Acta Ophthalmologica

Acta Ophthalmologica 2022

Refractive error, accommodation and lens opacification in adults born preterm and full-term: Results from the Gutenberg Prematurity Eye Study (GPES)

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ABSTRACT.

Purpose: **To evaluate the long-term effects of different degrees of prematurity, retinopathy of prematurity (ROP) and associated perinatal factors on refractive error, accommodation and lens opacification development in adults born preterm aged 18–52 years.**

Methods: **The Gutenberg Prematurity Eye Study (GPES) investigated adults born preterm and full-term at 18–52 years in Germany to assess refractive error, accommodation amplitude and lens opacification. The participants were grouped into normal gestational age (GA) ≥37 weeks (control group), preterm participants without ROP and GA 33–36 weeks (group 2), GA 29–32 weeks (group 3), GA ≤28 weeks (group 4) and those with ROP without (group 5) or with treatment (group 6). Main outcome measures were refractive error, anisometropia, accommodation amplitude and lens opacification.**

Results: **In total, 856 eyes of 433 preterm and full-term individuals (aged 28.4 +/− 8.6 years, 242 females) were included. A myopic refractive error of >6 diopter was observed in 4% (11/278), 2.7% (7/264), 1.2% (2/174), 5.6% (2/36), 10.5% (8/78) and 26.9% (7/26) of eyes and anisometropia ≥2 diopter in 2.9% (4/139), 2.3% (3/132), 3.5% (3/87), 11.1% (2/18), 9.5% (4/44) and 38.5% (5/13) of participants in the respective groups. Spherical equivalent did not differ between participants without postnatal ROP born moderately, very and extremely preterm compared to the full-term control group. ROP treatment was associated with lower accommodation and more lens opacifications.**

Conclusion: **Retinopathy of prematurity treatment using cryocoagulation and laser coagulation increases refractive error associated with increased lens opacifications and reduced accommodation. Preterm delivery has little effect on absolute refractive error but is associated with anisometropia in adulthood.**

Key words: accommodation – birth weight – cataract – epidemiology – gestational age – retinopathy of prematurity

Pfeiffer N receives financial support and grants from Novartis, Ivantis, Santen, Thea, Boehringer Ingelheim Deutschland GmbH & Co. KG, Alcon and Sanoculis. Schuster AK receives research support from Allergan, Bayer, Heidelberg Engineering, PlusOptix and Norvartis. All authors: The Gutenberg Prematurity Eye Study (GPES) was supported by the Ernst- und Berta-Grimmke Stiftung, Stufe 1 support of the UMCM and the Else-Kröner-Fresenius Stiftung. The funders had no role in study design, data collection and analysis, decision to publish or preparation of the manuscript. Schuster AK holds the professorship for ophthalmic healthcare research endowed by "Stiftung Auge" and financed by "Deutsche Ophthalmologische Gesellschaft" and "Berufsverband der Augenärzte Deutschlands e.V.".

Conceived and designed the study: AFi, AKS; analysed the data: AFi, AFa, EM, MSU and AKS; wrote the paper: AFi, critically revised the manuscript: AFi, AFa, EM, MSU, HME, FZ, BS, NP and AKS, all authors read and approved the final manuscript. This study contains parts of the thesis of Agnes Fauer.

Acta Ophthalmol. 2022: 100: e1439–e1450

doi: 10.1111/aos.15116

1. Introduction

Preterm birth is associated with several severe ocular sequelae and complications after birth and in early life, leading to retinopathy of prematurity (ROP), a vasoproliferative disorder of the retina, with a potential need for treatment (Hellström et al. 2013). This is of clinical significance, as the number of extremely preterm newborns and the prevalence of postnatal ROP are still dramatically increasing (Blencowe et al. 2013) with nearly every tenth newborn worldwide born too early (Blencowe et al. 2016). Due to premature birth and postnatal ROP development and treatment, various ocular complications can occur such as reduced visual acuity and impaired stereopsis (Holmstrom et al. 1999; Schalij-Delfos et al. 2000; Fieß et al. 2017a) as well as strabismus and amblyopia (Holmstrom et al. 1999; Schalij-Delfos et al. 2000; Fieß et al. 2017b). Various studies report an increased risk for myopic refractive error, astigmatismus, and anisometropia in children and adolescents born preterm particularly in those who experienced advanced stages of ROP and ROP treatment (Fledelius 1996; Darlow et al. 1997; Larsson et al. 2003; O'Connor et al. 2006; Fieß et al. 2017b).

However, there is a lack of data regarding the long-term effects of prematurity and postnatal ROP occurrence and treatment on the refractive state in adulthood focusing mainly on the effects of severe stages of ROP and its treatment (Ferrone et al. 1998; Kaiser et al. 2001; Smith & Tasman 2005; Kaiser et al. 2008; Darlow et al. 2018). Pétursdóttir et al. (Pétursdóttir et al. 2021a) and Darlow et al. (Darlow et al. 2018) reported that adults born preterm had a higher prevalence of myopia and anisometropia. In a recent population-based report of the Gutenberg Health Study, the authors found an association between low birth weight (<2500 g) as a proxy for preterm birth and an increased risk for myopic refractive error in adults aged 35–74 years (Fieß et al. 2019a). However, this study did not differentiate birth weight, gestational age (GA) and postnatal ROP occurrence and treatment, hence, there is a lack of data assessing the long-term effects of the different levels of prematurity with and without postnatal ROP occurrence and treatment in adulthood.

Children who had been treated for ROP show an increased lens thickness (Fledelius 1980; Wu et al. 2012; Fieß et al. 2017a) which might be associated with an altered lens consistence potentially contributing to increased lens opacifications and/or cataracts in later life. In individuals with postnatal ROP stages 4 and 5, an increased rate of cataracts was observed in infancy (Christiansen & Bradford 1995) but no data exist about the effects of prematurity and associated factors on lens long-term development. New devices are currently available which enable an objective measurement of lens opacifications. Lower accommodation was observed in children born preterm (Larsson et al. 2012) which might also indicate, amongst others, alterations in lens development, while the long-term effects are less known.

Thus, this study assessed the refractive error, anisometropia, accommodation and lens opacification in individuals (18–52 years) with and without ROP born moderately, very and extremely preterm compared to a full-term control group.

2. Materials and methods

2.1. Study population

The Gutenberg Prematurity Eye Study (GPES) is a single-centre, retrospective cohort study conducted at the University Medical Center of the Johannes Gutenberg-University Mainz in Germany (UMCM) with prospective data acquisition including an ophthalmic examination in adulthood. The GPES examined individuals being born preterm or at term in the UMCM between 1969 and 2002 with an actual age between 18 and 52 years at examination. Every individual born preterm with a GA ≤32 weeks and every second random individual born preterm with a GA 33–36 weeks was invited to participate in this study. For each month from 1969 to 2002, three males and three females born at term with a birth weight between the 10th and 90th percentile were invited to serve as controls. The flow chart for eligibility and the effective recruitment efficacy proportion are displayed in Fig. 1.

The examinations were performed between 2019 and 2021. All participants underwent a detailed and comprehensive ophthalmic examination including evaluation of the refractive error and a medical history interview. Furthermore, the medical records of the study participants documenting their perinatal and postnatal history in the UMCM were assessed.

Written informed consent was obtained from all study participants before they entered the study and the GPES complies with Good Clinical Practice (GCP), Good Epidemiological Practice (GEP) and the ethical principles of the Declaration of Helsinki. The study protocol and documents were approved by the local ethics committee of the Medical Chamber of Rhineland-Palatinate, Germany (reference no. 2019–14161; original vote: 29.05.2019, latest update: 02.04.2020).

