pasirengimas mokyklai pagal pastaruosius biologinius parametrus. Tiek pasauliniu mastu, tiek Lietuvoje iki šiol nebuvo atlikta kompleksinių tyrimų, nagrinėjančių neišnešiotų naujagimių regos sistemos ir fizinės būklės ypatumus, vėlyvąsias buvusios NNR baigtis po gimimo, sirgusių NNR vaikų regos sistemos ir auksologinių rodiklių sąsajas priešmokykliniu 5–7 metų laikotarpiu.

Darbo aktualumas ir mokslinis naujumas

Šiame darbe pirmą kartą nustatyti neišnešiotų, NNR sirgusių vaikų vėlyvieji regos sistemos bei fizinės būklės ypatumai priešmokykliniu 5–7 metų amžiaus tarpsniu, atsižvelgiant į pastarųjų rodiklių būklę gimus ir retinopatijos sunkumą (panaudojant tų pačių vaikų retrospektyviuosius duomenis, surinktus iš 2006–2008 metų ligos istorijų). Gimusių neišnešiotų, NNR sirgusių 5–7 metų amžiaus vaikų akių būklei ištirti buvo panaudotas vienas moderniausių tinklainės ir gyslainės tyrimo metodų – optinė koherentinė tomografija (OKT). Išsiaiškinti tolesnės regos sistemos raidos rizikos veiksniai, individuali tokių vaikų augimo įvairovė. Išanalizuotas skirtingų buvusių NNR stadijų ryšys su vaiko regos sistemos būkle priešmokykliniu laikotarpiu. Pirmą kartą atlikta neišnešiotų vaikų, sirgusių NNR, kompleksinė daugiamatė regos sistemos ir fizinės būklės sąsajų analizė, kuri suteikė naujų neišnešiotų naujagimių ontogenezės žinių: gimimo metu nesubrendusio regos organo ir viso kūno raidos panašumų ir skirtumų.

Darbo tikslas ir uždaviniai

Darbo tikslas - vaiko raidos aspektu įvertinti gimusių neišnešiotų vaikų, sirgusių NNR, vėlyvųjų regos sistemos bei antropometrinių rodiklių sąsajas priešmokyklinio amžiaus laikotarpiu, atsižvelgiant į šių rodiklių būklę gimus ir NNR sunkumą.

Darbo uždaviniai:

1. Retrospektyviai įvertinti 2006–2008 metais Vilniaus universiteto Vaikų ligoninėje gydytų neišnešiotų naujagimių regos sistemą: NNR dažnį, sunkumą ir gydymo taktiką.
2. Retrospektyviai įvertinti neišnešiotų sirgusių NNR naujagimių pagrindinius antropometrinius rodiklius ir juos palyginti su neišnešiotų naujagimių, nesirgusių NNR, atitinkamais rodikliais.

3. Ištirti priešmokyklinio amžiaus vaikų, sirgusių NNR, pagrindinius regos sistemos funkcinius ir biometrinius rodiklius, atsižvelgiant į buvusį NNR sunkumą bei gimimo svorį, ir gautus duomenis palyginti su neišnešiotų nesirgusių NNR vaikų ir laiku gimusių vaikų duomenimis.
4. Ištirti priešmokyklinio amžiaus vaikų, sirgusių NNR, fizinės būklės rodiklius, atsižvelgiant į akių būklę bei gimimo svorį, ir gautus duomenis palyginti su neišnešiotų nesirgusių NNR vaikų ir laiku gimusių vaikų duomenimis.
5. Įvertinti neišnešiotumo, persirgtos NNR, regos sistemos bei antropometrinių rodiklių kompleksines sąsajas priešmokykliniu laikotarpiu.

Tyrimo medžiaga ir metodai

Tyrimas atliktas 2011–2015 metais Vilniaus universiteto Medicinos fakulteto Vaikų ligų klinikoje, Vaikų ligoninės, VšĮ VULSK filialo, Vaikų akių ligų skyriuje ir VULSK Akių ligų centre. Tyrimui atlikti buvo gautas Lietuvos bioetikos komiteto leidimas Nr. 158200-12-565-165. Biomedicininiam tyrimui atlikti gauti vaikų tėvų ar jų globėjų rašytiniai sutikimai.

