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# Prevalence of strabismus and risk factors in adults born preterm with and without retinopathy of prematurity: results from the Gutenberg Prematurity Eye study

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## ABSTRACT

**Aim** The purpose of this study was to assess the prevalence of strabismus and nystagmus and to analyse associated factors in preterm and full-term infants in adulthood.

**Methods** The Gutenberg Prematurity Eye Study is a retrospective cohort study with a prospective ophthalmological examination of participants born preterm and full-term (aged 18–52 years). Perinatal data were carefully assessed for risk factors and comprehensive ophthalmological examinations were conducted. The association between strabismus and nystagmus was assessed by analysing 16 different perinatal and actual risk factors in multivariable analysis. Participants were grouped into full-term controls (gestational age (GA) at birth ≥37 weeks), preterm participants without retinopathy of prematurity (ROP) and GA 33–36 weeks (group 2), GA 29–32 weeks (group 3), GA ≤28 weeks (group 4), non-treated ROP (group 5) and treated ROP (group 6).

**Results** In total, 892 eyes of 450 preterm and full-term individuals (mean age: 28.6 years, SD: ± 8.6 years, 251 females) were included. Strabismus was observed in 2.1% (3/140), 6.6% (9/137), 17.4% (16/92), 11.1% (2/18), 27.1% (13/48) and 60% (9/15) of participants and nystagmus in 0.7% (1/140), 1.5% (2/137), 4.3% (4/92), 5.6% (1/18), 10.4% (5/48) and 26.7% (4/15) of participants in the respective groups. In the multivariable regression model, strabismus was associated with GA (OR=0.90; p=0.046), anisometropia ≥1.5 diopter (OR=3.87; p=0.003), hypermetropia ≥2 diopter (OR=9.89; p<0.001) and astigmatism ≥1.5 diopter (OR=2.73; p=0.017). Esotropia was more frequent than exotropia and hypermetropia/hypometropia. Most strabismus cases occurred within the first 10 years of life. The strongest predictor associated with nystagmus was perinatal adverse events (OR=15.8; p=0.002).

**Conclusion** Low GA and refraction of the eye are independent risk factors for strabismus, which typically occurs in the first 10 years of life. Perinatal adverse events are the most important factors for the presence of nystagmus in adulthood.

### WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Preterm delivery and postnatal retinopathy of prematurity (ROP) occurrence are associated with an increased strabismus and nystagmus prevalence in infancy and childhood but the perinatal long-term effects on strabismus and nystagmus development in adulthood are less well known. We investigated to what extent different degrees of prematurity, ROP and associated factors may lead to strabismus and nystagmus in adults aged 18–52 years.

### WHAT THIS STUDY ADDS

⇒ The earlier participants were born, the higher the prevalence of strabismus and nystagmus in adulthood, with esotropia more frequent than exotropia and hypermetropia/hypometropia. Most participants developed strabismus within the first 10 years of life and the strongest predictor associated with nystagmus was the occurrence of perinatal adverse events.

### HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study extends previous findings in children that perinatal and postnatal origins cause strabismus in adults born preterm, as well as confirms that prematurity, particularly refractive errors, affects strabismus development in adulthood. Strabismus manifests particularly in the first 10 years of life, with perinatal adverse events leading to nystagmus in adults.

## INTRODUCTION

The prevalence of preterm birth and postnatal occurrence of retinopathy of prematurity (ROP) is dramatically increasing worldwide,[1] postnatal ROP is one of the main reasons for childhood blindness in developed countries,[2] with important long-term consequences for affected individuals.[3] Survival of extremely preterm individuals has increased since the 1990s. They face a higher risk of eye conditions like strabismus and nystagmus in childhood and adolescence, which can harm vision.[4 5] A recent

population-based study on adults aged 40–80 shows that strabismus affects their vision-related quality of life.[6]

Recent studies have examined strabismus prevalence in preterm individuals, including those with ROP, reporting rates of up to 42% in childhood.[7–10] They have also investigated risk factors, such as prematurity, low birth weight and ROP.[4 5 8–17] The factors alone cannot fully explain strabismus development in preterm individuals, necessitating a comprehensive analysis and assessment of their impact on different types of strabismus.

While extremely preterm individuals (22–25 weeks) have a higher strabismus prevalence compared with age-matched controls,[18] there is limited data on the long-term effects of prematurity and associated factors on strabismus prevalence in adulthood, especially for varying degrees of prematurity and postnatal ROP. Additionally, there is no long-term data spanning the first five decades of life, which is critical as most preterm infants worldwide are moderate or late preterm (≥32 weeks), and their long-term development is unknown.

This study aims to assess strabismus prevalence in individuals aged 18–52 born at different prematurity levels, with or without ROP, compared with full-term controls. It also analyses various risk factors to identify independent contributors and stratifies the analysis by different types of strabismus.

## Materials and methods

### Study population

The Gutenberg Prematurity Eye Study (GPES) is a cohort study conducted at the University Medical Center of Johannes Gutenberg-University Mainz in Germany (UMCM). It includes individuals born preterm or at term between 1969 and 2002, aged 18–52 years at enrolment. The study is a retrospective cohort study with a prospective acquisition of follow-up data. Participants were selected based on gestational age (GA) at birth and birth weight percentile. Every preterm with a GA at birth ≤32 weeks and every second randomly chosen preterm newborn with a GA of 33–36 weeks was invited to participate with controls chosen for each calendar month from 1969 to 2002 (six randomly selected full-term individuals).[19] The flow chart for effective recruitment efficacy proportion is displayed in online supplemental figure 1.

Between 2019 and 2021, examinations included visual acuity testing, refractive error measurement, orthoptic examination and medical history interview. Participants' medical records were reviewed, and written informed consent was obtained. The GPES complies with Good Clinical Practice, Good Epidemiological Practice and the ethical principles of the Declaration of Helsinki. The study protocol and documents were approved by the Medical Chamber of Rhineland-Palatinate, Germany (reference no. 2019-14161; original vote: 29 May 2019, latest update: 2 April 2020).

### Assessment of prenatal, perinatal and postnatal medical history

All patient-related information stored at the UMCM was reviewed and the following data were collected: GA (weeks), birth weight (g), presence of ROP, stage of ROP, ROP treatment, placental insufficiency, pre-eclampsia and breast feeding. Multiple other information about perinatal and postnatal maternal and child history were assessed, as well as specific parental information such as maternal age at birth, and so on. Birth weight percentiles were calculated according to Voigt *et al*.[20] The study involved participants providing information about their strabismus history and surgeries, as well as reviewing medical records from UMCM's Department of Ophthalmology to validate self-reported information.

### Categorization

For descriptive analysis, participants were grouped into participants born full-term with a GA ≥37 weeks (group 1), participants born preterm with a GA of 33–36 weeks without ROP (group 2), GA of 29–32 weeks without ROP (group 3), GA ≤28 weeks without ROP (group 4), GA ≤32 weeks and non-treated ROP (group 5) and treated ROP (group 6). If only one eye was affected by ROP, the other non-ROP eye was excluded from the analysis.