2.2. Assessment of pre-, peri- and postnatal medical history

Medical records archived at UMCM were assessed to obtain information about the peri- and postnatal medical course for each participant. The following parameters were collected: GA (weeks), birth weight (kg), presence of ROP, stage of ROP, ROP treatment, placental insufficiency, preeclampsia, maternal smoking, perinatal adverse events and breastfeeding. The birth weight percentiles were calculated according to Voigt et al. (Voigt et al. 2006).

2.3. 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 between 33 and 36 weeks without ROP (group 2), participants born preterm with a GA between 29 and 32 weeks without ROP (group 3), participants born preterm with a GA ≤28 weeks without ROP (group 4) and participants born preterm with a GA ≤32 weeks with postnatal ROP without (group 5) and with treatment (group 6). In the case that only one eye had ROP, the other non-ROP eye was excluded from the analysis.

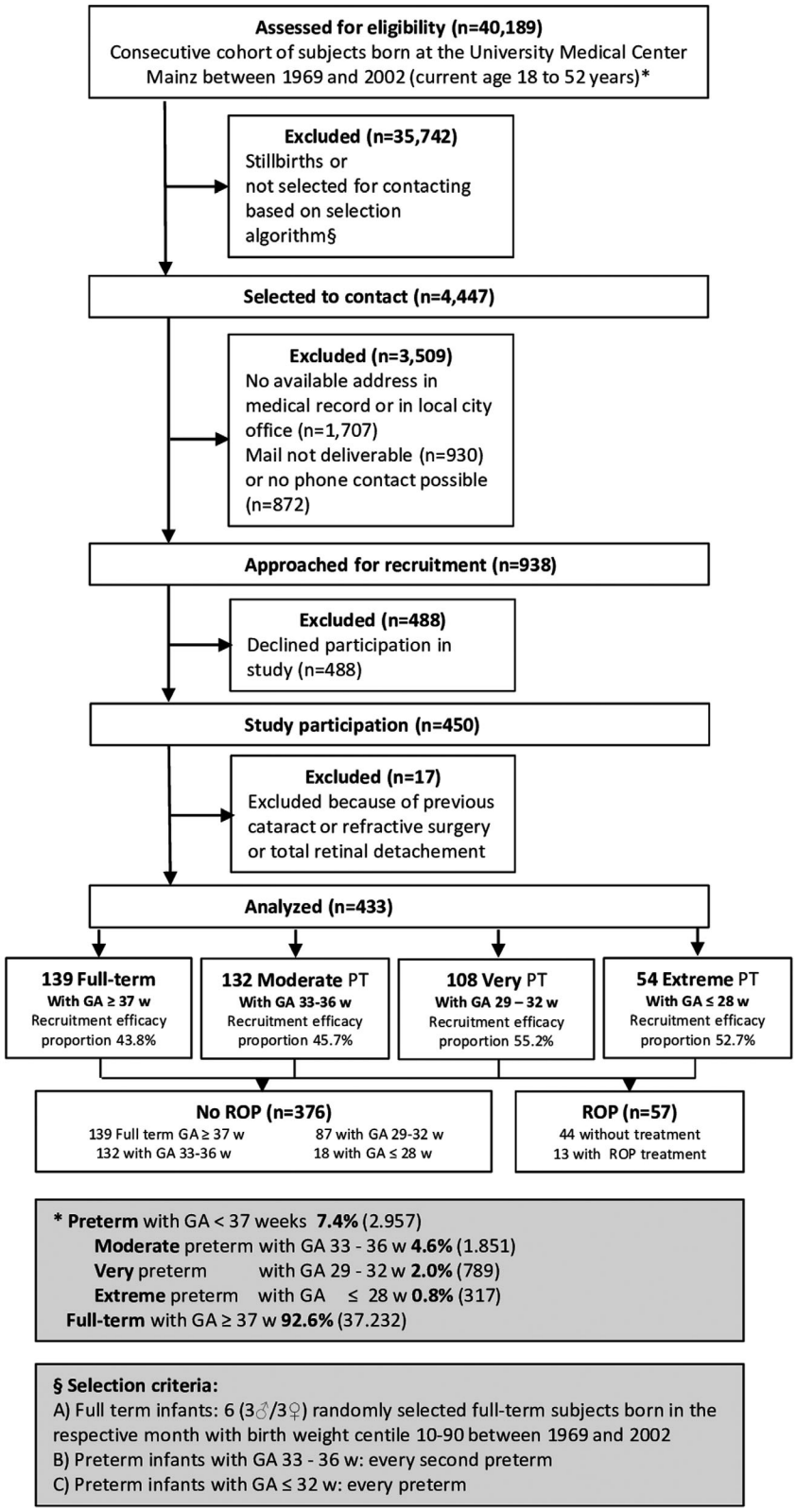

Fig. 1. Design of the Gutenberg Prematurity Eye Study. PT = preterm; w = weeks.

2.4. Ophthalmologic examination

Refractive error, accommodation, distant-corrected visual acuity and lens opacification were examined using an automatic refractometer (ARK-1 s, NIDEK, Oculus, Wetzlar, Germany). Intraocular pressure was measured with a non-contact tonometer (NT 2000™, Nidek Co./Japan). Visual acuity was converted from decimal to logMAR per the recommendations in the medical literature (Bach & Kommerell 1998).

2.5. Refractive error, accommodation and lens opacification

The refractive error was measured and the spherical equivalent was calculated by adding the sphere and half of the cylindric value. Anisometropia was assessed by calculating the difference in the spherical equivalent between the right and left eye. Anisoastigmatismus was calculated by the difference of the cylindric value between the right and left eye. The accommodation was measured while the participants focussed on a target moving from distance to near, and the absolute sphere value of accommodation was determined in addition to the minimal and maximal pupil size during accommodation. Every measurement was reviewed and graded for validity. Furthermore, opacifications of optical media were assessed on retro-illumination images. The device provides cataract indices giving information about the severity of the opacity: opacification size within a central 3 mm zone (COI-H); opacification proportion within the 3 mm central zone in % (COI-A), and opacity proportion in the entire periphery in % (POI). Every retro-illuminated picture was reviewed. In the case of irregular alignment or incorrect pupil detection, these measurements were excluded.

2.6. Inclusion and exclusion criteria

The inclusion criterion for the present analysis was the successful measurement of refractive error. Persons with previous cataracts or refractive corneal surgery and total retinal detachment were excluded.

2.7. Covariates

Factors that may affect the main outcome measures, such as sex (female), age (years), GA (weeks), birth weight (kg), birth weight percentile, ROP occurrence (yes), ROP treatment (yes), placental insufficiency (yes), preeclampsia (yes), maternal smoking (yes), breastfeeding (yes) and perinatal adverse events (yes) were considered. Perinatal adverse events were defined according to the German query for quality control of the neonatal clinics: intraventricular haemorrhage (at least grade 3 or parenchymal haemorrhage), necrotizing enterocolitis and moderate or severe bronchopulmonary dysplasia. These were summarized as adverse event. A structured assessment of socioeconomic status was conducted using the multidimensional index for surveys as part of national health reporting in Germany (Lampert et al. 2013). The index includes information on educational attainment, occupational status and income. Furthermore, every participant was asked about the average hours they spent reading.