Tiriamąjį kontingentą sudarė 103 vaikai, gimę neišnešioti 2006–2008 metais ir gydyti Vaikų ligoninėje. 81 vaikui buvo diagnozuota NNR, iš jų 40 (49,4 proc.) vaikams pasireiškė sunki NNR stadija, 41 (50,6 proc.) diagnozuota lengva NNR stadija. Taip pat buvo ištirti 22 vaikai, kuriems NNR požymiai nepasireiškė. Pastariesiems vaikams buvo diagnozuoti ne visai subrendusios tinklainės požymiai, jie sudarė nesirgusių NNR neišnešiotų naujagimių grupę. Šiame tyrime kontrolinę grupę sudarė 40 normalaus gimimo svorio vaikų, kurie gimė išnešioti 2006–2008 metais ir jiems nebuvo diagnozuota jokių įgimtų bei lėtinių sisteminių ligų bei akių patologijos priešmokykliniame amžiuje.

Vaikams, kuriems buvo diagnozuota NNR, ligos stadija ir laipsnis buvo nustatyti remiantis tarptautine NNR klasifikacija. Pirmą ar antrą NNR stadijas įvardijome kaip lengvą NNR formą, III–V stadijas pavadinome sunkia NNR. Nė vienam vaikui, kuriam diagnozuota lengva NNR, gydymo neprireikė, sunkios NNR atveju buvo gydyti 38 neišnešioti naujagimiai.

Visiems vaikams buvo atliktas išsamus oftalmologinis ištyrimas: regėjimo aštrumo, refrakcinės ydos, anizometropijos, ambliopijos bei žvairumo ir akių dugno įvertinimas, atlikta optinė koherentinė tomografija, kurios metu išmatuotas tinklainės geltonosios dėmės ir gyslainės storiai. Statistiškai patikimo skirtumo tarp dešiniosios ir kairiosios tiriamųjų akių nebuvo nustatyta ($P>0,05$). Tad į analizę įtraukti dabartinės geresnės akies rezultatai. Taip pat nebuvo rasta dabartinės akių būklės skirtumų tarp mergaičių ir berniukų bei tarp 5, 6, 7 metų grupių, todėl vertinant oftalmologinę būklę į lytį ir amžių nebuvo atsižvelgta. Pagal standartinę antropometrinę metodiką buvo matuoti vaikų fizinės būklės rodikliai – ūgis stovint ir sėdint, svoris, įvairios kūno apimtys (galvos, krūtinės, liemens, klubų, šlaunies, blauzdos, žasto, dilbio), kūno segmentų pločiai (pečių ir krūtinės plotis, krūtinės gylis, dubens plotis) bei galūnių diametrai (žastikaulio, dilbio, šlaunies, blauzdos kaulų distalinių epifizių plotis, toliau įvardijamas kaip alkūnės, riešo, kelio, čiurnos diametrai), įvairių kūno sričių odos klosčių (pomentinės, klubinės, pilvo, žasto, šlaunies, blauzdos) storis. Taip pat apskaičiuoti įvairūs kūno proporcijų ir sudėties indeksai ir rodikliai (KMI, riebalų

centrališkumo indeksas (pomentinės ir žasto trigalvio raumens odos riebalinių klosčių santykis), odos riebalinių klosčių suma ir santykinė pasyvioji masė pagal formules.

Vaikai pagal akių būklę tuoj po gimimo suskirstyti į grupes sirgę NNR (sunkia ir lengva NNR) ir nesirgę NNR. Nebuvo rasta dabartinės akių būklės skirtumų tarp mergaičių ir berniukų bei tarp 5, 6, 7 metų grupių, todėl vertinant oftalmologinę būklę į lytį ir amžių neatsižvelgta. Dabartiniai akių būklės rodikliai palyginti tarp neišnešiotų naujagimių pogrupių ir kontrolinės grupės rodiklių.