### Ophthalmologic examination

A comprehensive ophthalmological examination was performed including distant corrected visual acuity (DCVA) testing with an ARK-1s, NIDEK, Oculus (Wetzlar, Germany), and stereopsis was tested with the Lang II test. Visual acuity was converted from decimal to logMAR according to the medical literature.[21] Intraocular pressure was measured with a non-contact tonometer (NT 200, NIDEK Co, Japan). Participants were diagnosed as having amblyopia according to criteria previously published for a German cohort.[22] Additionally, a slit-lamp examination and funduscopy was performed on each participant. Myopia was defined as a refractive error of ≤ −2 diopters (more myopic or equal). It is important to note that within the broader research landscape, the definition of myopia varies, typically ranging from ≤−0.5 for any myopia to ≤−6 diopters for high myopia.[23] Due to the specific characteristics of our study, we determined that a threshold of ≤ −2 diopters was the most appropriate for our analysis. Similarly to myopia, the definition of hyperopia in our study was set as a refractive error of ≥+2 diopters.[24]

### Orthoptic examination

An orthoptic examination for strabismus was conducted including the cover–uncover test and alternate cover test, Hirschberg test and examination of fixation behaviour. Ocular movements were assessed. After correction for refractive error, the presence or absence of nystagmus was investigated. Strabismus was defined as constant or intermittent heterotropia of any dimension at distance and/or near fixation after having corrected refractive error.[25] Strabismus was categorised depending on the deviation from the primary position (esotropia, exotropia, hypertropia, hypotropia).

### Covariables

The risk factors that may affect the outcome measures such as gender (female), age (years), GA (weeks), birth weight percentile, ROP (yes), anisometropia ≥1.5 (diopter), refractive error: myopia ≤−2 (diopter) and hyperopia ≥+2 (diopter) (reference: −2 to 2 diopter), astigmatism ≥1.5 diopter (yes), maternal age at childbirth (years), maternal smoking (yes), maternal breast feeding (yes), perinatal adverse events (yes), pre-eclampsia (yes), placental insufficiency (yes) and caesarean section (yes) were considered as covariables. Perinatal adverse events were defined according to the German query for quality control of the neonatal clinics: occurrence of intraventricular haemorrhage (at least grade 3 or parenchymal haemorrhage) and/or the occurrence of necrotising enterocolitis and/or moderate or severe bronchopulmonary dysplasia were summarised as adverse events.[26]

### Statistical analysis

The main outcome measure was strabismus of any type on study examination. Secondary outcome variables were the presence of the different subtypes of strabismus (esotropia, exotropia, hypertropia/hypotropia) as well as the presence of nystagmus. Descriptive statistics were stratified by clinical group, with absolute and relative frequencies for dichotomous parameters and mean and SD for approximately normally distributed variables. Binary logistic regression models were used to assess associations. Two statistical models were used for risk factor analysis. First, separate univariate logistic regression analysis was performed with the presence of strabismus (any type and the different subtypes) as well as nystagmus as dependent variables and documented potential risk factors for strabismus as independent variables. Second, multivariable logistic regression analysis was performed to identify independently associated factors including all of the above-described factors that were associated with a p value <0.05 in the univariate analysis. The 95% CI and OR are given. Collinearity was assessed by pairwise Spearman correlation coefficients. Birth weight as a parameter was excluded in the multivariable models to avoid collinearity, as GA is highly correlated with birth weight. Sensitivity analyses were conducted for esotropia, exotropia, hypertropia/hypotropia and nystagmus. Kaplan-Meier survival statistics were applied to describe the cumulative probability of the non-occurence of strabismus for the different study groups. This was an explorative study, so no adjustments for multiple testing were performed and all calculations were performed using commercial software (IBM SPSS V.20.0; SPSS, Chicago, Illinois, USA).

## RESULTS

### Participant characteristics

The study included 310 preterm-born individuals and 140 full-term-born individuals, totaling 892 eyes examined for strabismus and nystagmus (table 1). The average age of participants was 28.6 years, with 251 females. Some individuals with ROP received treatments such as laser coagulation (seven participants, 14 eyes) and cryocoagulation (eight participants, 16 eyes). The recruitment process is detailed in online supplemental figure 1.

**Table 1** Characteristics of the sample (n=450) of the GPES stratified by study groups

| | Group 1 | Group 2 | Group 3 | Group 4 | Group 5 | Group 6 |
|---|---|---|---|---|---|---|
| **GA** | **GA ≥37** | **GA 33–36** | **GA 29–32** | **GA ≤28** | **GA ≤32** | **GA ≤32** |
| | | **No ROP** | **No ROP** | **No ROP** | **ROP without treatment** | **ROP with treatment** |
| Participants (n)/eyes (n) | **140/280** | **137/274** | **92/184** | **18/36** | **48/88** | **15/30** |
| Gender (women) | 81 (57.9%) | 82 (59.9%) | 50 (54.3%) | 9 (50.0%) | 24 (50.0%) | 5 (33.3%) |
| Age (years), mean±SD | 29.9±9.1 | 29.5±9.1 | 28.2±8.0 | 23.4±7.4 | 25.0±6.0 | 26.7±2.3 |
| Birth weight (g), mean±SD | 3420±392 | 2068±464 | 1559±330 | 918±197 | 1057±387 | 807±244 |
| Birth weight <1500 g (yes) | 0 (0%) | 13 (9.5%) | 38 (41.3%) | 18 (100%) | 41 (85.4%) | 15 (100%) |
| Birth weight <1000 g (yes) | 0 (0%) | 0 (0%) | 5 (5.4%) | 11 (61.1%) | 23 (47.9%) | 12 (80%) |
| Birth weight percentile, mean±SD | 48.6±21.4 | 25.2±24.1 | 45.3±25.0 | 42.9±25.0 | 38.2±28.0 | 24.8±22.5 |
| GA (weeks), mean±SD | 39.3±1.3 | 34.3±0.9 | 30.6±1.2 | 26.6±1.5 | 27.8±2.1 | 26.7±2.3 |
| (min–max) | (37–43) | (33–36) | (29–32) | (23–28) | (24–32) | (24–32) |
| ROP stadium (1/2/3/4/5) | 0/0/0/0/0 | 0/0/0/0/0 | 0/0/0/0/0 | 0/0/0/0/0 | 32/48/6/0/2 | 0/6/22/2/0 |
| Perinatal adverse events (yes)* | 1 (0.7%) | 4 (2.9%) | 6 (6.5%) | 3 (16.7%) | 17 (35.4%) | 11 (73.3%) |
| Intraventricular haemorrhage (yes)† | 0 (0%) | 0 (0%) | 1 (1.1%) | 0 (0%) | 2 (4.2%) | 1 (6.7%) |
| Bronchopulmonary dyplasyia (yes)‡ | 1 (0.7%) | 1 (0.7%) | 4 (4.3%) | 1 (5.6%) | 13 (27.1%) | 7 (46.7%) |
| Necrotising entercolitis (yes) | 0 (0%) | 3 (2.2%) | 1 (1.1%) | 2 (11.1%) | 4 (8.3%) | 6 (40.0%) |
| Pre-eclampsia (yes) | 11 (7.9%) | 24 (17.5%) | 10 (10.9%) | 3 (16.7%) | 10 (20.8%) | 4 (26.7%) |
| Placental insufficiency (yes) | 2 (1.4%) | 16 (11.7%) | 2 (2.2%) | 1 (5.6%) | 3 (6.2%) | 0 (0%) |
| HELLP-syndrome (yes) | 0 (0%) | 6 (4.4%) | 1 (1.1%) | 0 (0%) | 4 (8.3%) | 0 (0%) |
| Maternal smoking (yes)§ | 7 (5.0%) | 8 (5.8%) | 8 (8.7%) | 1 (5.6%) | 5 (10.4%) | 3 (20%) |
| Gestational diabetes (yes) | 1 (0.7%) | 7 (5.1%) | 1 (1.1%) | 1 (5.6%) | 1 (2.1%) | 0 (0%) |
| Breast feeding (yes) | 79 (56.4%) | 75 (54.7%) | 46 (50.0%) | 9 (50.0%) | 22 (45.8%) | 7 (46.7%) |
| Ocular parameters | | | | | | |
| Spherical equivalent (diopter) OD, mean±SD | −0.98±2.18 | −1.10±2.19 | −0.62±2.18 | −0.69±2.27 | −1.30±2.87 | −1.60±2.84 |
| Spherical equivalent (diopter) OS, mean±SD | −0.97±2.09 | −1.18±2.17 | −0.81±2.55 | −0.41±1.96 | −1.74±3.29 | −3.38±9.31 |
| Intraocular pressure (mmHg) OD, mean±SD | 15.3±2.8 | 14.6±3.0 | 15.1±3.2 | 16.7±3.3 | 15.3±4.2 | 18.2±4.3 |
| Intraocular pressure (mmHg) OS, mean±SD | 15.2±2.8 | 14.5±3.1 | 14.5±2.9 | 15.2±3.0 | 15.7±3.7 | 16.2±3.5 |

