OPEN ACCESS

Ocular geometry in adults born extremely, very and moderately preterm with and without retinopathy of prematurity: results from the Gutenberg Prematurity Eye Study

Achim Fieß ,[1] Hannah Nauen,[1] Eva Mildenberger,[2] Fred Zepp,[2] Michael S Urschitz,[3] Norbert Pfeiffer,[1] Alexander Karl-Georg Schuster[1]

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/bjophthalmol-2021-320907).

[1]Department of Ophthalmology, University Medical Center of the Johannes Gutenberg University Mainz, Mainz, Germany
[2]Department of Pediatrics, University Medical Center of the Johannes Gutenberg-University Mainz, Mainz, Germany
[3]Division of Pediatric Epidemiology, Institute for Medical Biostatistics, Epidemiology and Informatics, University Medical Center of the Johannes Gutenberg University Mainz, Mainz, Germany

Correspondence to
Dr Achim Fieß, University Medical Centre of the Johannes Gutenberg University Mainz, Mainz, Rheinland-Pfalz, Germany;
achim.fiess@gmail.com

Received 6 December 2021
Accepted 20 February 2022
Published Online First 10 March 2022

Check for updates

© Author(s) (or their employer(s)) 2023. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

To cite: Fieß A, Nauen H, Mildenberger E, *et al*. *Br J Ophthalmol* 2023;**107**:1125–1131.

ABSTRACT

Background/aims To evaluate whether anterior segment anatomy and axial length are associated with prematurity and perinatal factors in adults.

Methods The Gutenberg Prematurity Eye Study examined adults born preterm and term aged 18–52 years. All participants underwent a prospective ophthalmic examination (optical biometry via a LenStar 900, Haag-Streit) in Germany. The associations between gestational age (GA), birth weight (BW) and BW percentile, retinopathy of prematurity (ROP) occurrence, ROP treatment and other perinatal factors with the main outcome measures were evaluated by univariate and multivariable linear regression analyses. Main outcome measures were corneal radius, white-to-white distance, anterior chamber depth, lens thickness and axial length.

Results The study involved 861 eyes of 438 preterm and full-term individuals (aged 28.6±8.7 years, 245 females,). After adjustment for age and gender, a steeper corneal radius was associated with lower GA (B=0.02; p<0.001) and a lower BW percentile (B=0.003; p<0.001). A smaller white-to-white distance was linked to lower GA (B=0.02; p<0.001), a lower BW percentile (B=0.004; p<0.001) and postnatal ROP occurrence (B=−0.26; p<0.001). Decreased axial length was associated with lower GA at birth (B=0.05; p=0.002) and pre-eclampsia (B=−0.34; p=0.015). ROP-treated eyes had a shallower anterior chamber depth (B=−0.63; p=0.001) and increased lens thickness (B=0.64, p<0.001).

Conclusion Our analyses in adults demonstrate that the corneal morphology is influenced by GA and BW percentile, while the anterior chamber depth and lens thickness are affected by ROP treatment, namely laser therapy and cryotherapy. The present study highlights that perinatal factors lead to lifelong sequelae of ocular shape.

Key messages

What is already known on this topic?

⇒ Prematurity and retinopathy of prematurity (ROP) are associated with altered ocular morphology in childhood, so we ask whether perinatal factors have long-term effects on ocular geometry in adulthood?

What this study adds?

⇒ The present study shows that low gestational age (GA) and a low birth weight percentile are associated with a steeper corneal curvature and smaller corneal diameter, whereas ROP occurrence is only linked to a smaller corneal diameter. A shallower anterior chamber and a thicker lens were observed in ROP-treated eyes. Moreover, lower GA and pre-eclampsia are associated with a shorter axial length.

How this study might affects research or practice?

⇒ Our analyses demonstrate that prematurity affects the corneal geometry, while ROP treatment affects the anterior chamber depth and lens morphology. This highlights that perinatal factors lead to lifelong sequelae of ocular shape.

INTRODUCTION

Retinopathy of prematurity (ROP) is a major risk factor for childhood blindness worldwide. Despite various advances in neonatal management, ROP remains a decisive disease affecting ocular long-term outcomes in individuals born preterm.[1] This is of particular importance because of the growing proportion of preterm infants and the increasing number of very immature newborns surviving worldwide.

Recent reports demonstrated that premature delivery and ROP lead to altered ocular geometry in infancy,[2] childhood[3] and adolescence.[4] Typical changes in these young preterm individuals are a steeper corneal radius with increased corneal power, smaller anterior chamber depth, thicker lens and shorter axial length.[2–4] It is presumed that these changes persist until adulthood; however, there are scarce data analysing the long-term effects of ROP and associated factors, such as low gestational age (GA) and low birth weight (BW) on ocular geometry in newborns born extremely preterm in adulthood.

In the recent Gutenberg Health Study, lower BW was associated with a steeper corneal radius, smaller white-to-white distance and shorter axial length[5] but these data were limited due to the self-reported BW data as well as missing information

Br J Ophthalmol: first published as 10.1136/bjophthalmol-2021-320907 on 10 March 2022. Downloaded from http://bjo.bmj.com/ on April 18, 2024 by guest. Protected by copyright.

regarding other perinatal parameters such as ROP and GA. Individuals born preterm are at an increased risk of refractive error in childhood[6] and as adults.[7] Ocular geometric changes affect the occurrence of eye diseases such as age-related macular degeneration,[8 9] open-angle glaucoma[10] and diabetic retinopathy,[11] which are major causes of severe vision loss and blindness in developed countries.