2.8. Statistical analysis

The main outcome measures were spherical equivalent, astigmatismus, anisometropia, anisoastigmatismus, accommodation and lens opacification. Descriptive statistics were computed stratified by prematurity group. Absolute and relative frequencies were calculated for dichotomous parameters, mean and standard deviation for approximately normally distributed variables, otherwise median and interquartile range. Linear regression models (if approximately normal distributed) using general estimating equations (GEE) to account for correlations between corresponding eyes were used to assess associations. If parameters were not normally distributed (astigmatismus, anisometropia, anisoastigmatismus and accommodation), quantile regression was applied and only right eyes were included. For spherical equivalent (diopter), astigmatism (diopter), anisometropia (diopter), anisoastigmatismus (diopter) and accommodation (diopter), univariate analyses were conducted investigating the relationship with sex (female), age (years), GA (weeks), birth weight (kg), birth weight percentile, ROP (yes), ROP treatment (yes), placental insufficiency (yes), preeclampsia (yes), maternal smoking (yes), perinatal adverse events (yes) and breastfeeding (yes). In multivariable linear regression model #1, all univariate associated parameters were included except birth weight, ROP occurrence and ROP treatment due to its high correlation with GA. The univariate associated parameters and postnatal ROP occurrence and ROP treatment (if associated in univariate analyses) were included in a second model. A sensitivity analysis was performed for spherical equivalent with the inclusion of socioeconomic status and daily hours of reading in childhood in a multivariable model. This was an explorative study, so there was no adjustment for multiple testing. The statistical analyses were performed using commercial software (IBM SPSS 20.0; SPSS, Inc., Chicago, IL, USA).

3. Results

3.1. Participant characteristics

In the present analysis, 578 eyes of 294 preterm and 278 eyes of 139 full-term individuals were included (aged 28.4 +/− 8.6 years, 242 females). There were 278 eyes of 139 participants with GA ≥37 weeks (control group), 264 eyes of 132 participants with a GA between 33–36 weeks without ROP (group 2), 174 eyes of 87 participants with a GA between 29–32 weeks without ROP (group 3), 36 eyes of 18 participants with a GA ≤28 weeks without ROP (group 4), 78 eyes of 44 participants with a GA between 24–32 weeks with ROP without treatment (group 5) and 26 eyes of 13 participants with a GA between 24–32 and with postnatal treatment for ROP (group 6). For the participants treated for ROP, 6 participants (12 eyes) underwent laser coagulation and 7 participants (14 eyes) had cryocoagulation. The recruitment efficacy proportion for each group is presented in Fig. 1. Furthermore, 8 eyes without ROP for which the fellow eye had postnatal ROP were excluded. The participants' characteristics are described in Table 1. Overall, 17 participants were excluded because of invalid or impossible measurement (n = 2), total retinal detachment (n = 1), refractive corneal (n = 12) or cataract surgery (n = 2).

3.2. Spherical equivalent

Table 2 presents the spherical equivalent results, showing that the ROP treated group had significantly more myopic refractive error than the control group ($p < 0.001$) (Fig 2). The prevalence of a myopic refractive error of >6 diopters was 4% (11/278), 2.7% (7/264), 1.2% (2/174), 5.6% (2/36), 10.5% (8/78) and 26.9% (7/26) in the respective groups. Furthermore, myopic refractive error was descriptively higher in cryocoagulation-treated participants than in laser-treated participants (−6.67 ± 9.04 diopters *vs.* -0.57 ± 4.76 diopters; $p = 0.053$) (Fig. 3).

The univariate model analysis revealed a significant association of low birth weight percentile ($p = 0.002$), ROP occurrence ($p = 0.02$), and ROP

Table 1. Characteristics of the study sample (n = 433) of the Gutenberg Prematurity Eye Study (GPES) stratified by group.

Gestational age (weeks)	Group 1 GA ≥37	Group 2 GA 33–36 No ROP	Group 3 GA 29–32 No ROP	Group 4 GA ≤28 No ROP	Group 5 GA ≤32 ROP without treatment	Group 6 GA ≤32 ROP treatment
Participants (n)/eyes (n)	139/278	132/264	87/174	18/36	44/78	13/26
Sex (women) (%)	81 (58.3)	79 (59.8)	47 (54.0)	9 (50.0)	22 (50.0)	4 (30.8)
Age (years)	29.9 ± 9.2	29.5 ± 9.2	27.8 ± 8.0	23.4 ± 7.4	24.0 ± 4.0	27.1 ± 5.4
Birth weight (g)	3420 ± 393	2064 ± 471	1569 ± 333	918 ± 197	1044 ± 394	815 ± 262
Birth weight < 1500 g (yes)	0 (0%)	13 (9.8%)	35 (40.2%)	18 (100%)	38 (86.4%)	13 (100%)
Birth weight < 1000 g (yes)	0 (0%)	0 (0%)	5 (5.7%)	11 (61.1%)	22 (50.0%)	10 (76.9%)
Birth weight percentile	48.7 ± 21.4	25.3 ± 24.4	45.2 ± 24.5	42.9 ± 25.0	37.8 ± 28.6	22.2 ± 22.8
Gestational age (weeks)	39.3 ± 1.3	34.3 ± 1.0	30.7 ± 1.1	26.6 ± 1.5	27.8 ± 2.1	27.0 ± 2.3
(Min–max)	(37–43)	(33–36)	(29–32)	(23–28)	(24–32)	(24–32)
ROP stage (1/2/3)	0/0/0	0/0/0	0/0/0	0/0/0	26/46/6	0/4/22
Perinatal adverse events (yes)*	1 (0.7%)	4 (3.0%)	6 (6.9%)	3 (16.7%)	16 (36.4%)	9 (69.2%)
Intraventricular haemorrhage (yes)#	0 (0%)	0 (0%)	1 (1.1%)	0 (0%)	2 (4.5%)	1 (7.7%)
Bronchopulmonary dyplasy (yes)+	1 (0.7%)	1 (0.8%)	4 (4.6%)	1 (5.6%)	13 (29.5%)	6 (46.2%)
Necrotizing entercolitis (yes)	0 (0%)	3 (2.3%)	1 (1.1%)	2 (11.1%)	3 (6.8%)	5 (38.5%)
Preeclampsia (yes)	11 (7.9%)	23 (17.4%)	9 (10.3%)	3 (16.7%)	9 (20.5%)	4 (30.8%)
Placental insufficiency (yes)	2 (1.4%)	16 (12.1%)	2 (2.3%)	1 (5.6%)	2 (4.5%)	0 (0%)
HELLP-syndrome	0 (0%)	6 (4.5%)	1 (1.1%)	0 (0%)	4 (9.1%)	0 (0%)
Maternal smoking (yes)##	7 (5.0%)	7 (5.3%)	8 (9.2%)	1 (5.6%)	5 (11.4%)	2 (15.4%)
Gestational diabetes (yes)	1 (0.7%)	6 (4.5%)	1 (1.1%)	1 (5.6%)	1 (2.3%)	0 (0%)
Breastfeeding (yes)	78 (56.1%)	71 (53.8%)	45 (51.7%)	9 (50.0%)	19 (43.2%)	6 (46.2%)
Socioeconomic status (score)	13.4 ± 3.7	12.5 ± 3.8	12.7 ± 3.3	11.9 ± 3.3	10.6 ± 3.1	10.8 ± 1.9
Reading in childhood (hours per day)	1.8 ± 1.6	1.7 ± 1.4	1.7 ± 1.2	2.0 ± 1.4	1.9 ± 1.6	1.4 ± 1.6
Outdoor activity in childhood (hours per day)	3.5 ± 1.4	3.7 ± 1.5	3.9 ± 1.5	3.5 ± 1.6	4.1 ± 1.9	3.4 ± 0.5

OD = right eye; OS = left eye; GA = gestational age; ROP = retinopathy of prematurity.
*Perinatal adverse events were defined as occurrence of intraventricular haemorrhage# (at least grade 3 or parenchymal haemorrhage) and/or occurrence of necrotizing enterocolitis and/or moderate or severe bronchopulmonary dysplasia+ (IQTIG 2017). ##maternal smoking during pregnancy.

treatment (p = 0.03) with the spherical equivalent. In the multivariable model, after adjustment for sex and age, low birth weight percentile still showed an association with the spherical equivalent (B = 0.02; 95% CI: 0.01, 0.02; p = 0.002) as in model #2 (B = 0.01; 95% CI: 0.00, 0.02; p = 0.004) (Table 3).