*Perinatal adverse events were defined as occurrence of intraventricular haemorrhage (at least grade 3 or parenchymal haemorrhage) and / or occurence of necrotising enterocolitis and / or occurrence of moderate or severe bronchopulmonary dysplasia.
†At least grade 3 or parenchymal haemorrhage
‡Moderate or severe.
§Maternal smoking during pregnancy.
GA, gestational age; GPES, Gutenberg Prematurity Eye Study; HELLP, Haemolysis, Elevated Liver enzymes, Low Platelet count; n, number; OD, right eye; OS, left eye; ROP, retinopathy of prematurity.

**Table 2** Visual acuity, visual field and amblyopia parameters as well as NEI VFQ-25 items (National Eye Institute Visual Function Questionnaire) for the GPES sample (n=450) for each study group

| | Group 1 | Group 2 | Group 3 | Group 4 | Group 5 | Group 6 |
|---|---|---|---|---|---|---|
| **GA** | **GA ≥37** | **GA 33–36** | **GA 29–32** | **GA ≤28** | **GA ≤32** | **GA ≤32** |
| | | **No ROP** | **No ROP** | **No ROP** | **ROP without treatment** | **ROP with treatment** |
| Participants/eyes (n) | **140/280** | **137/274** | **92/184** | **18/36** | **48/88** | **15/30** |
| Uncorrected visual acuity (logMAR) OD | 0.0 (0.0; 0.1) | 0.0 (0.0; 0.3) | 0.1 (0.0; 0.3) | 0.1 (0.0; 0.2) | 0.1 (0.0; 0.3) | 0.5 (0.0; 0.9) |
| Uncorrected visual acuity (logMAR) OS | 0.0 (0.0; 0.2) | 0.0 (0.0; 0.4) | 0.1 (0.0; 0.3) | 0.0 (0.0; 0.2) | 0.1 (0.0; 0.6) | 0.3 (0.2; 1.3) |
| Presenting visual acuity (logMAR) OD | 0.0 (0.0; 0.0) | 0.0 (0.0; 0.1) | 0.0 (0.0; 0.1) | 0.0 (0.0; 0.1) | 0.1 (0.0; 0.2) | 0.2 (0.1; 0.3) |
| Presenting visual acuity (logMAR) OS | 0.0 (0.0; 0.0) | 0.0 (0.0; 0.0) | 0.0 (0.0; 0.1) | 0.1 (0.0; 0.4) | 0.1 (0.1; 0.1) | 0.4 (0.2; 1.3) |
| DCVA (logMAR) OD | 0.0 (0.0; 0.0) | 0.0 (0.0; 0.0) | 0.0 (0.0; 0.0) | 0.0 (0.0; 0.0) | 0.0 (0.0; 0.1) | 0.1 (0.0; 0.3) |
| DCVA (logMAR) OS | 0.0 (0.0; 0.0) | 0.0 (0.0; 0.0) | 0.0 (0.0; 0.0) | 0.0 (0.0; 0.0) | 0.0 (0.0; 0.1) | 0.3 (0.1; 0.8) |
| Visual acuity better eye (logMAR) OS | 0.0 (0.0; 0.0) | 0.0 (0.0; 0.0) | 0.0 (0.0; 0.0) | 0.0 (0.0; 0.0) | 0.0 (0.0; 0.0) | 0.1 (0.0; 0.3) |
| Visual acuity worse eye (logMAR) OS | 0.0 (0.0; 0.0) | 0.0 (0.0; 0.0) | 0.0 (0.0; 0.0) | 0.0 (0.0; 0.0) | 0.0 (0.0; 0.1) | 0.4 (0.1; 1.0) |
| **Visual acuity better eye** | | | | | | |
| <20/20 (decimal) (n (%)) | 9 (6.4%) | 7 (5.1%) | 8 (8.7%) | 2 (11.2%) | 10 (20.8%) | 9 (60%) |
| <20/25 (decimal) (n (%)) | 1 (0.7%) | 2 (1.5%) | 6 (6.5%) | 1 (5.6%) | 6 (12.5%) | 6 (40%) |
| <20/40 (decimal) (n (%)) | 0 (0%) | 0 (0%) | 4 (4.3%) | 0 (0%) | 6 (12.5%) | 1 (6.7%) |
| <20/60 (decimal) (n (%)) | 0 (0%) | 0 (0%) | 2 (2.2%) | 0 (0%) | 4 (8.3%) | 1 (6.7%) |
| <20/200 (decimal) (n (%)) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 2 (4.2%) | 1 (6.7%) |
| <20/400 (decimal) (n (%)) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 1 (2.1%) | 1 (6.7%) |
| Eyes without light perception (n (%)) | 0 (0%) | 0 (0%) | 1 (1.1%) | 0 (0%) | 0 (0%) | 1 (1.1%) |
| VFT successfully conducted (eyes) | 271 | 261 | 168 | 32 | 66 | 21 |
| VFT≥2 abnormal fields per eye (n (%))<br>≥2 abnormal fields (p<1%) | 14 (5.2%) | 7 (2.7%) | 4 (2.4%) | 2 (6.2%) | 4 (6.1%) | 8 (38.1%) |
| No stereopsis (Lang test II) (n (%)) | 2 (1.4%) | 9 (6.6%) | 14 (15.2%) | 3 (16.7%) | 13 (27.1%) | 9 (60.0%) |
| Red–green colour vision deficiency (n (%)) | 0 (0%) | 3 (2.2%) | 3 (3.3%) | 0 (0%) | 4 (8.3%) | 0 (0%) |
| Self-reported amblyopia (n (%)) | 10 (7.1%) | 8 (5.8%) | 15 (6.3%) | 3 (16.7%) | 13 (27.1%) | 9 (60%) |
| History of amblyopia treatment (n (%)) | 5 (3.6%) | 6 (4.4%) | 6 (6.5%) | 3 (16.7%) | 10 (20.8%) | 9 (60%) |
| Unilateral amblyopia at examination (n (%)) | 2 (1.4%) | 4 (2.9%) | 5 (5.4%) | 1 (5.6%) | 3 (6.2%) | 3 (20%) |
| Bilateral amblyopia at examination (n (%)) | 1 (0.7%) | 2 (1.5%) | 5 (5.4%) | 0 (0%) | 5 (10.6%) | 4 (26.7%) |
| Any amblyopia at examination (n (%)) | 3 (2.1%) | 6 (4.4%) | 10 (10.9%) | 1 (5.6%) | 8 (16.7%) | 7 (46.7%) |
| NEI VFQ-25 items | | | | | | |
| Car driving (yes) (n (%)) | 127 (90.7%) | 123 (89.8%) | 86 (93.5%) | 12 (66.7%) | 32 (66.7) | 8 (53.3%) |
| Cancelled car driving due to low VA (n (%)) | 0 (0%) | 1 (0.7%) | 0 (0%) | 1 (5.6%) | 1 (2.1%) | 1 (6.7%) |
| Difficulties with reading (n (%)) | 25 (17.9%) | 35 (25.5%) | 22 (23.9%) | 4 (22.2%) | 15 (31.2%) | 7 (46.7%) |

Visual acuity is described as median and interquartile range.
DCVA, distant corrected visual acuity; GA, gestational age; n, number; OD, right eye; OS, left eye; ROP, retinopathy of prematurity; VA, Visual Acuity; VFT, visual field test.