Hence, the focus of this investigation was to compare the ocular geometry of subjects born at different degrees of prematurity with and without ROP to full-term controls now aged between 18 and 52 years, assessing the associations of ocular geometric parameters with GA, BW percentile, ROP occurrence and treatment and other perinatal factors.

Materials and methods

Study population

The Gutenberg Prematurity Eye Study (GPES) is a single-centre cohort study at the University Medical Center of the Johannes Gutenberg-University Mainz (UMCM) in Germany that recruits individuals who (1) have been born preterm or at term between 1969 and 2002 and (2) were between 18 and 52 years of age at the time of study enrolment. According to these design elements, the study is a retrospective cohort study with a prospective acquisition of follow-up data. For the GPES, every preterm newborn with GA at birth≤32 weeks and every second randomly chosen preterm newborn with GA 33–36 weeks was contacted and invited to participate. From each month from 1969 to 2002, six (three males and three females) randomly selected full-term subjects with a BW between the 10th and 90th percentile were also invited to serve as controls.

The study examinations were performed between June 2019 and November 2021. The flow chart for eligibility and recruitment efficacy proportion is shown in online supplemental figure 1. Every participant underwent a detailed ophthalmological examination including ocular biometry and a medical history interview. Furthermore, their medical records documenting the perinatal and postnatal history were assessed.

Assessment of prenatal, perinatal and postnatal medical history

The medical histories were assessed from their medical records stored at the UMCM. Data were collected regarding GA (weeks), BW (kg), presence of ROP, stage of ROP, ROP treatment, placental insufficiency, pre-eclampsia, breast feeding and maternal smoking. BW percentiles were also calculated according to Voigt *et al*.[12]

Categorisation

For descriptive analysis, participants were allocated to group 1: full-term participants (GA at birth≥37 weeks), group 2: preterm participants with GA at birth between 33 and 36 weeks without ROP (moderate-to-late preterm), group 3: preterm participants with GA at birth between 29 and 32 weeks without ROP, group 4: preterm participants with GA at birth≤28 weeks without ROP, group 5: preterm participants with GA≤32 weeks at birth with postnatal ROP without ROP treatment and group 6: preterm participants with GA≤32 weeks at birth with postnatal ROP and ROP treatment. In the case that only one eye of a participant had ROP, the other non-ROP eye was excluded from the analysis.

Ophthalmological examination

Objective refraction and best-corrected visual acuity were measured in both eyes (ARK-1s, NIDEK, Oculus, Wetzlar, Germany). Ocular biometry was performed using the LenStar 900

Table 1 Characteristics of the study sample (n=438) of the Gutenberg Prematurity Eye Study stratified by study groups

	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6
	GA≥37	GA 33–36	GA 29–32	GA≤28	GA≤32	GA≤32
Gestational age (GA)		No ROP	No ROP	No ROP	ROP without treatment	ROP with treatment
Participants/eyes (n)	140/280	134/267	88/175	20/36	43/80	13/23
Sex (women) (%)	81 (57.9)	80 (59.7)	47 (53.4)	10 (50.0)	23 (45.0)	4 (30.8)
Age (years)	29.9±9.2	29.4±9.2	28.3±8.1	24.7±8.5	24.7±5.6	27.2±5.4
Birth weight (BW) (g)	3420±392	2063±468	1549±329	926±189	1041±390	815±262
BW<1500 g (yes)	0 (0%)	13 (9.7%)	37 (42.0%)	20 (100%)	37 (86%)	13 (100%)
BW<1000 g (yes)	0 (0%)	0 (0%)	5 (5.7%)	12 (60%)	21 (48.8%)	10 (76.9%)
BW percentile	48.6±21.4	25.4±24.3	44.0±24.3	42.9±24.7	35.6±27.2	21.3±23.0
GA (weeks) (min–max)	39.3±1.3 (37–43)	34.3±0.9 (33–36)	30.7±1.1 (29–32)	26.7±1.5 (23–28)	27.8±2.1 (24–32)	27.0±2.3 (24–32)
ROP stage (1/2/3)	0/0/0	0/0/0	0/0/0	0/0/0	30/44/6	0/4/19
Pre-eclampsia (yes)	11 (7.9%)	24 (17.9%)	10 (11.4%)	3 (15.0%)	9 (20.9%)	4 (30.8%)
Placental insufficiency (yes)	2 (1.4%)	16 (11.9%)	2 (2.3%)	5 (25%)	2 (4.7%)	0 (0%)
HELLP syndrome (yes)	0 (0%)	6 (4.5%)	1 (1.1%)	0 (0%)	4 (9.3%)	0 (0%)
Maternal smoking (yes)	7 (5%)	7 (5.2%)	8 (9.1%)	1 (5.0%)	5 (11.6%)	2 (15.4%)
Gestational diabetes (yes)	1 (0.7%)	7 (5.2%)	1 (1.1%)	1 (5.0%)	1 (2.3%)	0 (0%)
Breast feeding (yes)	79 (56.4%)	73 (54.5%)	44 (50%)	9 (45.0%)	18 (41.9%)	6 (46.2%)
Ocular parameters						
Spherical equivalent (diopter) OD	−0.24±2.58	−0.02±3.15	0.16±1.80	0.40±1.26	0.50±4.30	0.90±2.40
Spherical equivalent (diopter) OS	−0.23±2.60	−0.01±3.10	0.17±1.79	0.39±1.24	0.49±4.28	0.89±4.38
Intraocular pressure (mm Hg) OD	15.2±2.8	14.7±2.9	15.3±3.3	16.6±3.4	15.3±4.3	16.8±4.5
Intraocular pressure (mm Hg) OS	15.1±2.8	14.6±2.8	15.2±3.2	15.1±3.0	15.2±4.2	16.7±4.3

OD, right eye; OS, left eye; ROP, retinopathy of prematurity.