3.3. Astigmatismus

Astigmatismus was significantly increased in the ROP treated group (p < 0.001) compared to the control participants born full-term (Table 2, Fig. 2). The univariate quantile regression analysis revealed that ROP treatment (p = 0.02) and perinatal adverse events (p = 0.05) were associated with astigmatismus. In multivariable models #1 and #2, neither perinatal adverse events nor ROP treatment revealed a significant association (Table 3).

3.4. Anisometropia and anisoastigmatismus

Anisometropia was significantly increased in group 3 (GA 29–32 without ROP; p < 0.05), group 5 (GA ≤32 with postnatal ROP occurrence; p < 0.05) and group 6 (GA ≤32 with postnatal ROP treatment; p < 0.001) compared to the full-term control group. Anisometropia ≥2 diopters was observed in 2.9% (4/139), 2.3% (3/132), 3.5% (3/174), 11.1% (2/18), 9.5% (4/44) and 38.5% (5/13) of participants in the respective groups.

In univariate quantile regression anisometropia was associated with GA (p = 0.008), birth weight (p = 0.002), ROP treatment (p = 0.04), and breastfeeding (p = 0.02). In multivariable quantile analyses after adjustment for age and sex, anisometropia was only associated with GA (B = −0.01; 95% CI: −0.02, −0.00; p = 0.009). In multivariable model #2, only GA showed an association (B = −0.01; 95% CI: −0.02, −0.00; p = 0.04) (Table 3).

Anisoastigmatismus was increased in group 2 (GA 33–36 without ROP; p < 0.05), group 3 (GA 29–32 without ROP; p < 0.05), and in the ROP treated subjects (group 6; p < 0.005) compared to the full-term control group (Table 4, Fig. 4).

In univariate quantile analyses, anisoastigmatismus was associated with GA (p = 0.02), birth weight (p = 0.015), and placental insufficiency (p = 0.025). In multivariable analyses of model #1, there was an association with GA (B = −0.01; 95% CI: −0.015, −0.004; p < 0.001) but not with placenta insufficiency (Table 3).

3.5. Accommodation and lens opacification

Accommodation amplitude was significantly reduced in the ROP treated eyes (p < 0.001) compared to the control group. In univariate quantile analyses, accommodation was associated with ROP treatment (p < 0.001) after adjustment for sex and age (B = −1.76; 95% CI: −2.47, −1.05; p < 0.001) (Table 3). Furthermore, lens opacification size within the central 3 mm zone and lens opacification proportion within the 3 mm central zone was significantly increased (p < 0.001) in the ROP treated eyes compared to the control group (Fig. 5).

3.6. Sensitivity analyses

The results for spherical equivalent remained comparable when socioeconomic status and daily hours of reading were included in the multivariable analyses and low birth weight

Table 2. Refractive parameters for the Gutenberg Prematurity Eye Study sample (n = 433) for each group.

Gestational age (weeks)	Group 1 GA ≥37	Group 2 GA 33–36 No ROP	Group 3 GA 29–32 No ROP	Group 4 GA ≤28 No ROP	Group 5 GA ≤32 ROP without treatment	Group 6 GA ≤32 ROP treatment
Participants (n)/eyes (n)	139/278	132/264	87/174	18/36	44/78	13/26
Wearing glasses (yes)	56 (40.3%)	62 (46.9%)	49 (56.3%)	7 (40.9%)	18 (40.9%)	13 (100%)
Spherical equivalent (diopter) OD	−0.98 ± 2.19	−1.11 ± 2.20	−0.63 ± 2.20	−0.69 ± 2.27	−1.29 ± 2.98	−5.63 ± 6.88#
Spherical equivalent (diopter) OS	−0.97 ± 2.09	−1.18 ± 2.18	−0.63 ± 2.17	−0.41 ± 1.96	−1.74 ± 3.41	−2.24 ± 8.64**
SE < −6 diopter OD + OS (eyes (%))	11 (4.0%)	7 (2.7%)	2 (1.2%)	2 (5.6%)	8 (10.5%)	7 (26.9%)
SE −6 to <−3 diopter OD + OS (eyes (%))	27 (9.7%)	36 (13.6%)	20 (11.6%)	3 (8.3%)	5 (6.6%)	6 (23.1%)
SE −3 to <−0.5 diopter OD + OS (eyes (%))	90 (32.4%)	90 (34.1%)	60 (34.7%)	6 (16.7%)	28 (36.8%)	2 (7.7%)
SE −0.5 to <0.5 diopter OD + OS (eyes (%))	112 (40.3%)	111 (42.0%)	61 (35.3%)	19 (52.8%)	25 (32.9%)	3 (11.5%)
SE 0.5 to <3.0 diopter OD + OS (eyes (%))	36 (12.9%)	16 (6.1%)	23 (13.3%)	6 (16.7%)	10 (13.2%)	5 (19.2%)
SE 3.0 to <6.0 diopter OD + OS (eyes (%))	2 (0.7%)	4 (1.5%)	4 (2.3%)	0 (0%)	0 (0%)	2 (7.7%)
SE ≥ 6.0 diopter OD + OS (eyes (%))	0 (0%)	0 (0%)	3 (1.7%)	0 (0%)	0 (0%)	1 (3.8%)
Astigmatism (diopter) OD	−0.76 ± 0.75	−0.76 ± 0.69	−0.86 ± 0.82	−0.69 ± 0.40	−1.08 ± 1.10	−2.90 ± 2.10**
Astigmatism (diopter) OS	−0.72 ± 0.66	−0.83 ± 0.74	−0.87 ± 0.83	−0.87 ± 1.01	−1.04 ± 1.24	−1.56 ± 1.08#
<0.5 diopter OD + OS (eyes (%))	131 (47.1%)	109 (41.3%)	70 (40.5%)	14 (38.9%)	29 (38.2%)	3 (11.5%)
0.5 to <1.0 diopter OD + OS (eyes (%))	84 (30.2%)	89 (33.7%)	52 (30.1%)	13 (36.1%)	23 (30.3%)	2 (7.7%)
1.0 to <1.5 diopter OD + OS (eyes (%))	29 (10.4%)	33 (12.5%)	26 (15.0%)	7 (19.4%)	8 (10.5%)	3 (11.5%)
1.5 to <2 diopter OD + OS (eyes (%))	17 (6.1%)	14 (5.3%)	8 (4.6%)	1 (2.8%)	2 (2.6%)	7 (26.9%)
2 to <4.0 diopter OD + OS (eyes (%))	16 (5.8%)	17 (6.4%)	14 (8.1%)	0 (0%)	12 (15.8%)	7 (26.9%)
≥4.0 diopter OD + OS (eyes (%))	1 (0.4%)	2 (0.8%)	3 (1.7%)	1 (2.8%)	2 (2.6%)	4 (15.4%)
Measurement lens opacification (eyes)	259	251	139	34	61	16
Opacification size within the 3 mm central zone	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	0.1 (0.0; 0.0)	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	0.3 (0.0; 0.3)#
Opacification proportion within 3 mm central zone	0.2 (0.0; 0.0)	0.0 (0.0; 0.0)	0.3 (0.0; 0.0)	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)#
Opacity prop. Within the entire periphery	2.4 (0.0; 1.0)	2.7 (0.0; 1.0)	2.7 (0.0; 2.0)	2.4 (0.0; 4.3)#	2.5 (0.0; 2.0)	1.5 (0.0; 1.0)
Measurement accomodation (eyes)	263	253	138	34	65	16
Accomodation (diopters)	2.96 ± 1.79	3.16 ± 1.98	2.66 ± 1.98	3.54 ± 2.19	3.21 ± 1.75	1.02 ± 0.58**
Maximal pupil size during accomodation (mm)	6.21 ± 1.14	6.07 ± 1.19	6.00 ± 1.26	5.91 ± 1.28	5.76 ± 0.95#	4.68 ± 1.16**
Minimal pupil size during accommodation (mm)	5.01 ± 1.31	4.83 ± 1.24	4.94 ± 1.35	4.51 ± 1.09#	4.50 ± 1.00#	3.95 ± 1.06**