Eight eyes without ROP were excluded when the fellow eye had postnatal ROP. Additionally, some participants in various groups had retinal issues in adulthood, including retinal breaks and detachment.

Table 2 presents the DCVA and amblyopia prevalence stratified for the different study groups and for participants with and without strabismus. Overall, the more preterm participants were born, the more frequent the reduced DCVA and amblyopia, particularly for participants with postnatal ROP and treatment revealing strabismus.

Strabismus was observed in 2.1% (3/140), 6.6% (9/137), 17.4% (16/92), 11.1% (2/18), 27.1% (13/48) and 60% (9/15) of participants; esotropia in 1.4% (2/140), 4.4% (6/137), 9.8% (9/92), 11.1% (2/18), 27.1% (13/48) and 60% (9/15) of participants; exotropia in 0.7% (1/140), 2.2% (3/137), 7.6% (7/92), 0.0% (0/18), 6.3% (3/48) and 13.3% (2/15) of participants; hypermetropia and hypometropia in 0.7% (1/140), 0% (0/137), 2.2% (2/92), 0.0% (0/18), 4.2% (2/48) and 6.7% (1/15) in the respective groups. Overall, the most frequent type of concomitant strabismus was esotropia followed by exotropia and hypermetropia/hypometropia. Concomitant strabismus was particularly observed in advanced stages of ROP and the need for treatment (figure 1). Nystagmus was present in 0.7% (1/140), 1.5% (2/137), 4.3% (4/92), 5.6% (1/18), 10.4% (5/48) and 26.7% (4/15) in the respective groups. Most strabismus cases occurred within the first 10 years of life (figure 2).

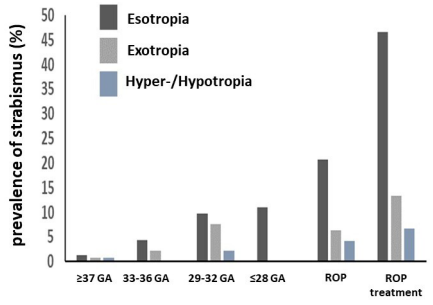


**Figure 1** Prevalence of esotropia, exotropia and hypermetropia/hypometropia in the different study groups. GA, gestational age; ROP, retinopathy of prematurity.

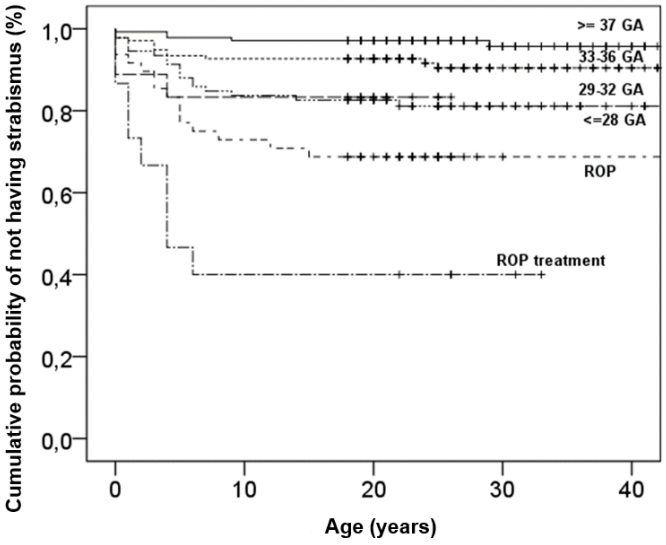


**Figure 2** Cumulative probability of non-occurrence of strabismus in the different study groups. GA, gestational age; ROP, retinopathy of prematurity.

### Association analyses

In the univariate analysis, an association between strabismus and the following parameters was detected: GA, ROP, sex, anisometropia ≥1.5 diopter, hyperopia ≥+2 diopter, astigmatism ≥1.5 diopter and perinatal adverse events (all p<0.05). In the multivariable regression model, strabismus was associated with GA (OR=0.90; p=0.046), anisometropia ≥1.5 diopter (OR=3.87; p=0.003), hypermetropia ≥2 diopter (OR=9.89; p<0.001) and astigmatism ≥1.5 diopter (OR=2.73; p=0.017) (table 3).

Esotropia was associated in the univariate model with GA, birth weight percentile, ROP, sex, anisometropia ≥1.5 diopter, hyperopia ≥2 diopter, astigmatism ≥1.5 diopter, maternal smoking, breast feeding and perinatal adverse events (all p<0.05). After including these parameters in the multivariable model, esotropia was associated with sex (OR=0.40; p=0.039), hypermetropia ≥2 diopter (OR=12.1; p<0.001) and astigmatism≥1.5 diopter (OR=2.67; p<0.041) (online supplemental table 1).

Exotropia revealed a univariate association with GA, anisometropia ≥1.5 diopter and placental insufficiency (all p<0.05). In the multivariable model after the inclusion of these three univariately associated parameters in one model, only anisometropia ≥1.5 diopter remained significantly associated with exotropia (online supplemental table 2).

In univariate analyses, hypertropia/hypotropia was associated with ROP, anisometropia ≥1.5 diopter and myopia ≥2 diopter (all p<0.05). In the multivariable model, only anisometropia (OR=11.2; p=0.037) showed a significant association with hypertropia/hypotropia (online supplemental table 3).

Nystagmus was associated in univariate analyses with GA, ROP occurrence, sex, anisometropia ≥1.5 diopter, hypermetropia ≥2.0 diopter, astigmatism ≥1.5 diopter and perinatal adverse events (all p<0.05), whereas only astigmatism (OR=5.44; p=0.014) and perinatal adverse events (OR=15.8, p=0.002) remained associated in the multivariable analysis (online supplemental table 4).

**Table 3** Values of risk factors for subjects with and without strabismus, and OR and 95% CI for development of strabismus