Br J Ophthalmol: first published as 10.1136/bjophthalmol-2021-320907 on 10 March 2022. Downloaded from http://bjo.bmj.com/ on April 18, 2024 by guest. Protected by copyright.

(Haag-Streit, Köniz, Switzerland). Three single measurements were conducted in each examination and the average value was computed. For the present study, the following LenStar parameters were recorded: corneal radius, white-to-white distance as a surrogate for corneal diameter (measurement of the horizontal diameter of a best-fitted circle to the outer border of the iris), anterior chamber depth, lens thickness and axial length. Each parameter was controlled for outliers.

Covariates

Covariates were factors that may affect the main outcome measures such as sex (female), age (years), GA at birth (weeks), BW (kg), BW percentile, ROP (yes), ROP treatment (yes), placental insufficiency (yes), pre-eclampsia (yes), maternal smoking during pregnancy (yes) and breast feeding (yes). Participants with a history of corneal or cataract surgery were excluded as this may have contributed to altered ocular anatomy.

Statistical analysis

The main outcome measures were corneal radius, white-to-white distance, anterior chamber depth, lens thickness and axial length. Descriptive statistics were computed for the main outcome measures stratified by clinical group. Absolute and relative frequencies were calculated for dichotomous parameters, the mean and SD were calculated for approximately normally distributed variables, otherwise median and IQR. Linear regression models with general estimating equations were used to assess associations and account for correlations between corresponding eyes. First, univariate analyses of the main outcome measures and sex (female), age (years), GA (weeks), BW (kg), BW percentile, ROP (yes), ROP treatment (yes), placental insufficiency (yes), pre-eclampsia (yes), breast feeding (yes) and maternal smoking during pregnancy (yes) were computed. Then, only parameters associated in the univariate analyses were included in a second model. In a further model, the potential effect of ROP occurrence (yes) was analysed. BW was excluded in the multivariable models to avoid collinearity, which was strong between GA and BW. Furthermore, a sensitivity analysis was performed for axial length with additional inclusion of refractive error in the multivariable model. As this is an explorative study, a significance level was not defined and no adjustment for multiple testing was carried out. Thus, p values are reported only for descriptive purposes and should be interpreted with caution.[13] Calculations were performed using commercial software (IBM SPSS V.20.0; SPSS, Inc.).

RESULTS

Participant characteristics

In the present study, 861 eyes of 438 preterm and full-term individuals were included (age 28.6±8.7 years, 245 females). Overall, 280 eyes of 140 participants with GA≥37 weeks (group 1), 267 eyes of 134 participants with a GA between 33 and 36 weeks without ROP (group 2), 175 eyes of 88 participants with a GA between 29 and 32 weeks without ROP (group 3), 36 eyes of 20 participants with a GA≤28 weeks without ROP (group 4), 80 eyes of 43 participants with a GA between 24 and 32 weeks with ROP without treatment (group 5) and 23 eyes of 13 participants with a GA between 24 and 32 and with postnatal treatment for ROP were assessed (group 6). Of the ROP-treated group, 6 (11 eyes) participants underwent laser coagulation, while 7 (12 eyes) participants had cryocoagulation. The recruitment efficacy proportion for each group is presented in online supplemental figure 1. Overall, seven participants were excluded because of previous corneal refractive surgery or cataract surgery and five because no biometric measurement was possible. Furthermore, eight eyes without ROP were excluded in which the fellow eye had postnatal ROP (table 1).

Descriptive ocular geometric parameters

The corneal radius was steeper the more preterm the participants were born (table 2). The ROP group showed descriptively a steeper corneal radius than the extremely preterm group without ROP. A linear relationship between corneal radius and GA was observed over the entire range of GA and BW percentiles (figure 1). With respect to the white-to-white distance, the relationship was steeper up to a GA of 32 weeks, then it flattened. A smaller anterior chamber depth and increased lens thickness

Table 2 Ocular geometric parameters of the Gutenberg Prematurity Eye Study study sample (n=438) for each study group