Lens opacification is described as median and interquartile range. All other parameters as mean ± standard deviation.
For parameters with normal distribution linear regression analysis and for parameters with not normal distribution Man-Whitney-U-tests were applied to compare the different groups with the full-term control group (reference).
GA = gestational age; OD = right eye; OS = left eye; ROP = retinopathy of prematurity; mm = millimeter; SE = spherical equivalent
# Statistical difference ($p < 0.05$) compared to the full-term control group.
** Statistical difference ($p < 0.001$) compared to the full-term control group.

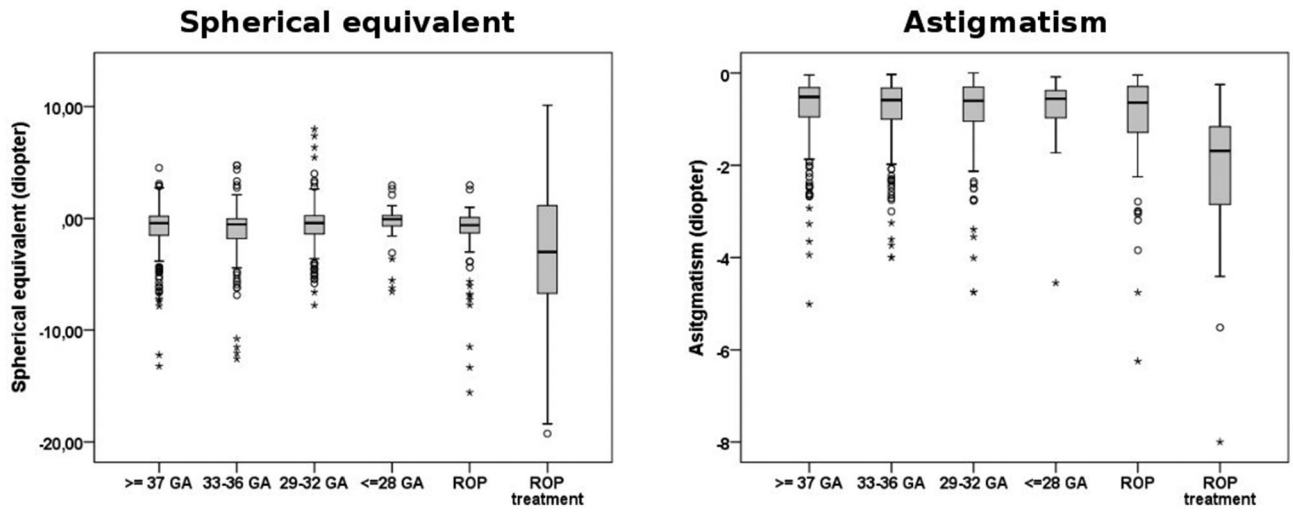

Fig. 2. Spherical equivalent and astigmatism of the Gutenberg Prematurity Eye Study sample (n = 433) for each group. GA = gestational age (weeks); ROP = retinopathy of prematurity.

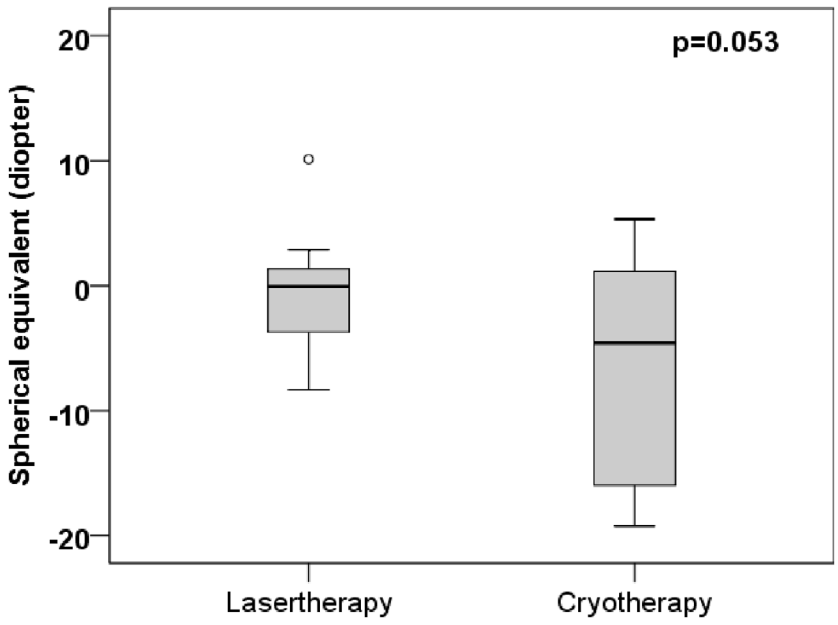

Fig. 3. Comparison of ROP treated participants with laser versus cryotherapy.

percentile remained significantly associated in the multivariable model.

4. Discussion

This study shows that ROP treatment in individuals born preterm increases the risk for myopic refractive error > 6 diopters, increased anisometropia, astigmatismus and anisoastigmatismus as well as increased lens opacifications and reduced accommodation in adulthood. Myopic refractive error was descriptively higher in participants with a history of cryocoagulation compared to laser treatment, whereas preterm delivery without postnatal ROP had little effect on refractive error development in adulthood. The clinical significance is evidenced by every ROP treated participant requiring glasses for distance. Furthermore, the increased lens

Table 3. Association analyses of spherical equivalent, astigmatism, anisometropia, anisoastigmatism and accomodation in the sample of the Gutenberg Prematurity Eye Study (GPES).