Taip pat vaikai sugrupuoti pagal gimimo svorį: ypač mažo gimimo svorio (<1000 g), labai mažo gimimo svorio (<1500 g, bet >1000 g) ir mažo gimimo svorio (>1500 g). Dabartiniai akių būklės ir antropometriniai rodikliai, atsižvelgiant į gimimo svorį, palyginti tarp grupių ir su kontrolinės grupės rodikliais.

Tyrimų rezultatams sisteminti naudota aprašomoji statistika (vidurkiai, standartiniai nuokrypiai, minimalios ir maksimalios parametrų reikšmės). Vertinant skirtumus tarp lyginamų grupių buvo taikomas Stjudento t kriterijus, o lyginant tarpusavyje kelias grupes atlikta vienfaktorinė dispersinė analizė (ANOVA). Kelių grupių proporcijoms lyginti naudotas χ^2 testas. Statistinė analizė atlikta, naudojant „MS Excel“ ir „IBM SPSS *Statistics* 23.0“ programas. Pasirinktas reikšmingumo lygmuo buvo $p<0,05$.

Rezultatai

Retrospektyvioji iširtųjų vaikų antropometrinių rodiklių gimimo momentu analizė parodė, kad sirgusių sunkia NNR forma vaikų gimimo svoris ir KMI buvo patikimai mažesni negu sirgusių lengva ir nesirgusių NNR vaikų ($p<0,05$ ir $p<0,005$). Reikšmingo gimimo ūgio skirtumų tarp lengvos ir sunkios NNR vaikų grupių nebuvo rasta ($p>0,47$), tačiau sirgę NNR vaikai buvo patikimai mažesni už nesirgusius ($p<0,001$). Sirgusių sunkia NNR vaikų galvos ir krūtinės apimtys gimimo momentu taip pat buvo reikšmingai mažesnės negu kitų pogrupių ($p<0,05$). Sirgę sunkia NNR vaikai buvo ne tik mažiausių matmenų, bet ir trumpiausios gestacijos, taigi labiausiai nebrandūs. Lyginant 5–7 metų išnešiotų ir neišnešiotų vaikų ūgį, išilginius ir skeleto stambumo antropometrinius rodiklius, išryškėjo, kad neišnešiotų vaikų ūgio vidurkis buvo statistiškai patikimai mažesnis už kontrolinės grupės vaikų ūgio vidurkį visose amžiaus grupėse, nesvarbu, kaip vaikai suskirstyti – pagal akių būklę ar pagal gimimo svorį. Tačiau ūgio skirtumai tarp pačių neišnešiotų vaikų patikimiau išryškėjo suskirsčius juos pagal gimimo svorį.

Ūgio sėdint ir kojos ilgio amžinė dinamika buvo panaši, bet kojos ilgio skirtumai buvo didesni ir labiau atsiliko nuo kontrolinės grupės negu ūgio sėdint. Pečių plotis nuo kontrolės patikimai skyrėsi neišnešiotų penkiamečių ir šešiamečių grupėse, nuo kontrolės patikimai atsiliko tik ypač mažo gimimo svorio septynmečių rodiklis. Panaši buvo ir neišnešiotų vaikų krūtinės pločio skirtumų amžinė dinamika, tačiau krūtinės gylis patikimai skyrėsi tik ypač mažo svorio penkiamečių ir septynmečių grupėse, kiti skirtumai buvo nepatikimi, vadinasi, krūtinės gylis santykinai mažėjo lėčiau, tai yra neišnešiotų vaikų krūtinės ląsta ilgiau plokštėjo. Ilgiau išliekanti apvalesnė krūtinės ląsta turėtų būti laikoma nebrandumo požymiu. Dubens pločio skirtumai didžiausi tarp penkiamečių, mažiausi – tarp septynmečių. Patikimai nuo kontrolės ir tarpusavyje skyrėsi visų grupių neišnešiotų penkiamečių ilgųjų kaulų distalinių epifizių diametrai (išskyrus riešo), augant tik kai kurie ypač mažo gimimo svorio ir NNR sirgusių