	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6
	GA≥37	GA 33–36	GA 29–32	GA≤28	GA≤32	GA≤32
Gestational age (GA)		No ROP	No ROP	No ROP	ROP without treatment	ROP with treatment
Participants/eyes (n)	140/280	134/267	88/175	20/36	43/80	13/23
Right eye						
Mean corneal radius (mm)	7.89±0.30	7.77±0.28*	7.71±0.43*	7.73±0.20	7.63±0.32†	7.66±0.26*
White-to-white distance (mm)	12.23±0.35	12.2±0.4	12.1±0.4*	11.9±0.3†	11.8±0.5†	11.5±0.4†
Anterior chamber depth (mm)	2.93±0.32	3.01±0.32*	3.04±0.30*	2.88±0.31	3.00±0.44	2.36±0.69
Lens thickness (mm)	3.78±0.33	3.78±0.33	3.76±0.27	3.76±0.24	3.61±0.26*	4.46±0.45*
Axial length (mm)	23.7±1.2	23.6±1.1	23.3±1.1*	23.0±0.9*	23.3±1.3*	22.8±1.7*
Left eye						
Mean corneal radius (mm)	7.88±0.32	7.77±0.27*	7.71±0.31*	7.72±0.21	7.64±0.30†	7.47±0.30*
White-to-white distance (mm)	12.2±0.6	12.2±0.4	12.1±0.5*	11.9±0.4†	11.8±0.5†	11.5±0.5†
Anterior chamber depth (mm)	2.94±0.33	3.03±0.32*	3.04±0.34*	2.97±0.27	3.00±0.36	2.36±0.46
Lens thickness (mm)	3.76±0.34	3.77±0.32	3.75±0.32	3.61±0.26	3.61±0.26*	4.27±0.48*
Axial length (mm)	23.7±1.2	23.6±1.1	23.4±1.1*	23.3±1.3*	23.4±1.2*	22.4±2.2*

Linear regression analysis was applied to compare the different groups with the full-term control group (reference).
*Statistical difference (p<0.05) compared with the control group.
†Statistical difference (p<0.001) compared with the control group.
n, number; ROP, retinopathy of prematurity.

Br J Ophthalmol: first published as 10.1136/bjophthalmol-2021-320907 on 10 March 2022. Downloaded from http://bjo.bmj.com/ on April 18, 2024 by guest. Protected by copyright.

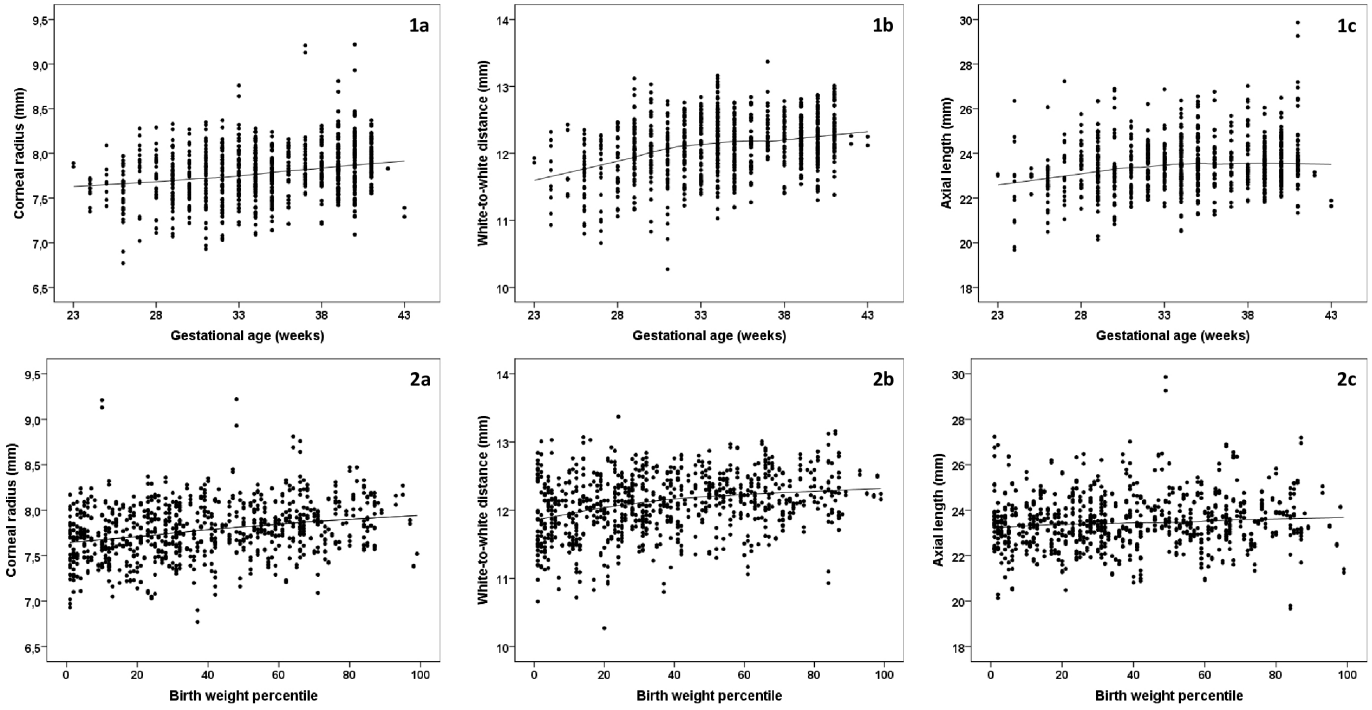

Figure 1 Relationship between (1A) gestational age and corneal radius, (1B) gestational age and white-to-white distance, (1C) gestational age and axial length and (2A) birth weight percentile and corneal radius, (2B) birth weight percentile and white-to-white distance, (2C) birth weight percentile and axial length in the Gutenberg Prematurity Eye Study (n=438). The line (—) presents the locally weighted scatterplot smoothing curve.

were observed in the treated ROP group (figure 2). There was a tendency for a descriptively decreased axial length in subjects born extremely preterm with and without ROP, especially before a GA of 32 weeks (figure 1, table 2).