	Univariable		Model 1		Model 2	
	B [95% CI]	p	B [95% CI]	p	B [95% CI]	p
Spherical equivalent (diopter)						
Gestational age (weeks)	0.04 (−0.03; 0.11)	0.27	-	-	-	-
Birth weight (kg)	0.28 (−0.02; 0.58)	0.071	*	*	*	*
Birth weight percentile	0.02 (0.01; 0.03)	0.002	0.02 (0.01; 0.02)	0.002	0.01 (0.00; 0.02)	0.004
ROP (yes)	−1.40 (−2.58; −0.21)	0.021	-	-	−0.73 (−1.71; 0.25)	0.14
ROP treatment (yes)	−3.87 (−7.38; −0.36)	0.031	-	-	−3.11 (−6.68; 0.47)	0.089
Perinatal adverse events (yes)	−1.04 (−2.40; 0.34)	0.14	-	-	-	-
Smoking during pregnancy (yes)	0.41 (−0.34; 1.16)	0.28	-	-	-	-
Preeclampsia (yes)	0.03 (−0.68; 0.73)	0.95	-	-	-	-
Breastfeeding (yes)	0.11 (−0.38; 0.60)	0.66	-	-	-	-
Placental insufficiency (yes)	−0.03 (−1.12; 1.05)	0.95	-	-	-	-
Astigmatism (diopter)	B [95% CI]	p	B [95% CI]	p	B [95% CI]	p
Gestational age (weeks)	−0.01 (−0.03; 0.003)	0.11	-	-	-	-
Birth weight (kg)	−0.04 (−0.11; 0.02)	0.21	*	*	*	*
Birth weight percentile	0.00 (0.00; 0.00)	0.96	-	-	-	-
ROP (yes)	0.42 (−0.06; 0.90)	0.09	-	-	-	-
ROP treatment (yes)	1.55 (0.26; 2.84)	0.019	-	-	1.29 (−0.08; 2.66)	0.067
Perinatal adverse events (yes)	0.62 (0.001; 1.24)	0.050	0.55 (−0.11; 1.20)	0.10	0.26 (−0.18; 0.71)	0.24
Smoking during pregnancy (yes)	0.15 (−0.021; 2.77)	0.42	-	-	-	-
Preeclampsia (yes)	0.08 (−0.14; 0.30)	0.48	-	-	-	-
Breastfeeding (yes)	−0.06 (−0.17; 0.05)	0.30	-	-	-	-
Placental insufficiency (yes)	−0.07 (−0.28; 0.14)	0.51	-	-	-	-
Anisometropia (diopter)	B [95% CI]	p	B [95% CI]	p	B [95% CI]	p
Gestational age (weeks)	−0.01 (−0.02; −0.003)	0.008	−0.01 (−0.02; −0.003)	0.009	−0.01 (−0.02; −0.00)	0.038
Birth weight (kg)	−0.07 (−0.11;-0.02)	0.002	*	*	*	*
Birth weight percentile	−0.002 (−0.003; 0.00)	0.071	-	-	-	-
ROP (yes)	1.20 (−0.54; 0.11)	0.20	-	-	-	-
ROP treatment (yes)	4.17 (0.052; 3.17)	0.043	-	-	1.53 (−0.003; 3.06)	0.051
Perinatal adverse events (yes)	0.20 (−0.11; 0.51)	0.21	-	-	-	-
Smoking during pregnancy (yes)	−0.015 (−0.02; 0.07)	0.71	-	-	-	-
Preeclampsia (yes)	0.15 (−0.002; 0.30)	0.055	-	-	-	-
Breastfeeding (yes)	−0.11 (−0.19; −0.019)	0.017	−0.07 (−0.16; 0.02)	0.12	−0.05 (−0.14; 0.04)	0.27
Placental insufficiency (yes)	0.12 (−0.37; 0.14)	0.37	-	-	-	-

Table 3. (Continued)

Anisoastigmatism (diopter)	B [95% CI]	p	B [95% CI]	p	B [95% CI]	p
Gestational age (weeks)	−0.008 (−0.01; −0.001)	0.022	−0.01 (−0.015; −0.004)	<0.001		
Birth weight (kg)	−0.032 (−0.057; −0.007)	0.015	*	*		
Birth weight percentile	−0.00 (−0.00; 0.00)	0.28	-	-		
ROP (yes)	0.02 (−0.12; 0.16)	0.77	-	-		
ROP treatment (yes)	0.52 (−0.40; 1.44)	0.27	-	-		
Perinatal adverse events (yes)	0.09 (−0.13; 0.31)	0.41	-	-		
Smoking during pregnancy (yes)	0.00 (−0.06; 0.06)	1.0	-	-		
Preeclampsia (yes)	0.03 (−0.02; 0.08)	0.28	-	-		
Breastfeeding (yes)	−0.02 (−0.08; 0.04)	0.51	-	-		
Placental insufficiency (yes)	0.08 (0.01; 0.15)	0.025	0.06 (−0.03; 0.15)	0.16		
Accomodation (diopter)	**B [95% CI]**	**p**	**B [95% CI]**	**p**	**B [95% CI]**	**p**
Gestational age (weeks)	−0.002 (−0.06; 0.06)	0.95	-	-	-	-
Birth weight (kg)	0.005 (−0.28; 0.27)	0.97	*	*	*	*
Birth weight percentile	−0.005 (−0.01; 0.01)	0.39	-	-	-	-
ROP (yes)	−0.39 (−1.12; 0.34)	0.30	-	-	-	-
ROP treatment (yes)	−1.97 (−2.58; −1.36)	<0.001	-	-	−1.76 (−2.47; −1.05)	<0.001
Perinatal adverse events (yes)	−0.69 (−1.87; 0.49)	0.25	-	-	-	-
Smoking during pregnancy (yes)	0.35 (−0.88; 1.58)	0.58	-	-	-	-
Preeclampsia (yes)	−0.51 (−1.47; 0.45)	0.30	-	-	-	-
Breastfeeding (yes)	0.69 (0.19; 1.18)	0.006	0.54 (0.21; 0.88)	0.001	0.47 (0.13; 0.81)	0.007
Placental insufficiency (yes)	0.74 (−0.56; 2.04)	0.26	-	-	-	-

For spherical equivalent linear regression models and for astigmatismus, anisometropia, anisoastigmatismus and accommodation quantile regression models were conducted.
Univariate model; (Model 1) Multivariable model with inclusion of univariable associated parameters with adjustment for age and sex; (Model 2) Multivariable model with inclusion of associated parameters of model 1 and additional inclusion of ROP occurrence and ROP treatment if these were significantly associated in the univariate model.
Abbreviations: B = beta estimate; CI = Confidence interval; ROP = retinopathy of prematurity.
* Birth weight was not included into the multivariable model because of the high correlation between gestational age and birth weight.

Table 4. Anisometropia and anisoastigmatismus for the Gutenberg Prematurity Eye Study sample (n = 433) for each group.

Gestational age	Group 1 GA ≥37	Group 2 GA 33–36 No ROP	Group 3 GA 29–32 No ROP	Group 4 GA ≤28 No ROP	Group 5 GA ≤32 ROP without treatment	Group 6 GA ≤32 ROP treatment
Participants (n)/eyes (n)	139/278	132/264	87/174	18/36	44/78	13/26
Anisometropia (diopter)	0.42 ± 0.53	0.43 ± 0.52	0.60 ± 0.65#	0.92 ± 1.39	0.76 ± 1.40#	4.69 ± 5.90**
Anisometropia <0.5 diopter	105 (75.5%)	97 (73.5%)	47 (54.7%)	9 (50.0%)	24 (57.1%)	3 (23.1%)
Anisometropia 0.5 to <1.0 diopter	19 (13.7%)	19 (14.4%)	24 (27.9%)	5 (27.8%)	10 (23.8%)	0 (0.0%)
Anisometropia 1.0 to <1.5 diopter	9 (6.5%)	9 (6.8%)	8 (9.3%)	2 (11.1%)	4 (9.5%)	1 (7.7%)
Anisometropia 1.5 to <2.0 diopter	2 (1.4%)	4 (3.0%)	4 (4.7%)	0 (0.0%)	0 (0.0%)	4 (30.8%)
Anisometropia ≥ 2.0 diopter	4 (2.9%)	3 (2.3%)	3 (3.5%)	2 (11.1%)	4 (9.5%)	5 (38.5%)
Anisoastigmatismus (diopter)	0.30 ± 0.41	0.33 ± 0.32#	0.42 ± 0.54#	0.52 ± 0.94	0.38 ± 0.49	1.58 ± 1.90#
Anisoastigmatismus < 0.5 diopter	129 (92.8%)	114 (86.4%)	76 (88.4%)	16 (88.9%)	36 (85.7%)	11 (84.6%)
Anisoastigmatismus 0.5 to <1.0 diopter	8 (5.8%)	13 (9.8%)	6 (7.0%)	1 (5.6%)	3 (7.1%)	2 (15.4%)
Anisoastigmatismus 1.0 to <1.5 diopter	0 (0.0%)	4 (3.0%)	3 (3.5%)	0 (0.0%)	3 (7.1%)	0 (0.0%)
Anisoastigmatismus 1.5 to <2.0 diopter	2 (1.4%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Anisoastigmatismus ≥2.0 diopter	0 (0.0%)	0 (0.0%)	1 (1.2%)	1 (5.6%)	0 (0.0%)	0 (0.0%)