septynmečių diametrai išliko patikimai mažesni. Taip pat nustatyta, kad neišnešiotų vaikų svorio vidurkis buvo reikšmingai mažesnis už kontrolinės grupės vaikų svorio vidurkį visose amžiaus grupėse (patikimumai sumažėjo lyginant septynmečius), nesvarbu, kaip vaikai suskirstyti – pagal akių būklę ar pagal gimimo svorį. Svorio skirtumai tarp pačių neišnešiotų vaikų patikimiau išryškėjo suskirsčius juos pagal gimimo svorį ir išliko visose amžiaus grupėse. Tarp neišnešiotų vaikų akių būklės pogrupių statistiškai patikimų svorio skirtumų nebuvo. Nors ir nebuvo gautas statistiškai patikimas skirtumas, bet mažiausią svorį turėjo vaikai, kurie sirgo NNR. Neišnešiotų vaikų pogrupių KMI vidurkiai buvo mažesni negu kontrolinės grupės, bet patikimi skirtumai nustatyti tarp penkiamečių ir šešiamečių bei tarp ypač mažo gimimo svorio septynmečių. KMI analizė parodė ankstesnį neišnešiotų vaikų tuklumo grąžos momentą. Nepriklausomai nuo to, kaip jie buvo suskirstyti į pogrupius, penkiamečių KMI buvo mažiausias ir didėjo 6–7 metais, išskyrus vaikus, gimusius didesnio kaip 1,5 kg svorio (jų mažiausias KMI fiksuotas 6 metų, kaip ir kontrolinės grupės).

Visų neišnešiotų vaikų pogrupių galvos apimties vidurkis buvo mažesnis už kontrolinės grupės, visų penkiamečių, ypač mažo ir mažo gimimo svorio vaikų ir vaikų, sirgusių NNR skirtumai buvo patikimi. Tarp akių būklės pogrupių patikimų skirtumų nenustatyta, tarp skirtingo gimimo svorio grupių reikšmingai mažiausia apimtis buvo ypač mažo gimimo svorio penkiamečių. 5–6 metų neišnešiotų vaikų galūnių ir liemens apimtys daugiau ar mažiau patikimai mažesnės negu kontrolinės grupės vaikų, 7 metų ypač mažo gimimo svorio visos apimtys ir sirgusių NNR vaikų dauguma apimčių (išskyrus blauzdos) taip pat buvo patikimai mažesnės.

Daugumos odos riebalinių klosčių vidurkiai ir klosčių sumos vidurkis reikšmingai nesiskyrė tarp neišnešiotų vaikų pogrupių ir kontrolinės grupės, išskyrus ypač mažo gimimo svorio penkiamečius – jų riebalinės klostės buvo patikimai plonesnės. Kai kurių pogrupių septynmečių neišnešiotų vaikų pilvo ir klubų klosčių vidurkiai buvo didesni negu išnešiotų vaikų, didžiausią klosčių sumą, kuri buvo patikimai didesnė negu kontrolinės grupės vaikų, turėjo sirgę NNR ir labai mažo gimimo svorio septynmečiai. Santykinės pasyviosios masės vidurkių palyginimas parodė daug mažesnius ir nepatikimus skirtumus tiek tarp neišnešiotų vaikų pogrupių ir kontrolės, tiek tarp pačių pogrupių. Riebalų centrališkumo indekso palyginimas, nors daugeliu atveju ir nepatikimas, atskleidė neišnešiotų vaikų riebalinio audinio centralizacijos tendenciją: didesnį indeksą negu kontrolinė grupė turėjo visi šešiamečiai, išskyrus ypač mažo gimimo svorio vaikus, ir ypač mažo gimimo svorio septynmečiai.

Kontrolinės grupės ir neišnešiotų ikimokyklinukų regėjimo aštrumo palyginimas, atsižvelgiant į jų akių būklę naujagimystės laikotarpiu, atskleidė, kad blogiausias GKRA buvo sirgusių sunkia NNR forma vaikų. Nesirgusių NNR regėjimo aštrumas reikšmingai nesiskyrė nuo kontrolės ($p>0,05$). Apskaičiuotas sferinis ekvivalentas ir nustatyta, kad sirgusių sunkia NNR vaikų jis buvo daug mažesnis, lyginant su kitomis grupėmis ($p<0,05$).