Univariable and multivariable analyses

The univariate analysis revealed that gestational age, BW, BW percentile and pre-eclampsia were associated with corneal radius and white-to-white distance (table 3) but not with anterior chamber depth and lens thickness (online supplemental table 1). Furthermore, gestational age, BW and pre-eclampsia were associated in univariate analysis with axial length. ROP was associated with corneal radius and white-to-white distance (table 3), and ROP treatment was associated with a flatter corneal radius, a smaller white-to-white distance, a shallower anterior chamber depth and increased lens thickness (table 3 and online supplemental table 1).

In multivariable analyses, there was an association between a steeper corneal radius and low gestational age (B=0.017 mm (95% CI: 0.011 to 0.023) per GA week; p<0.001) and low BW percentile (B=0.003 mm (95% CI: 0.002 to 0.004) per BW percentile; p<0.001; model 1) but not ROP occurrence (model 2; table 3).

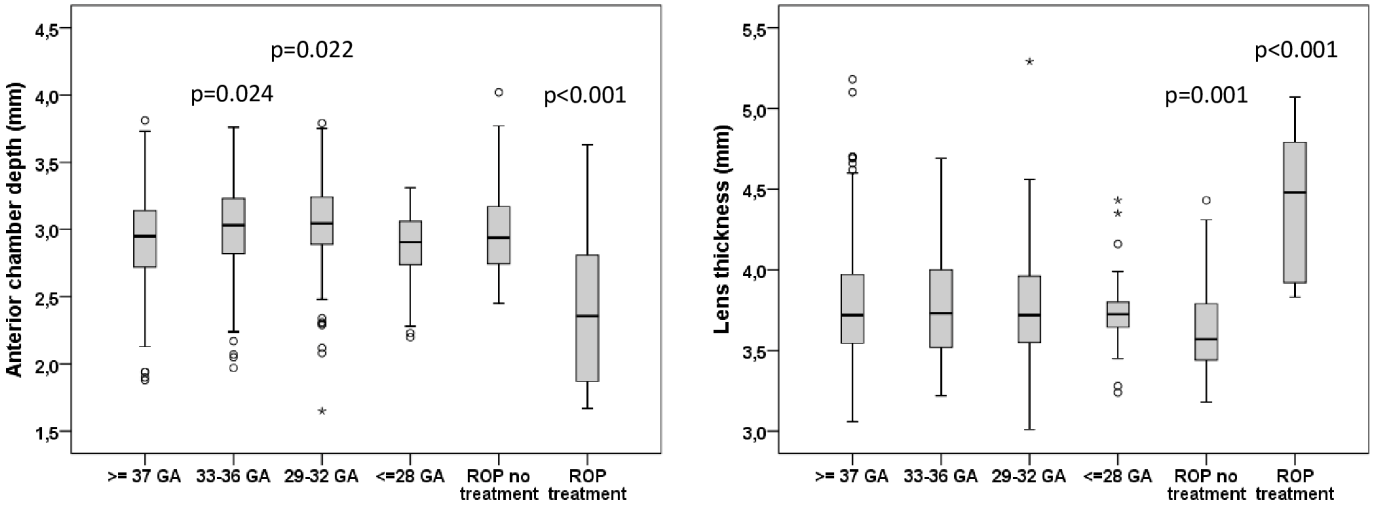

Figure 2 Anterior chamber depth and lens thickness for the different study groups. The group with ROP-treated individuals (group 6) revealed smaller anterior chamber depths and increased lens thickness. GA, gestational age; ROP, retinopathy of prematurity. p-value: statistical difference compared to the control group.

Br J Ophthalmol: first published as 10.1136/bjophthalmol-2021-320907 on 10 March 2022. Downloaded from http://bjo.bmj.com/ on April 18, 2024 by guest. Protected by copyright.

Table 3 Linear associations of corneal geometric parameters and axial length with different perinatal parameters (n=438) for the sample of the Gutenberg Prematurity Eye Study