| Strabismus | Description* | | Univariate analysis† | | Multivariable analysis‡ | |
|---|---|---|---|---|---|---|
| | Characteristics in participants with strabismus n = 52 | Characteristics in participants without strabismus n = 398 | OR (95% CI) | P value | OR (95% CI) | P value |
| Gestational age (weeks) | 30.3 ± 3.8 | 34.3 ± 4.5 | 0.81 (0.75 to 0.87) | <0.001 | 0.90 (0.81 to 0.99) | 0.046 |
| Birth weight percentile | 33.5 ± 24.8 | 39.3 ± 25.9 | 0.99 (0.98 to 1.0) | 0.13 | – | – |
| ROP (yes) | 22 (42.3%) | 41 (10.3%) | 6.39 (3.37 to 12.09) | <0.001 | 1.59 (0.56 to 0.62) | 0.38 |
| Sex (female) | 19 (36.5%) | 232 (58.3%) | 0.41 (0.23 to 0.75) | <0.001 | 0.52 (0.25 to 1.07) | 0.074 |
| Age at examination (years) | 29.6 ± 8 | 28.4 ± 8.7 | 1.02 (0.98 to 1.05) | 0.36 | – | – |
| Anisometropia ≥1.5 D (yes) | 15 (32.6%) | 22 (5.5%) | 8.27 (3.9 to 17.53) | <0.001 | 3.87 (1.59 to 9.41) | 0.003 |
| Refractive error: ≤–2 (diopter)§ | 15 (28.8%) | 80 (20.1%) | 1.61 (0.84 to 3.08) | 0.15 | – | – |
| ≥ +2 (diopter)§ | 8 (15.4%) | 8 (2.0%) | 8.86 (3.17 to 24.79) | <0.001 | 9.89 (3.24 to 30.15) | <0.001 |
| Astigmatism (diopter) ≥ 1.5 D (yes) | 17 (37.0%) | 42 (10.6%) | 4.96 (2.52 to 9.80) | <0.001 | 2.73 (1.19 to 6.23) | 0.017 |
| Maternal age at childbirth (years) | 30.8 ± 4.8 | 31.1 ± 5.1 | 0.99 (0.93 to 1.05) | 0.67 | – | – |
| Maternal smoking (yes)† | 6 (11.5%) | 26 (6.5%) | 1.87 (0.73 to 4.77 | 0.19 | – | – |
| Breast feeding (yes) | 24 (46.2%) | 214 (53.8%) | 0.74 (0.41 to 1.32) | 0.3 | – | – |
| Perinatal adverse events (yes)¶ | 17 (32.7%) | 25 (6.3%) | 7.25 (3.57 to 14.69) | <0.001 | 2.29 (0.84 to 6.24) | 0.11 |
| Pre-eclampsia (yes) | 10 (19.2%) | 52 (13.1%) | 1.58 (0.75 to 3.35) | 0.23 | – | – |
| Placental insufficiency (yes) | 5 (9.6%) | 19 (4.8%) | 2.12 (0.76 to 5.95) | 0.15 | – | – |
| Sectio cescarea (yes) | 31 (59.6%) | 181 (45.5%) | 1.77 (0.98 to 3.19) | 0.06 | – | – |

Data of the right eye was included in univariate and multivariable regression analysis for refractive error and astigmatism.
*Variables are expressed as mean±SD or as number of participants (n (%)).
†Based on univariate logistic regression analysis.
‡Based on multivariable logistic regression model. Presented factors were included in the multivariable analysis when p value was <0.05 in univariate analysis.
§Reference was refractive error between –2 diopter and +2 diopter.
¶Perinatal adverse events were defined as occurrence of intraventricular haemorrhage (at least grade 3 or parenchymal haemorrhage) and / or occurence of necrotising enterocolitis and / or occurrence of moderate or severe bronchopulmonary dysplasia.
n, number of participants; ROP, retinopathy of prematurity.

## DISCUSSION

The present study provides new data on strabismus prevalence in individuals born preterm and full-term in adulthood, demonstrating that the more preterm participants were born, the higher the risk of strabismus in adulthood, particularly in individuals with postnatal ROP and treatment. The multivariable analysis revealed an association between strabismus and low GA, anisometropia (≥1.5 D), hypermetropia (≥2 D) and astigmatism (≥1.5 D). It is of clinical significance that strabismus occurs particularly in the first 10 years of age.

The highlight of the present study is the inclusion of a broad spectrum of previously reported risk factors for strabismus in children. Several studies have reported multiple risk factors for strabismus in childhood,[4 5 8–17] however, they explored different subsets of risk factors in childhood and did not incorporate the interaction between these risk factors. Furthermore, no data about long-term development in adulthood are available. The present study emphasises the importance of incorporating this structure as multiple perinatal parameters showed a significant association with strabismus in univariate analyses but not in multivariable analyses. The multivariable analysis in the present study revealed that only low GA, anisometropia (≥1.5 D), hypermetropia (≥2 D) and astigmatism (≥1.5 D) were significantly associated with any type of strabismus in adulthood.

Different studies have analysed the effects of low GA and low birth weight and their impact on strabismus development in childhood with inconclusive results.[4 5 8 11–15] GA and low birth weight are correlated and few studies have considered the effects of perinatal hypotrophy indicated by low birth weight in relation to GA. Low birth weight is associated with an increased prevalence of strabismus, so we considered the birth weight percentile in correlation to GA in the multivariable analyses and found that the low birth weight percentile was not associated with an increased risk for strabismus. Inconclusive results exist in children where two studies reported an increased risk for strabismus in preterm infants with low GA,[5 8] while authors in two retrospective, population-based cohort studies reported an association with low birth weight[11 14] and Torp-Pedersen *et al*[11] found an additional association with GA. In contrast, Gulati *et al*[14] did not find a correlation between strabismus and GA when considering birth weight. Previous research suggested that a birth weight below 2000 g might be a more critical risk factor for strabismus, but these studies had limitations.

The Wiesbaden Prematurity Study identified low GA, higher refractive error and astigmatism as key risk factors for childhood strabismus. This current study extended these findings to adulthood, showing that only GA, not birth weight percentile, was associated with strabismus in multivariable analyses. This highlights that perinatal immaturity, rather than adverse fetal growth, is the primary risk factor for adult strabismus.

In our multivariable model, hyperopia ≥2 diopters was independently associated with strabismus and esotropia. Similarly, the Sydney Childhood Eye Study found a relationship between increased hyperopic refractive error and strabismus.[4] The Wiesbaden Prematurity Study authors observed that hypermetropia above 3 diopters has the strongest effects on the prevalence of strabismus and its subtype esotropia.[25] Our data extend these findings by demonstrating that hyperopic refractive error is a major risk factor for strabismus and esotropia in adults born preterm.

In a population-based study of Robaei *et al*,[4] children aged 6 years with strabismus had an increased astigmatism of 0.32 diopters compared with children without strabismus. This study found that astigmatism is an independent risk factor for strabismus and esotropia in adults, significantly influencing long-term strabismus development until adulthood.

Strabismus prevalence in adulthood varies among clinical groups, with higher rates in prematurely born individuals. The full-term control group had low prevalence, while preterm individuals without ROP had 17.4%, ROP without treatment had 27.1% and ROP-treated participants had a high 60% prevalence. These variations in prevalence are due to differences in study populations and designs. Prior reports have shown strabismus prevalence in preterm children reaching up to 42%,[7–10] compared with 0.5%–9.9% for individuals born full term.[25 27 28] Hardly any data exist about strabismus prevalence in individuals born preterm in adulthood. Jain *et al*[18] reported a prevalence of strabismus in individuals born extremely preterm (22–25 weeks of GA) in early adulthood (mean age 19 years) of 36% compared with 0% in age-matched controls which was comparable to our adult participants. Pétursdóttir *et al* reported a strabismus prevalence rate of 12% (7 out of 59 individuals) in a study of young adults aged 25–29 years, who were born preterm with a mean GA of 29 weeks.[29]

However, we can provide evidence that each level of immaturity, as well as the occurrence and treatment of ROP, are independent risk factors.

In our study, the most frequent type of strabismus was esotropia, followed by exotropia, hypertropia and hypotropia, similar to three previous studies in children reporting that esotropia was the most common type of strabismus.[7 30] Different pathophysiological mechanisms are discussed that may lead to the different types of strabismus such as injuries during decisive periods of brain development.[4 31] Individuals born preterm have an increased risk of brain injuries,[32] thus this may be one parameter for the increased rates in individuals born preterm.[25] This study emphasises the need to identify specific risk factors associated with distinct types of strabismus, as previous studies often underanalysed these factors separately. Nystagmus prevalence increased with greater prematurity, ranging from 0.7% in full-term individuals to 1.5%–5.6% in more preterm individuals. Significantly higher rates were observed in those with postnatal ROP, particularly those who received treatment (10.4% and 26.7%, respectively), consistent with previous childhood data.[25] Nystagmus signals severe vision loss and impaired binocular vision. In this study, those with nystagmus often had low-amplitude, high-frequency nystagmus, possibly linked to a higher risk of white matter damage in preterm-born individuals[33 34] as suggested by the finding that the occurrence of perinatal adverse events is a strong predictor for nystagmus.