Akies optinių komponentų analizės rezultatai parodė, kad ragenos kreivumo spindulys, taigi jos forma, tarp visų tiriamųjų grupių reikšmingai nesiskyrė ($p>0,05$), tačiau matome, kad sirgusių sunkia NNR forma vaikų ragena buvo smailiausia. Vertinant priekinės kameros gylį ir lęšiuko storį visose tiriamųjų grupėse išryškėjo tam tikri skirtumai. Nustatyta, kad tiek sunkios tiek lengvos sirgusių NNR forma vaikų priekinė kamera buvo reikšmingai seklesnė ($p<0,01$), o lęšiukas storesnis ($p<0,001$ ir $p<0,01$) negu kitų grupių vaikų. Taip pat buvo rasti akivaizdūs reikšmingi akies ašies ilgio

skirtumai: sirgusių sunkia ir lengva NNRvaikų ašys buvo trumpiausios ($p<0,005$). Tiek sunkia tiek lengva sirgusių NNR vaikų grupės vidutinis tinklainės geltonosios dėmės storis buvo reikšmingai didesnis lyginant su kitomis grupėmis p(<0,01).
Refrakcinių ydų analizė parodė, kad didžiausias toliaregystės (>/=2D) paplitimas buvo tarp sirgusių NNR vaikų, nepriklausomai nuo to, kokia forma pasireiškė. Tačiau statistiškai reikšmingo skirtumo tarp išnešiotų ir neišnešiotų vaikų grupių nebuvo ($p >0,05$). Trumparegystės paplitimo skirtumai tarp neišnešiotų ir išnešiotų vaikų buvo reikšmingi, jie priklausė nuo akių būklės naujagimystės laikotarpiu: daugiausiai trumparegių buvo tarp sirgusių sunkia NNR forma vaikų ($p<0,001$). Sirgę sunkia NNR forma vaikai statistiškai reikšmingai dažniau turėjo ir didesnį astigmatizmą ($p<0,005$), nors mažesnis, bet reikšmingas astigmatizmas dažniau pasitaikė ir tarp kitų neišnešiotų vaikų. Sirgusiems sunkia NNR forma vaikams dažniausiai pasireiškė ir reikšminga bei didelė anizometropija ($p<0,05$). Taip pat akivaizdus didžiausias ambliopijos paplitimas tarp sirgusių NNR vaikų, ypač tarp sunkios formos ($p<0,0005$). Nustatyta, kad dažniau pasireiškė vidinis nei išorinis žvairumas ($p<0,005$). Abu žvairumo tipai dažniau pasitaikė sirgusiems sunkia NNR forma ikimokyklinukams ($p<0,001$).
Taip pat atlikta detalesnė dabartinių akių būklės rodiklių, atsižvelgiant į tiriamųjų gimimo svorį, analizė. Jos rezultatai parodė, kad tiek funkciniai (GKRA), tiek į tolį, tiek iš arti, tiek kai kurie biometriniai akių būklės rodikliai (ragenos forma, priekinės kameros gylis, lęšiuko storis) reikšmingai skyrėsi priklausomai nuo gimimo svorio ($p<0,05$). Akies ašies ilgis reikšmingai nesiskyrė ($p>0,05$). Labai reikšmingas skirtumas ($p<0,001$) nustatytas tarp ypač mažo gimimo svorio ir labai mažo gimimo svorio vaikų tinklainės storių. Ikimokyklinukų refrakcinių ydų ir ambliopijos paplitimas taip pat reikšmingai skyrėsi ir buvo didesnis tarp ypač mažo ir labai mažo gimimo svorio vaikų negu tarp mažo gimimo svorio vaikų ($p<0,05$). Reikšmingų skirtumų tarp žvairumo ir anizometropijos paplitimo nerasta ($p>0,05$).