	Univariate		Model 1		Model 2	
	B (95% CI)	P value	B (95% CI)	P value	B (95% CI)	P value
Mean corneal radius (mm)						
Gestational age (weeks)	0.017 (0.011 to 0.023)	<0.001	0.017 (0.011 to 0.023)	<0.001	0.016 (0.009 to 0.022)	<0.001
Birth weight (BW) (kg)	0.102 (0.074 to 0.129)	<0.001	–		–	
BW percentile	0.003 (0.002 to 0.004)	<0.001	0.003 (0.002 to 0.004)	<0.001	0.003 (0.002 to 0.004)	<0.001
ROP (yes)	−0.155 (−0.238 to −0.071)	<0.001	–		−0.04 (−0.13 to 0.05)	0.38
ROP treatment (yes)	−0.183 (−0.334 to −0.033)	0.017	–		–	
Placental insufficiency (yes)	−0.036 (−0.196 to 0.124)	0.65	–		–	
Pre-eclampsia (yes)	−0.116 (−0.191 to −0.041)	0.003	−0.04 (−0.11 to 0.04)	0.34	−0.035 (−0.110 to 0.040)	0.36
Breast feeding (yes)	0.005 (−0.053 to 0.062)	0.87	–		–	
Smoking pregnancy (yes)	−0.079 (−0.196 to 0.038)	0.18	–			
White-to-white distance (mm)						
Gestational age (weeks)	0.032 (0.023 to 0.040)	<0.001	0.031 (0.023 to 0.040)	<0.001	0.021 (0.011 to 0.030)	<0.001
BW (kg)	0.174 (0.137 to 0.211)	<0.001	–		–	
BW percentile	0.005 (0.003 to 0.006)	<0.001	0.004 (0.003 to 0.006)	<0.001	0.004 (0.002 to 0.005)	<0.001
ROP (yes)	−0.414 (−0.555 to −0.273)	<0.001	–		−0.264 (−0.411 to −0.116)	<0.001
ROP treatment (yes)	−0.626 (−0.873 to -0.378)	<0.001	–		–	
Placental insufficiency (yes)	-0.105 (-0.379 to 0.031)	0.21	–		–	
Pre-eclampsia (yes)	−0.185 (−0.309 to −0.061)	0.004	−0.07 (−0.19 to 0.05)	0.25	−0.056 (−0.171 to 0.058)	0.33
Breast feeding (yes)	0.063 (−0.020 to 0.145)	0.14	–		–	
Smoking pregnancy (yes)	−0.032 (−0.166 to 0.102)	0.64				
Axial length (mm)						
Gestational age (weeks)	0.047 (0.021 to 0.073)	<0.001	0.042 (0.015 to 0.068)	0.002	0.046 (0.016 to 0.075)	0.002
BW (kg)	0.219 (0.100 to 0.337)	<0.001	–		–	
BW percentile	0.004 (0.000 to 0.008)	0.07	0.002 (−0.002 to 0.007)	0.38	0.002 (−0.003 to 0.007)	0.39
ROP (yes)	−0.284 (−0.664 to 0.096)	0.14	–		0.101 (−0.308 to 0.511)	0.63
ROP treatment (yes)	−0.735 (−1.725 to 0.254)	0.15	–		–	
Placental insufficiency (yes)	−0.289 (−0.817 to 0.240)	0.28	–		–	
Pre-eclampsia (yes)	−0.420 (−0.672 to −0.168)	<0.001	−0.34 (−0.61 to −0.07)	0.015	−0.34 (−0.62 to −0.07)	0.015
Breast feeding (yes)	0.002 (−0.218 to 0.223)	0.98	–		–	
Smoking pregnancy (yes)	−0.322 (−0.813 to 0.169)	0.2	–		–	

Linear regression analysis using generalised estimating equations to control for correlations between right and left eyes.
Model 1 included sex (female), age (years), gestational age (weeks), BW percentile and pre-eclampsia (yes). BW (kg) was not included into this model due to the high correlation with gestational age.
Model 2 included sex (female), age (years), gestational age (weeks), BW percentile, ROP (yes) and pre-eclampsia (yes).
B, beta; ROP, retinopathy of prematurity.

With respect to white-to-white distance, a lower gestational age (B=0.031 mm (95% CI: 0.023 to 0.040) per GA week; p<0.001) and lower BW percentile (B=0.004 mm (95% CI: 0.003 to 0.006) per BW percentile; p<0.001) were associated in the multivariable model 1, while model 2 also showed an influence of ROP occurrence (p<0.001).

Axial length was associated with gestational age (B=0.042 mm (95% CI: 0.015 to 0.068) per GA week; p=0.002) and pre-eclampsia (B=−0.34 mm (95% CI: −0.61 to −0.07); p=0.015) but not with BW percentile (p=0.38) (model 1). ROP occurrence did not show an association in model 2 (p=0.63) (table 3). The sensitivity analysis with additional inclusion of spherical equivalent in the multivariable models revealed comparable results and gestational age (B=0.047 mm (95% CI: 0.018 to 0.076) per GA week; p=0.002) and pre-eclampsia (B=−0.311 mm (95% CI: −0.590 to −0.033); p=0.029) remained significantly associated with axial length.

DISCUSSION

The present analysis provides new data regarding the long-term effects of different degrees of prematurity, ROP and perinatal factors on ocular geometry in adults. It was shown that the more preterm the participants were born, the steeper the corneal radius, the smaller the corneal diameter and the shorter the axial length were. Postnatal ROP treatment by laser or cryotherapy was associated with a shallower anterior chamber depth and an increased lens thickness. These findings are of clinical importance because altered ocular geometry predisposes individuals born extremely preterm to refractive error and associated age-related eye diseases.

Furthermore, corneal radius and the white-to-white distance as a surrogate marker for corneal diameter were smaller the more premature the participants were born and the lower their BW percentile, resulting in a steeper corneal radius in adulthood. Several studies have reported that this association between prematurity/low BW and a steeper corneal radius in infancy[2 14] and childhood[3] and that ROP and ROP treatment are decisive factors contributing to a steeper corneal shape.[15–18] Differences in corneal shape between children born preterm and at term may diminish step by step in childhood[3] but the National Health and Nutritional Examination Survey showed that in 12–15-year-old adolescents, low BW subjects (<2500 g) had a steeper corneal

Br J Ophthalmol: first published as 10.1136/bjophthalmol-2021-320907 on 10 March 2022. Downloaded from http://bjo.bmj.com/ on April 18, 2024 by guest. Protected by copyright.

shape compared with the normal BW group (2500–4000 g).[19] There are few studies in adults. In an Australian population-based twin study, Sun *et al*[20] observed that individuals with a low BW had a steeper corneal shape aged between 5 and 80 years, which is in line with data from the German Gutenberg Health Study showing a steeper corneal radius in low BW participants (<2500 g) in adulthood.[7] In contrast to these two population-based approaches, our study reflects the effects of extreme prematurity and associated factors rather than the effect of low BW at a population level. We demonstrated that low gestational age and a low BW percentile were associated with corneal shape morphology. One explanation for this association was postulated by Fielder *et al*[21] who suggested that a temperature difference of 2° after preterm birth compared with the previous intrauterine environment may lead to developmental retardation of the cornea contributing to less flattening of the cornea in individuals born preterm compared with individuals born at term.