The Gutenberg Health Study found that strabismus in adulthood leads to decreased vision-related quality of life.[6] This study found that increased immaturity and strabismus prevalence increase amblyopia and reduced visual acuity. Preterm birth may cause reduced visual acuity due to anatomic changes such as foveal hypoplasia, retinal scars and detachment. In a previous report investigating extremely low birth weight infants, the authors observed changes in optical radiation and visual cortex in individuals born preterm compared with the control group,[35] which might additionally lead to visual dysfunction in individuals born preterm. It is of clinical significance that strabismus affects individuals with increased rates of amblyopia and reduced visual acuity, especially in the first 10 years of life. Regular ophthalmic control appointments are crucial to detect affected individuals early and prevent amblyopia.

### Strengths and limitations

This study has limitations, including its single-centre design and some potential participants declining to take part. The low number of participants with advanced ROP stages and ROP requiring treatment may lead to lower statistical power and less precise estimates in these groups. The generalisability of the findings is limited to mostly Caucasian participants. Self-reported strabismus history could introduce bias, but efforts were made to validate it with medical records, although not available for all participants.

Strengths of this study include a large sample size and inclusion of preterm individuals with varying degrees of prematurity, regardless of ROP status. Comprehensive perinatal data enabled multivariable analyses with different perinatal factors.

## CONCLUSION

This study shows that the main determinants for strabismus are low GA, anisometropia, hypermetropia and astigmatism. The more immature the participants were born, the more frequently strabismus was present in adulthood. In addition, this is one of the few studies reporting data for esotropia, exotropia, hypertropia/hypotropia and nystagmus separately with individual risk factors, demonstrating that esotropia is the most frequent type of strabismus followed by exotropia and hypertropia/hypotropia. Of special note, strabismus occurs in affected individuals particularly in premature born subjects within in the first years of life highlighting the need to evaluate whether screening in this high-risk population for amblyopia should be recommended.

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**Patient consent for publication** Consent obtained directly from patient(s).

**Ethics approval** The study protocol and study documents were approved by the local ethics committee of the Medical Chamber of Rhineland-Palatinate, Germany (reference no. 2019-14161; original vote: 29 May 2019, latest update: 2 April 2020). Participants gave informed consent to participate in the study before taking part.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** Data are available upon reasonable request. Access to data, responsibility and analysis: AF had full access to all the study data and takes responsibility for the data integrity and the accuracy of the data analysis. Statistical analyses were performed by AF. The analysis presents the clinical data of a cohort. This project constitutes a major scientific effort with high methodological standards and detailed guidelines for analysis and publication to ensure scientific analyses are on the highest level, therefore, data are not made available for the scientific community outside the established and controlled workflows and algorithms. To meet the general idea of verification and reproducibility of scientific findings, we offer access to data at the local database upon request at any time. Interested researchers should make their requests to the coordinating PI of the GPES (Achim Fieß; achim.fiess@unimedizin-mainz.de). More detailed contact information is available at the homepages of the UM (www.unimedizin-mainz.de).



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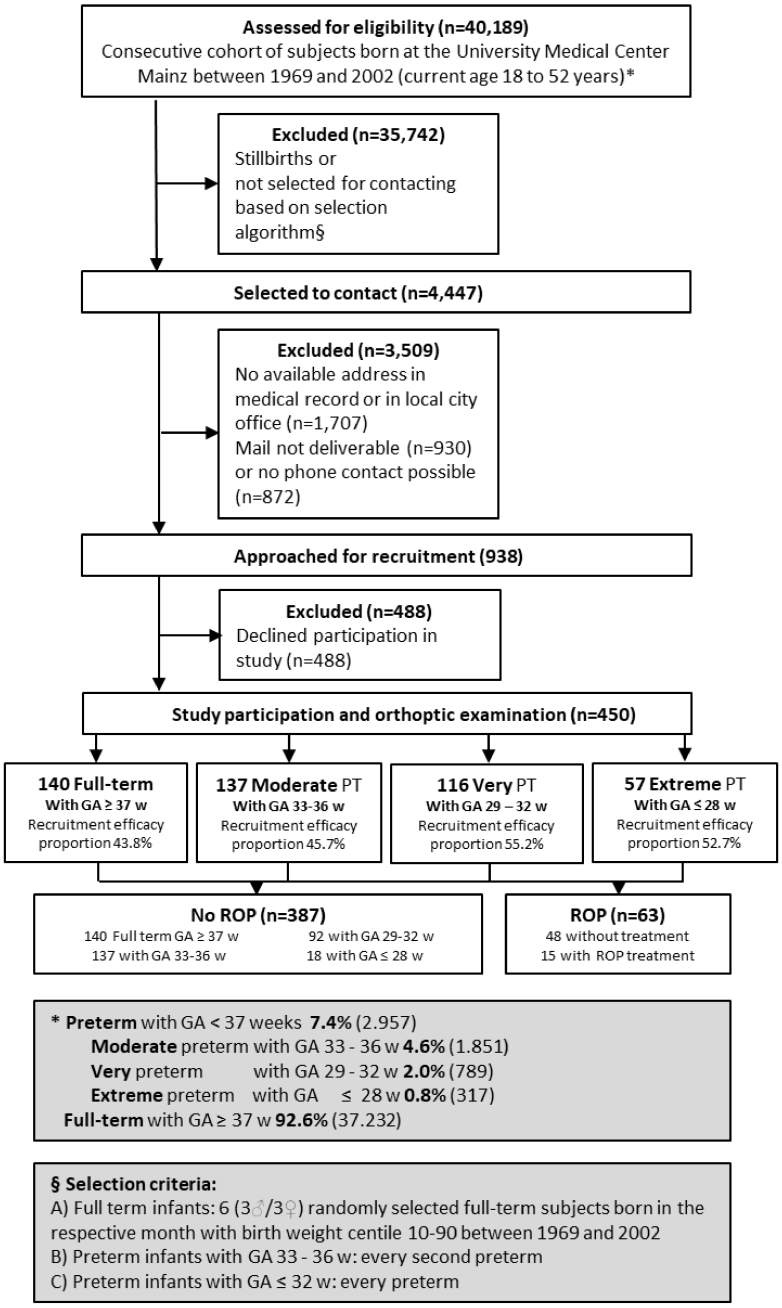
**Supplementary Figure 1: Design of the Gutenberg Prematurity Eye Study (GPES)**