GA = gestational age; ROP = retinopathy of prematurity.
For parameters with normal distribution linear regression analysis and for parameters with not normal distribution Mann-Whitney-U-tests were applied to compare the different groups with the full-term control group (reference).
Statistical difference ($p < 0.05$) compared to the full-term control group.
** Statistical difference ($p < 0.001$) compared to the full-term control group.

opacifications may contribute to the increased refractive errors and lower accommodation amplitude, possibly predisposing ROP treated participants to earlier cataract development in later life.

Several studies assessed the effects of preterm delivery and postnatal ROP occurrence and treatment on the development of refractive error in early life and school-aged children (Fledelius 1996; Darlow et al. 1997; Larsson et al. 2003; O'Connor et al. 2006; Fieß et al. 2017b) reporting an association between preterm birth and myopic refractive error. Others hypothesized that refractive

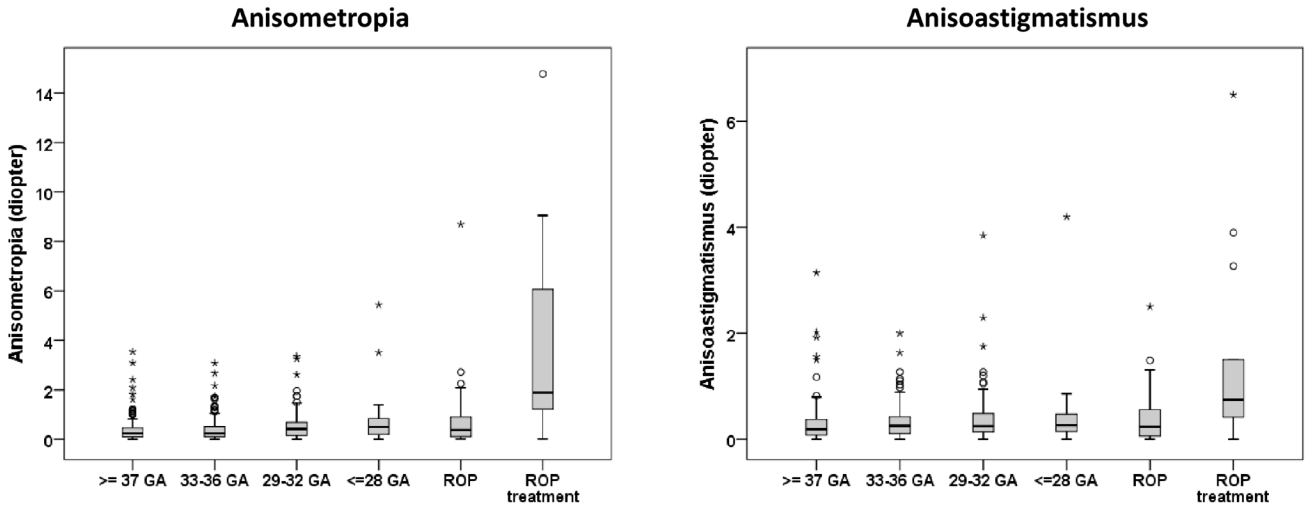

Fig. 4. Anisometropia and anisoastigmatismus of the Gutenberg Prematurity Eye Study sample (n = 433) for each group. GA = gestational age (weeks); ROP = retinopathy of prematurity.

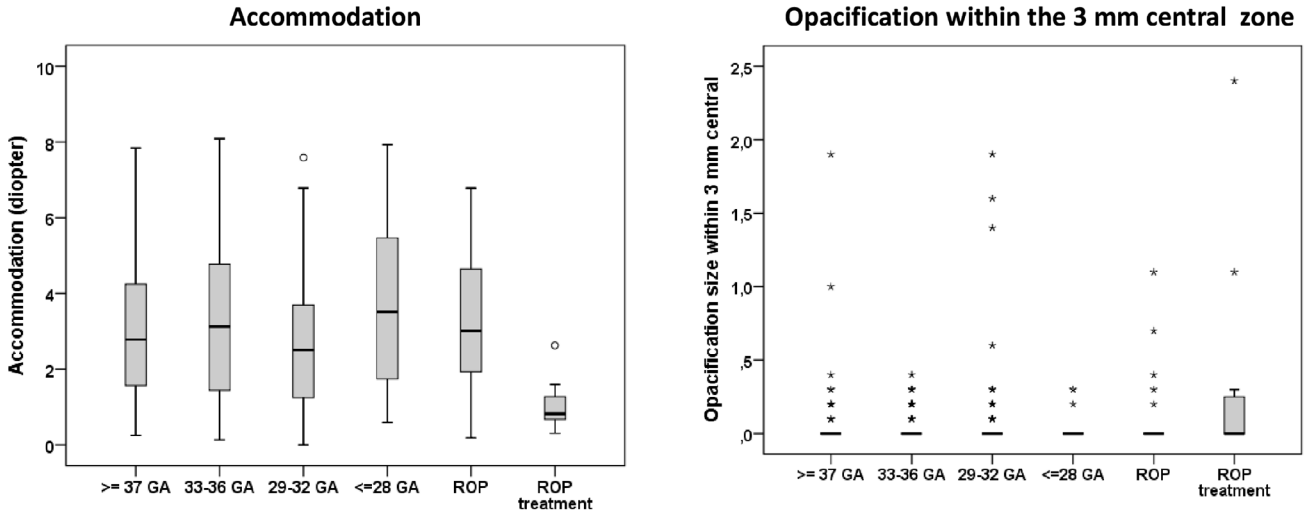

Fig. 5. Accommodation and lens opacification in the Gutenberg Prematurity Eye Study sample (n = 433) for each group. GA = gestational age (weeks); ROP = retinopathy of prematurity.

error differences diminish between children born preterm and at term within the first 8 years of life (Fieß et al. 2017a). However, less is known about the long-term effects of different levels of prematurity and associated factors in later life. A few reports have assessed the effects of low birth weight as a proxy for prematurity on the refractive error in adulthood. While some authors observed no association between low birth weight and refractive error (Dirani et al. 2009; Sun et al. 2010) the population-based Gutenberg Health Study (GHS) found that low birth weight was associated with increased myopic refractive error in their sample aged 35–74 years (Fieß et al. 2019b). However, these analyses are restricted because GA and the postnatal occurrence of ROP were not documented.