In contrast to corneal shape, we did not observe an association between gestational age or BW percentile with anterior chamber depth or lens thickness, similar to data reported in children[22 23] and adults.[7 20] However, there was an association between ROP treatment and a shallower anterior chamber depth and a thicker human lens, highlighting the long-lasting effects of postnatal laser and cryotherapy on ocular morphology, which may contribute to an increased risk for angle closure and cataract in later life.

A low gestational age was associated with a smaller axial length, as shown in extremely preterm children with and without ROP.[3 24 25] There are only data available for the association of low BW with axial length in adulthood but not for gestational age and ROP, so the present study extends these previous reports demonstrating that premature birth affects axial length, potentially contributing to an increased refractive error.

The present results are of clinical importance because altered ocular geometry is associated with refractive error and may be related to eye diseases such as age-related macular degeneration,[8 9] glaucoma[10] and diabetic retinopathy,[11] the main causes of visual impairment and blindness in industrialised countries.

Strengths and limitations

The present study has several limitations. The study was a single-centre, hospital-based cohort study. Several former newborns could not be contacted and some declined to take part in the study, thus there is the risk of selection bias. Also, ocular geometry measurements were not possible in a few participants, particularly in those with low visual acuity. Furthermore, it is noteworthy that the number of participants treated for ROP was rather small, so should be considered when interpreting our results. Nonetheless, the present study involved the examination of the largest cohort of adults born preterm at different degrees of prematurity with and without ROP and a large control group. Furthermore, a detailed assessment of perinatal medical history was conducted by reviewing medical charts. The comprehensive data collection enabled the analysis including potential perinatal parameters that may have affected the development of ocular geometry. In addition, all measurements were conducted according to strict standardised operating procedures to reduce examiner-dependent variations and all investigators were masked to participants' birth characteristics.

CONCLUSION

In conclusion, our results highlight that preterm delivery and adverse prenatal growth affect ocular geometry and these effects persist into adulthood. A low gestational age and low BW percentile are associated with a steeper corneal radius and a smaller corneal diameter, whereas the anterior chamber is shallower and the human lens is thicker in ROP-treated eyes. These results indicate that newborn status has lifelong effects on ocular geometry.

Acknowledgements The authors thank all participants who took part in this study and the Gutenberg Prematurity Eye Study, which includes an enthusiastic team to explore perinatal factors on long-term eye development. This study contains parts of the thesis of Hannah Nauen.

Contributors Conceived and designed the study: AF and AK-GS. Analysed the data: AF, HN, EM, MSU and AK-GS. Wrote the paper: AF. Critically revised the manuscript: AF, HN, EM, MSU, FZ, NP and AK-GS. All authors read and approved the final manuscript. AF had full access to all study data and takes responsibility for the integrity of the data and the accuracy of the data analysis. AF takes the responsibility of overall content as the guarantor. Statistical analyses were performed by AF.

Funding AF was supported by the Intramural Research Funding (Stufe I) of the University Medical Center of the Johannes Gutenberg-University Mainz. The present study was supported by the Ernst-und-Berta-Grimmke-Stiftung and the Else Kröner-Fresenius-Stiftung. There are no grant numbers available. The funders had no role in the study design, data collection and analysis, decision to publish or preparation of the manuscript.

Competing interests AKS holds the professorship for ophthalmic healthcare research endowed by 'Stiftung Auge' and financed by 'Deutsche Ophthalmologische Gesellschaft' and 'Berufsverband der Augenärzte Deutschlands e.V'. 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.

Patient consent for publication Not applicable.

Ethics approval Written informed consent was obtained from all participants prior to their entry into the study and the Gutenberg Prematurity Eye Study 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 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). 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. AF had full access to all study data and takes responsibility for the integrity of the data and the accuracy of the data analysis. Statistical analyses were performed by AF. 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 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 may make their requests to the coordinating principal investigator of the GPES (Achim Fieß; achim.fiess@unimedizin-mainz.de). More detailed contact information is available at the homepages of the University Medical Center Mainz (www.unimedizin-mainz.de).

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

ORCID iD

Achim Fieß http://orcid.org/0000-0002-3867-2350

Br J Ophthalmol: first published as 10.1136/bjophthalmol-2021-320907 on 10 March 2022. Downloaded from http://bjo.bmj.com/ on April 18, 2024 by guest. Protected by copyright.