**w – weeks; GA – gestational age**

**Supplementary Table 1 Association analysis with respect to esotropia. Data from the Gutenberg Prematurity Eye Study**

| | Description[#] | | Univariate Analysis[##] | | Multivariable analysis[###] | |
|---|---|---|---|---|---|---|
| | Characteristics in participants with esotropia n = 36 | Characteristics in participants without esotropia n = 414 | OR [95% CI] | p-value | OR [95% CI] | p-value |
| Gestational age [weeks] | 30 ± 4 | 34.2 ± 4.5 | 0.8 [0.74; 0.88] | <0.001 | 0.91 [0.80; 1.04] | 0.15 |
| Birth weight percentile | 30.3 ± 21.6 | 39.4 ± 26 | 0.99 [0.97; 0.999] | 0.04 | 0.99 [0.97; 1.00] | 0.14 |
| ROP [yes] | 17 (47.2%) | 46 (11.1%) | 7.16 [3.48; 14.74] | <0.001 | 2.52 [0.75; 8.43] | 0.13 |
| Sex [female] | 12 (33.3%) | 239 (57.7%) | 0.37 [0.18; 0.75] | 0.01 | 0.40 [0.18; 0.96] | 0.039 |
| Age at examination [years] | 29.7 ± 7.7 | 28.5 ± 8.7 | 1.02 [0.98; 1.06] | 0.41 | - | - |
| Anisometropia ≥ 1,5 D [yes] | 10 (27.8%) | 27 (6.6%) | 5.91 [2.57; 13.62] | <0.001 | 2.06 [0.73; 5.78] | 0.17 |
| Refractive error: ≤ -2 [diopter] * | 12 (33.3%) | 83 (20.0%) | 1.99 [0.96; 4.15] | 0.065 | - | - |
| ≥ +2 [diopter] * | 6 (16.7%) | 10 (2.4%) | 8.08 [2.75; 23.7] | <0.001 | 12.1 [3.46; 42.5] | <0.001 |
| Astigmatism [diopter] ≥ 1.5 D [yes] | 14 (38.9%) | 45 (11.0%) | 5.68 [2.68; 12.0) | <0.001 | 2.67 [1.04; 6.84] | 0.041 |
| Maternal age at childbirth [years] | 30.6 ± 4.1 | 31.1 ± 5.1 | 0.98 [0.92; 1.05] | 0.59 | - | |
| Maternal smoking [yes] | 6 (16.7%) | 26 (6.3%) | 2.98 [1.14; 7.81] | 0.03 | 2.17 [0.61; 7.68] | 0.23 |
| Breastfeeding [yes] | 13 (36.1%) | 225 (54.3%) | 0.47 [0.23; 0.96] | 0.04 | 0.69 [0.29; 1.62] | 0.40 |
| Perinatal adverse events [yes][**] | 14 (38.9%) | 28 (6.8%) | 8.77 [4.05; 18.99] | <0.001 | 1.99 [0.65; 6.09] | 0.22 |
| Preeclampsia [yes] | 9 (25%) | 53 (12.8%) | 2.27 [1.01; 5.09] | 0.051 | - | - |
| Placental insufficiency [yes] | 2 (5.6%) | 22 (5.3%) | 1.05 [0.24; 4.65] | 0.95 | - | - |
| Sectio cesarea [yes] | 22 (61.1%) | 190 (45.9%) | 1.85 [0.92; 3.72] | 0.083 | - | - |

n = number of participants, OR = odds ratio, CI = confidence interval, ROP = retinopathy of prematurity; Data of the right eye was included in univariate and multivariable regression analysis for refractive error and astigmatism.

[#]Variables are expressed as mean ± standard deviation (SD) or as number of participants (n (%)).

## based on univariate logistic regression analysis

### based on multivariable logistic regression model. Presented factors were included in the multivariable analysis when P value was <0.05 in univariate analysis

*Reference was refractive error between -2 diopter and +2 diopter

** Perinatal adverse events were defined as occurrence of intraventricular hemorrhage# (at least grade 3 or parenchymal hemorrhage), occurrence of necrotizing enterocolitis and bronchopulmonary dysplasia (+moderate or severe). ##: maternal smoking during pregnancy

**Supplementary Table 2 Association analysis with respect to exotropia. Data from the Gutenberg Prematurity Eye Study.**

| **Exotropia** | **Description[#]** | | **Univariate Analysis[##]** | | **Multivariable analysis[###]** | |
|---|---|---|---|---|---|---|
| | Characteristics in participants with exotropia n = 16 | Characteristics in participants without exotropia n = 434 | OR [95% CI] | p-value | OR [95% CI] | p-value |
| Gestational age [weeks] | 30.9 ± 3.3 | 34 ± 4.6 | 0.86 [0.77; 0.97] | 0.01 | 0.94 [0.82; 1.07] | 0.33 |
| Birth weight percentile | 40.8 ± 30.5 | 38.6 ± 25.6 | 1 [0.98; 1.02] | 0.74 | - | - |
| ROP [yes] | 5 (31.3%) | 58 (13.4%) | 2.95 [0.99; 8.79] | 0.052 | - | - |
| ROP treatment [yes] | 2 (12.5%) | 13 (3%) | 4.63 [0.95; 22.48] | 0.06 | - | - |
| Sex [female] | 7 (43.8%) | 244 (56.2%) | 0.61 [0.22; 1.66] | 0.33 | - | - |
| Age at examination [years] | 29.3 ± 8.7 | 28.5 ± 8.6 | 1.01 [0.96; 1.07] | 0.72 | - | - |
| Anisometropia ≥ 1.5 D [yes] | 5 (31.3%) | 32 (7.4%) | 8.93 [2.68; 29.73] | <0.001 | 7.32 [2.08; 25.8] | 0.002 |
| Refractive error: ≤ -2 [diopter] * | 3 (18.8%) | 92 (21.2%) | 0.97 [0.27; 3.56] | 0.97 | - | - |
| ≥ +2 [diopter] * | 2 (12.5%) | 14 (3.2%) | 4.26 [0.86; 21.1] | 0.076 | - | - |
| Astigmatism [diopter] ≥ 1.5 D [yes] | 3 (18.8%) | 56 (13.0%) | 2.24 [0.59; 8.52] | 0.24 | - | - |
| Maternal age at childbirth [years] | 31.1 ± 6.2 | 31 ± 5 | 1 [0.91; 1.11] | 0.95 | - | - |
| Maternal smoking [yes] | 0 (0%) | 32 (7.4%) | 0.00 [0.00; 0.00] | >0.99 | - | - |
| Breastfeeding [yes] | 11 (68.8%) | 227 (52.3%) | 2.01 (0.69; 5.87) | 0.2 | - | - |
| Perinatal adverse events [yes]** | 3 (18.8%) | 39 (9%) | 2.34 [0.64; 8.56] | 0.2 | - | - |
| Preeclampsia [yes] | 1 (6.3%) | 61 (14.1%) | 0.41 [0.05; 3.14] | 0.39 | - | - |
| Placental insufficiency [yes] | 3 (18.8%) | 21 (4.8%) | 4.54 [1.2; 17.16] | 0.03 | 3.58 [0.68; 18.8] | 0.13 |
| Sectio cesarea [yes] | 9 (56.2%) | 203 (46.8%) | 1.46 [0.54; 3.99] | 0.46 | - | - |

n = number of participants, OR = odds ratio, CI = confidence interval, ROP = retinopathy of prematurity; Data of the right eye was included in univariate and multivariable regression analysis for refractive error and astigmatism.
[#]Variables are expressed as mean ± standard deviation (SD) or as number of participants (n (%)), P-values below 0.05 were marked in bold
## based on univariate logistic regression analysis
### based on multivariable logistic regression model. Presented factors were included in the multivariable analysis when P value was <0.20 in univariate analysis
*Reference was refractive error between -2 diopter and +2 diopter
** Perinatal adverse events were defined as occurrence of intraventricular hemorrhage# (at least grade 3 or parenchymal hemorrhage), occurrence of necrotizing enterocolitis and bronchopulmonary dysplasia (+moderate or severe). ##: maternal smoking during pregnancy