Išvados

1. 2006–2008 metais VUVL buvo gydyti 876 neišnešioti naujagimiai, iš jų 150 (17 proc.) naujagimių diagnozuota NNR, 78 (52 proc.) pasireiškė sunki NNR, 77 buvo gydyti chirurginiu būdu.
2. Sirgę tiek sunkia, tiek lengva NNR naujagimiai buvo trumpesnės gestacijos ir mažesnio svorio, palyginti su nesirgusiais NNR. Sirgusių sunkia NNR naujagimių gimimo svoris, KMI, krūtinės ir galvos apimtys buvo reikšmingai mažesnės nei sirgusių lengva NNR ar nesirgusių NNR.
3. Atsižvelgiant tik į akių būklę, priešmokyklinio amžiaus vaikų, sirgusių NNR, funkciniai ir biometriniai akių būklės rodikliai reikšmingai skyrėsi nuo nesirgusių NNR vaikų ir laiku gimusių vaikų: sirgusių sunkia NNR vaikų grupėje nekoreguotas ir geriausias koreguotas regėjimo aštrumas buvo blogiausias, SE mažiausias; daugiausia vaikų turėjo trumparegystę, didelį astigmatizmą (≥2D), ambliopiją ir žvairumą. Abiejų NNR formų grupėse priekinė kamera buvo reikšmingai seklesnė, o lęšiukas storesnis. Šių vaikų tinklainė buvo reikšmingai storesnė, o gyslainė plonesnė.

   Atsižvelgiant į NNR sirgusių vaikų gimimo svorį nustatyta, kad ypač mažo ir labai mažo gimimo svorio vaikų, refrakcinių ydų ir ambliopijos paplitimas buvo reikšmingai didesnis. Šių grupių vaikų tinklainė buvo reikšmingai storesnė, o gyslainė plonesnė negu mažo gimimo svorio grupės vaikų.

4. a. Atsižvelgiant tik į akių būklę, nenustatyta reikšmingų skirtumų tarp sirgusių ir nesirgusių NNR neišnešiotų vaikų antropometrinių rodiklių; daugelis šių vaikų rodiklių (išskyrus galvos ir kai kurias kitas apimtis) patikimai nesiskyrė ir nuo populiacijos vidurkio, tačiau nuo populiacijos vidurkio atsiliko penkiamečių neišnešiotų vaikų rodikliai.

   b. Atsižvelgiant į NNR sirgusių vaikų gimimo svorį nustatyta, kad reikšmingai nuo populiacijos vidurkio atsiliko penkiamečių ypač mažo gimimo svorio vaikų dauguma antropometrinių rodiklių; augant skirtumai mažėjo netolygiai: šešiamečių ypač mažo gimimo svorio vaikų ūgio vidurkis pavijo populiacijos vidurkį, tačiau šie vaikai liko mažesnio svorio ir KMI, jų kūno apimtys ir kai kurie skeleto stambumo rodikliai buvo mažesni, o odos klostės santykinai stambesnės visose amžiaus grupėse. Ypač mažo gimimo svorio vaikai turėjo mažiau aktyviosios kūno masės, bet patyrė ankstesnę tuklumo grąžą, santykinai daugiau jų riebalinio audinio buvo susikaupusio liemens srityje.

   c. Labai mažo ir mažo gimimo svorio vaikų ūgis visose amžiaus grupėse buvo artimas Lietuvos sveikų bendraamžių vidurkiui arba netgi didesnis už jį, svoris ir KMI pasivijo sveikų bendraamžių rodiklius septynerių metų amžiuje, labai mažo gimimo svorio vaikų tuklumo grąža buvo ankstesnė, o mažo gimimo svorio vaikų sutapo su sveikų vaikų tuklumo grąža.