Two major reports assessed refractive error in adults born preterm. Pétursdóttir and colleagues examined 59 individuals born preterm with a birth weight ≤ 1500 g and 43 full-term control subjects born between 1988 and 1990 with an actual age at examination of 25 to 29 years (Pétursdóttir et al. 2020). In another study, Darlow and colleagues (Darlow et al. 2018) investigated 229 individuals born preterm with low birth weight (<1500 g) compared to 100 term-born controls in young adulthood (age 27–29 years). Overall, 45 had a history of postnatal ROP but were not treated because at that time ROP treatment was not introduced in New Zealand. Furthermore, both studies did not analyse the outcome of different types of ROP treatment and different levels of prematurity without ROP. This is of major importance because nearly 80% of all preterm individuals are moderately or late preterm individuals with GA >32 weeks. Darlow and colleagues (Darlow et al. 2018) found no difference in those participants with postnatal ROP for low myopia (>2 diopters) but a significant difference in higher

myopia (>5 diopters). In contrast, Pétursdóttir et al. (Pétursdóttir et al. 2020) observed no relationship between birth weight and GA and myopia but found a wider range and altered distribution of spherical equivalent. This is in congruence to our data as we only found an association with lower birth weight percentile, not with GA or birth weight. Furthermore, the present study indicates that cryotherapy has a larger effect on refractive error than laser treatment. The effects of cryotherapy on an increased risk for refractive error are known from studies in childhood (Quinn et al. 2001). Furthermore, Pétursdóttir et al. (Pétursdóttir et al. 2021a) observed a higher prevalence of hypermetropia (≥1.5 diopters), while Darlow et al. (Darlow et al. 2018) found no difference. In the present analysis, the ROP treated group descriptively revealed the highest rate of hypermetropia ≥ 3 diopter, while the other groups were comparable. Furthermore, previous data supports that refractive error development after ROP treatment with anti-VEGF-therapy is less than after laser treatment (Marlow et al. 2021), the life-long effects of laser- and cryotherapy on refractive error are of importance for future decisions regarding ROP treatment.

The present data revealed that the more preterm the participants were born, the higher the anisometropia, particularly manifested in the ROP treated group in adulthood. This is in line with the data of Pétursdóttir (Pétursdóttir et al. 2021b) who reported more anisometropia in participants in the cryotreated group. Furthermore, our analyses revealed higher astigmatismus and anisoastigmatismus for the ROP treated group. An association between preterm birth and increased astigmatismus in childhood has been described previously (Davitt et al. 2009). Within the GHS, the authors found no difference between participants with low (<2500 g) and normal (2500–4000 g) birth weight with astigmatismus. In line to this data, Pétursdóttir et al. (Pétursdóttir et al. 2021b) reported a slightly increased risk of astigmatismus in the participants born preterm compared to those born full-term. Darlow and colleagues showed that an astigmatismus >2 diopters was more frequently observed in individuals born preterm compared to the control group (Darlow et al. 2018).

The special feature of the present study is that we considered a wide range of possible associated parameters and confounders. However, we showed that particularly advanced stages of ROP and the consequent need for treatment are the major factors for increased refractive error, anisometropia and astigmatismus. Various factors were previously found to affect refractive error development and cause myopic shift such as outdoor activity (Mutti & Zadnik 2000) and level of education (Mirshahi et al. 2014). This is of particular importance because participants born preterm were more likely to have a lower socioemotional status (SES), so we performed sensitivity analyses including SES and reading time in childhood and the results remained comparable, indicating that the effects of prematurity and associated factors on refractive error are independent of SES and associated living conditions.

In a Swedish study (Pétursdóttir et al. 2021b), the authors reported that the development of spherical equivalent from 6 months to 25 to 29 years in adulthood diminishes with a stable refractive error at 10 years old. The present study highlights the important long-term effects of postnatal ROP treatment, particularly of cryotherapy on the refractive error in adulthood.

When investigating accommodation, the amplitude was comparable between participants born preterm and full-term except for the ROP treated group which revealed significantly reduced amplitudes. This finding is in congruence to previous reports of individuals born preterm in childhood (Larsson et al. 2012) and young adulthood (Pétursdóttir et al. 2021a) while Lindqvist et al. (Lindqvist et al. 2008) did not observe differences in accommodation in participants with low birth weight in adolescence. Previous authors speculated that low accommodation amplitudes can have multiple origins, such as a consequence of neurological deficits (Almog 2008; Hussaindeen & Murali 2020). Since we did not exclude participants with neurologic complications, we cannot rule out that these contributed to the low accommodation amplitude in the ROP treated participants. However, because our analyses of a large cohort including participants born extremely preterm with postnatal ROP without treatment and individuals born extremely preterm without ROP occurrence and both showed normal accommodation, our data highlights that ROP treatment, in particular, leads to reduced accommodation. This is supported by the results of the multivariable analysis where only ROP treatment revealed a significant association. We can only speculate whether the energy absorbed during ROP treatment or effects on the lens and/or iris and/or ciliary muscle leads to this effect. In this context, our finding of increased lens opacifications in the ROP treated group suggests that ROP treatment led to alterations of lens consistency and increased opacifications.

The present study reports new data about the objective measurement of the size and proportion of lens opacifications, as we observed increased lens opacification size and proportion in ROP treated participants. Christiansen et al. (Christiansen & Bradford 1995) observed by slit-lamp examination an increased rate of lens opacifications and cataracts after ROP treatment in infancy. However, the long-term outcome is unknown, therefore we provide new objective data that ROP treatment leads to increased size and proportion of lens opacifications in adulthood. This finding may have clinical significance because altered lens anatomy may contribute to increased refractive error and lower accommodation amplitude, possibly predisposing these individuals to cataract development in later life.

4.1. Strengths and limitations

The limitations of the present analyses are the single-centre hospital-based study design. Although some subjects refused to take part in the study examination, the recruitment efficacy proportion was acceptable, especially in a cohort with a high level of potential comorbidities (see Fig. 1). Additionally, it should be considered that only a few participants with advanced ROP stages and the need for ROP treatment were included. This should be considered when interpreting the effects of ROP treatment in the present study. Most participants were Caucasians and conclusions from the present study should only be drawn for this ethnicity. Furthermore, our

present data may be influenced by other non-adjusted factors, such as a family history of myopia or hyperopia. Moreover, no cyclopelgia was conducted which could restrict our data, particularly in younger participants with a hyperopic refractive error.

The main strength of the present study is the examination of the largest and oldest cohort of individuals born preterm in the medical literature with different levels of prematurity in adulthood. The birth registry of more than 40,000 newborns in the present study gives a unique view of the long-term effects of prematurity and associated factors on refractive error, accommodation and lens opacification in adulthood. The comprehensive assessment of perinatal parameters from medical files enabled association analyses testing a wide spread of these parameters on their relationship with the main outcome measures in adulthood. Furthermore, all examinations were performed by masked investigators without knowledge about the participants' birth history, thus, reducing the risk of investigator-dependent bias, and every examination was performed per strict standardized operating procedures to avoid examiner-dependent variations.

5. Conclusion

This study presents new data about the refractive long-term outcome of individuals born moderately, very and extremely preterm in adulthood, showing that ROP treatment, in particular, leads to a severely increased risk of myopic refractive error, anisometropia, astigmatismus and anisoastigmatismus. The reduced accommodation and increased lens opacifications observed in ROP treated participants may be caused by the treatment itself in childhood or have been due to an earlier cataract development later in life. The clinical significance of this finding is highlighted by each ROP treated participant requiring glasses for distance at examination. The present study also demonstrates that preterm delivery without postnatal ROP or treatment has little effect on the refractive error in adulthood.

Acknowledgements

The whole study team thanks all participants who took part in this study, and the whole GPES, which includes an enthusiastic team to explore perinatal factors in long-term eye development.

Data availability statement

AFi had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Statistical analyses were performed by AFi. The analysis presents 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 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 make their requests to the coordinating PI of the Gutenberg Prematurity Eye Study (GPES) (Achim Fieß; achim.fiess@unimedizin-mainz.de). More detailed contact information is available at the homepages of the UMCM (www.unimedizin-mainz.de).

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Received on December 7th, 2021.
Accepted on February 14th, 2022.

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