**Supplementary Table 3 Association analysis with respect to hyper/hypometropia. Data from the Gutenberg Prematurity Eye Study.**

| **Hyper/Hypotropia** | **Description#** | | **Univariate Analysis##** | | **Multivariable analysis###** | |
|---|---|---|---|---|---|---|
| | Characteristics in participants with hyper/hypotropia n = 6 | Characteristics in participants without hyper/hypotropia n = 444 | OR [95% CI] | p-value | OR [95% CI] | p-value |
| Gestational age [weeks] | 31 ± 5.2 | 33.9 ± 4.6 | 0.87 [0.72; 1.04] | 0.13 | - | - |
| Birth weight percentile | 37.5 ± 25.9 | 38.7 ± 25.8 | 1 [0.97; 1.03] | 0.91 | - | - |
| ROP [yes] | 3 (50%) | 60 (13.5%) | 6.4 [1.26; 32.45] | 0.03 | 2.41 [0.33; 17.8] | 0.39 |
| Sex [female] | 2 (33.3%) | 249 (56.1%) | 0.39 [0.07; 2.16] | 0.28 | - | - |
| Age at examination [years] | 25.7 ± 7.9 | 28.6 ± 8.6 | 0.95 [0.85; 1.07] | 0.42 | - | - |
| Anisometropia ≥ 1.5 D [yes] | 2 (33.3%) | 35 (8%) | 7.7 [1.24; 47.6] | 0.03 | 11.2 [1.16; 108.9] | 0.037 |
| Refractive error: ≤ -2 [diopter] * | 4 (66.7%) | 91 (20.5%) | 7.47 [1.34; 41.1] | 0.022 | 2.88 [0.38; 22.1] | 0.31 |
| ≥ +2 [diopter] * | 0 (0%) | 16 (3.6%) | 0 [0; 0] | >0.99 | - | - |
| Astigmatism [diopter] ≥ 1.5 D [yes] | 2 (33.3%) | 57 (13.0%) | 4.47 [0.73; 27.3] | 0.1 | - | - |
| Maternal age at childbirth [years] | 33.2 ± 5.5 | 31 ± 5 | 1.09 [0.93; 1.28] | 0.3 | - | - |
| Maternal smoking [yes] | 0 (0%) | 32 (7.2%) | 0 [0; 0] | >0.99 | - | - |
| Breastfeeding [yes] | 3 (50%) | 235 (52.9%) | 0.89 [0.18; 4.45] | 0.89 | - | - |
| Perinatal adverse events [yes]** | 2 (33.3%) | 40 (9%) | 5.05 [0.9; 28.43] | 0.07 | - | - |
| Preeclampsia [yes] | 0 (0%) | 62 (14%) | 0 [0; 0] | >0.99 | - | - |
| Placental insufficiency [yes] | 0 (0%) | 24 (5.4%) | 0 [0; 0] | >0.99 | - | - |
| Sectio cescarea [yes] | 5 (83.3%) | 207 (46.6%) | 5.72 [0.66; 49.4] | 0.11 | - | - |

n = number of infants, OR = odds ratio, CI = confidence interval, ROP = retinopathy of prematurity; Data of the right eye was included in univariate and multivariable regression analysis for refractive error and astigmatism.

#Variables are expressed as mean ± standard deviation (SD) or as number of participants (n (%)).

## based on univariate logistic regression analysis

### based on multivariable logistic regression model. Presented factors were included in the multivariable analysis when P value was <0.20 in univariate analysis

*Reference was refractive error between -2 diopter and +2 diopter

** Perinatal adverse events were defined as occurrence of intraventricular hemorrhage# (at least grade 3 or parenchymal hemorrhage), occurrence of necrotizing enterocolitis and bronchopulmonary dysplasia (+moderate or severe). ##: maternal smoking during pregnancy

**Supplementary Table 4 Association analysis with respect to nystagmus. Data from the Gutenberg Prematurity Eye Study**

| **Nystagmus** | **Description#** | | **Univariate Analysis##** | | **Multivariable analysis###** | |
|---|---|---|---|---|---|---|
| | Characteristics in children with nystagmus n = 17 | Characteristics in children without nystagmus n = 433 | OR [95% CI] | p-value | OR [95% CI] | p-value |
| Gestational age [weeks] | 29.2 ± 4.3 | 34 ± 4.5 | 0.77 [0.68; 0.88] | <0.001 | 0.94 [0.76; 1.16] | 0.54 |
| Birth weight percentile | 33.3 ± 20 | 38.9 ± 26 | 0.99 [0.97; 1.01] | 0.38 | - | - |
| ROP [yes] | 9 (52.9%) | 54 (12.5%) | 7.9 [2.92; 21.34] | <0.001 | 0.70 [0.09; 5.15] | 0.73 |
| Sex [female] | 5 (29.4%) | 246 (56.8%) | 0.32 [0.11; 0.91] | 0.03 | 0.66 [0.18; 2.43] | 0.53 |
| Age at examination [years] | 30.2 ± 7.1 | 28.5 ± 8.7 | 1.02 [0.97; 1.08] | 0.41 | - | - |
| Anisometropia ≥ 1.5 D [yes] | 6 (35.3%) | 31 (7.2%) | 9.65 [3.15; 29.58] | <0.001 | 3.61 [0.92; 14.2] | 0.067 |
| Refractive error: ≤ -2 [diopter] * | 6 (35.3%) | 89 (20.6%) | 2.79 [0.94; 8.25] | 0.064 | - | - |
| ≥ +2 [diopter] * | 3 (17.6%) | 13 (3.0%) | 9.55 [2.27; 40.2] | 0.002 | 11.9 [2.12; 66.4] | 0.005 |
| Astigmatism [diopter] ≥ 1.5 D [yes] | 8 (47.1%) | 51 (11.8%) | 9.91 [3.30; 29.7] | <0.001 | 5.44 [1.41; 21.0] | 0.014 |
| Maternal age at childbirth [years] | 29.8 ± 3.4 | 31.1 ± 5.1 | 0.95 [0.86; 1.04] | 0.29 | - | - |
| Maternal smoking [yes] | 3 (17.6%) | 29 (6.7%) | 2.99 [0.81; 10.98] | 0.1 | - | - |
| Breastfeeding [yes] | 7 (41.2%) | 231 (53.3%) | 0.61 [0.23; 1.64] | 0.33 | - | - |
| Perinatal adverse events [yes]** | 10 (58.8%) | 32 (7.4%) | 17.9 [6.39; 50.18] | <0.001 | 15.8 [2.68; 93.6] | 0.002 |
| Preeclampsia [yes] | 3 (17.6%) | 59 (13.6%) | 1.36 [0.38; 4.87] | 0.64 | - | - |
| Placental insufficiency [yes] | 1 (5.9%) | 23 (5.3%) | 1.11 [0.14; 8.77] | 0.92 | - | - |
| Sectio cesarea [yes] | 11 (64.7%) | 201 (46.4%) | 2.12 [0.77; 5.82] | 0.15 | - | - |

n = number of infants, OR = odds ratio, CI = confidence interval, ROP = retinopathy of prematurity; Data of the right eye was included in univariate and multivariable regression analysis for refractive error and astigmatism.

#Variables are expressed as mean ± standard deviation (SD) or as number of participants (n (%)).

## based on univariate logistic regression analysis

### based on multivariable logistic regression model. Presented factors were included in the multivariable analysis when P value was <0.05 in univariate analysis

*Reference was refractive error between -2 diopter and +2 diopter

** Perinatal adverse events were defined as occurrence of intraventricular hemorrhage# (at least grade 3 or parenchymal hemorrhage), occurrence of necrotizing enterocolitis and bronchopulmonary dysplasia (+moderate or severe). ##: maternal smoking during pregnancy