REFERENCES

1 Mora JS, Waite C, Gilbert CE, *et al*. A worldwide survey of retinopathy of prematurity screening. *Br J Ophthalmol* 2018;102:9–13.
2 Snir M, Friling R, Weinberger D, *et al*. Refraction and keratometry in 40 week old premature (corrected age) and term infants. *Br J Ophthalmol* 2004;88:900–4.
3 Fieß A, Kölb-Keerl R, Knuf M, *et al*. Axial length and anterior segment alterations in former preterm infants and full-term neonates analyzed with scheimpflug imaging. *Cornea* 2017;36:821–7.
4 Fledelius HC. Ophthalmic changes from age of 10 to 18 years. A longitudinal study of sequels to low birth weight. III. Ultrasound oculometry and keratometry of anterior eye segment. *Acta Ophthalmol* 1982;60:393–402.
5 Fieß A, Schuster AK, Nickels S, *et al*. Association of low birth weight with altered corneal geometry and axial length in adulthood in the German Gutenberg health study. *JAMA Ophthalmol* 2019;137:507–14.
6 Larsson EK, Rydberg AC, Holmström GE. A population-based study of the refractive outcome in 10-year-old preterm and full-term children. *Arch Ophthalmol* 2003;121:1430–6.
7 Fieß A, Schuster AK-G, Nickels S, *et al*. Association of low birth weight with myopic refractive error and lower visual acuity in adulthood: results from the population-based Gutenberg health study (GHS). *Br J Ophthalmol* 2019;103:99–105.
8 Fisher DE, Klein BEK, Wong TY, *et al*. Incidence of age-related macular degeneration in a multi-ethnic United States population: the multi-ethnic study of atherosclerosis. *Ophthalmology* 2016;123:1297–308.
9 Pan C-W, Ikram MK, Cheung CY, *et al*. Refractive errors and age-related macular degeneration: a systematic review and meta-analysis. *Ophthalmology* 2013;120:2058–65.
10 Marcus MW, de Vries MM, Junoy Montolio FG, *et al*. Myopia as a risk factor for open-angle glaucoma: a systematic review and meta-analysis. *Ophthalmology* 2011;118:1989–94.
11 Fu Y, Geng D, Liu H, *et al*. Myopia and/or longer axial length are protective against diabetic retinopathy: a meta-analysis. *Acta Ophthalmol* 2016;94:346–52.
12 Voigt M, Fusch C, Olbertz D. Analyse des Neugeborenenkollektivs der Bundesrepublik Deutschland 12. Mitteilung: Vorstellung engmaschiger Perzentilwerte (-kurven) für die Körpermaße Neugeborener. *Geburtsh Frauenheilk* 2006;66:956–70.
13 Greenland S, Senn SJ, Rothman KJ, *et al*. Statistical tests, P values, confidence intervals, and power: a guide to misinterpretations. *Eur J Epidemiol* 2016;31:337–50.
14 Friling R, Weinberger D, Kremer I, *et al*. Keratometry measurements in preterm and full term newborn infants. *Br J Ophthalmol* 2004;88:8–10.
15 Chen T-C, Tsai T-H, Shih Y-F, *et al*. Long-term evaluation of refractive status and optical components in eyes of children born prematurely. *Invest Ophthalmol Vis Sci* 2010;51:6140–8.
16 Kent D, Pennie F, Laws D, *et al*. The influence of retinopathy of prematurity on ocular growth. *Eye* 2000;14(Pt 1):23–9.
17 Wu W-C, Lin R-I, Shih C-P, *et al*. Visual acuity, optical components, and macular abnormalities in patients with a history of retinopathy of prematurity. *Ophthalmology* 2012;119:1907–16.
18 Yang C-S, Wang A-G, Shih Y-F, *et al*. Long-term biometric optic components of diode laser-treated threshold retinopathy of prematurity at 9 years of age. *Acta Ophthalmol* 2013;91:e276–82.
19 Fieß A, Schuster AK, Pfeiffer N, *et al*. Association of birth weight with corneal power in early adolescence: results from the National health and nutrition examination survey (NHANES) 1999-2008. *PLoS One* 2017;12:e0186723.
20 Sun C, Ponsonby A-L, Brown SA, *et al*. Associations of birth weight with ocular biometry, refraction, and glaucomatous endophenotypes: the Australian twins eye study. *Am J Ophthalmol* 2010;150:909–16.
21 Fielder AR, Levene MI, Russell-Eggitt IM, *et al*. Temperature--a factor in ocular development? *Dev Med Child Neurol* 1986;28:279–84.
22 Saw S-M, Tong L, Chia K-S, *et al*. The relation between birth size and the results of refractive error and biometry measurements in children. *Br J Ophthalmol* 2004;88:538–42.
23 Ojaimi E, Robaei D, Rochtchina E, *et al*. Impact of birth parameters on eye size in a population-based study of 6-year-old Australian children. *Am J Ophthalmol* 2005;140:535.e1–7.
24 Ecsedy M, Kovacs I, Mihaltz K, *et al*. Scheimpflug imaging for long-term evaluation of optical components in Hungarian children with a history of preterm birth. *J Pediatr Ophthalmol Strabismus* 2014;51:235–41.
25 Hirano S, Yamamoto Y, Takayama H, *et al*. [Ultrasonic observation of eyes in premature babies. Part 6: Growth curves of ocular axial length and its components (author's transl)]. *Nippon Ganka Gakkai Zasshi* 1979;83:1679–93.

Br J Ophthalmol: first published as 10.1136/bjophthalmol-2021-320907 on 10 March 2022. Downloaded from http://bjo.bmj.com/ on April 18, 2024 by guest. Protected by copyright.