   d. Visų gimimo svorio grupių NNR sirgusių vaikų galvos apimtis buvo reikšmingai mažesnė už populiacijos vidurkį visose amžiaus grupėse. Visų NNR sirgusių vaikų klubų ir apatinių galūnių rodikliai (diametrai ir apimtys) didėjo lėčiau negu viršutinės liemens dalies ir viršutinių galūnių. Vadinasi, ypač mažo gimimo svorio vaikų kūno dydis, sudėtis ir proporcijos priešmokykliniu laikotarpiu labiausiai siejosi su požymiais, būdingais metaboliniam sindromui ir vadinamajam taupiajam fenotipui.
5. Neišnešiotų sirgusių NNR vaikų fizinė būklė gimus, kūno dydis, centrinis tuklumas ir akių būklė priešmokykliniu laikotarpiu buvo veikiami skirtingų veiksnių (nustatytos sąsajos, kurias lėmė skirtingi faktoriai):
   - Logistinės regresijos duomenimis, priešmokykliniu laikotarpiu regėjimo aštrumas labiausiai priklausė nuo rageninio astigmatizmo.
   - Faktorių analizės duomenimis:
     a. sirgusių NNR vaikų kūno dydžio, proporcijų ir centrinio tuklumo rodiklius priešmokykliniu laikotarpiu lėmė veiksniai, mažai susiję su kitų faktorių kintamaisiais, be to, pirmieji du fizinės būklės faktoriai paaiškino beveik 50 proc. visos nagrinėtų požymių variacijos;
     b. regėjimo aštrumą priešmokykliniu laikotarpiu daugiausia lėmė atskiras faktorius, kuris tik iš dalies siejosi ir su naujagimio brandos kintamaisiais ir paaiškino beveik 12 proc. visos nagrinėtų požymių variacijos;
     c. gyslainės centrinės dalies storis labiausiai iš visų akies parametrų priešmokykliniu laikotarpiu buvo susijęs su fizinės būklės rodikliais;
     d. regos sistemos ir kūno raida vyksta lygiagrečiai, tačiau egzistuoja specifiniai mechanizmai minėtų sistemų sklandžiai ir optimaliai raidai užtikrinti, pirmiausia koncentruojantis funkciškai svarbesnei sistemai (regėjimui) tvarkyti.

9. PUBLICATIONS AND SCIENTIFIC CONFERENCE REPORTS

Publications:

1. **Donata Montvilaitė**, Inesa Skvarciany, Agnė Grizickaitė "Retinopathy of prematurity problem in the world" (Literature review). Lithuanian Ophthalmology 2014, Vol. XIII, No.1.(43): 16-20.
2. **Donata Montvilaitė**, Inesa Skvarciany, Agnė Grizickaitė, Aistė Augytė, Arūnas Barkus, Vytautas Usonis. "Ophthalmological follow-up of prematurely born children in preschool age: prospective study of visual acuity, refractive errors and strabismus". Acta Medica Lituanica, 2015, Vol.22, No 4: 205-215.
3. **Donata Montvilaitė**, Arūnas Barkus, Eglė Marija Jakimavičienė, Vytautas Usonis. "Preterm children growth and ophthalmological status at school entering age". Laboratory medicine, 2015, Vol.17, No 4(68): 174-188.

Conference reports

1. 2012 June. 12–15 Vilnius, Lithuania. „Evolutionary Medicine: new solutions new problems": presentation in English " Retinopathy of prematurity: challenges in Lithuania and worldwide".
2. 2014 May 27-30 Vilnius, Lithuania. Participated in the international conference „Evolutionary Medicine: perspectives in understanding health and disease. Presentation in English "Outcome of Retinopathy of Prematurity (ROP) in Lithuanian Preschool Children". Award for the best oral presentation.
3. 2015 June 24-26 Saint Petersburg, Russia. Participated in the international conference European pediatric Ophthalmology Society. Presentation in English "The association between changes in ophthalmological outcome and anthropometric measurements in Lithuanian preterm children at the preschool age", 2015-06-26.
4. 2015 May 2-3 Riga, Latvia. Participated in the 3rd Baltic Eye Surgeons Talk Show – BEST vol.3. Presentation in English "Ophthalmology and Neurosurgery – working hand in hand".
5. 2015 March 20 Vilnius, Lithuania. Participated in the international scientific conference of rare diseases. Presentation in English "Ocular features of treatable Lysosomal Storage Disorders".
6. 2015 November 12-14 Vilnius, Lithuania. Participated in the international 8th Morphological conference. Presentation in English "Ophthalmologic outcome and anthropometric measurements of preterm born 5-7 years old children in Lithuania".

10. **CURRICULUM VITAE**

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01-09-2009 – present: Ophthalmologist, Pediatric Ophthalmology Department, Children Hospital, Affiliate of VUHSK

01-05-2007 – present: Ophthalmologist, Centre for Optometry

02-01-2011– 02-01-2016 Ophthalmologist, Karoliniskiu clinic

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