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ORIGINAL ARTICLE

The role of preterm birth, retinopathy of prematurity and perinatal factors on corneal aberrations in adulthood: Results from the Gutenberg prematurity eye study

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Abstract

Introduction: Prematurity and retinopathy of prematurity (ROP) are associated with altered corneal shape and reduced visual acuity in childhood, but their long-term effects on corneal shape in later life are still unclear. This study evaluated whether prematurity and related perinatal factors are associated with corneal aberrations in adulthood.

Methods: The Gutenberg Prematurity Eye Study (GPES) is a cohort study using Scheimpflug imaging of the cornea. Associations were assessed between corneal Zernike aberrations and gestational age (GA), birth weight (BW), BW percentile, ROP occurrence, ROP treatment and other perinatal factors using univariate and multivariable linear regression analyses.

Results: This study involved 444 eyes of 256 individuals born preterm (aged 28.1 ± 8.4 years, 146 females) and 231 eyes of 132 individuals born full-term (aged 29.8 ± 8.9 years, 77 females). Multivariable analyses revealed an association between corneal higher-order aberrations and lower birth weight percentile (B = −0.001, $p < 0.001$) as well as ROP treatment (B = 0.120, $p = 0.03$). Corneal lower-order aberrations were also associated with lower birth weight percentile (B = −0.004; $p = 0.001$) and ROP treatment (B = 0.838, $p = 0.01$) but not with ROP occurrence. Increased corneal aberrations were correlated with lower visual acuity and the spherical equivalent refractive error.

Conclusions: Perinatal factors, particularly low birth weight percentile and ROP treatment lead to a more irregular corneal shape in adulthood, thereby reducing optical image quality and potentially contributing to reduced visual acuity and altered refractive error.

KEYWORDS
birth weight, corneal aberrations, corneal surface, gestational age, retinopathy of prematurity

INTRODUCTION

Corneal aberrations affect optical image quality. Alterations can lead to reduced visual acuity in human eyes.[1,2] Various parameters related to increased corneal aberrations, such as age and myopia,[1,2] have been discussed in the literature, with recent reports of prematurity and other associated factors increasing corneal aberrations in children born preterm.[3,4] This could be of importance because altered corneal aberrations might be a reason for reduced visual acuity in individuals born preterm. Preterm delivery and retinopathy of prematurity (ROP), a major risk factor for childhood blindness worldwide, are associated with changes in the ocular geometry in infancy,[5] childhood[6-9] and adolescence,[10,11] including a steeper corneal curvature with increased corneal power, a thicker lens, smaller anterior chamber depth and shorter axial length.[5,6,12] Furthermore, an increased central corneal thickness (CCT) in preterm newborns has been described.[13-15]

One explanation for altered corneal geometry is the lower extrauterine temperature after preterm birth compared to the higher intrauterine temperature in the maternal environment leading to reduced corneal flattening.[16] In a recent report of the Gutenberg Health Study, the authors reported that low birth weight (<2500 g), as a proxy for preterm delivery, is linked with reduced visual acuity,[17] steeper corneal shape,[18] altered ocular geometry[18-22] and increased corneal aberrations[23] compared to adults with a normal birth weight (2500–4000 g) between 40 and 80 years of age. However, these data were limited because gestational age and the postnatal occurrence of ROP were not surveyed. Hence, it remains unclear whether preterm delivery and associated factors contribute to the increased risk of reduced visual acuity in preterm individuals. Due to the dramatic increase in newborns worldwide, especially those with an extremely low gestational age,[24] it is important to evaluate these corneal changes due to the potential public health significance and economic burden.

Scheimpflug imaging enables the measurement of corneal geometry and aberrations with high reliability and validity.[25,26] The corneal shape can be described mathematically using Zernike (Z) coefficients. Altered corneal aberrations cause low optical image quality and deteriorated visual acuity.[2] However, the effects of an altered corneal shape in adults born preterm on reduced visual acuity and refractive error are still unclear. Therefore, this study evaluated changes in corneal aberration in participants with different degrees of prematurity both with and without ROP between 18 and 52 years of age, to determine the associations between corneal aberrations and gestational age, birth weight, birth weight percentile, ROP occurrence and treatment, as well as other perinatal factors.

Key points

- Prematurity and retinopathy of prematurity are associated with altered corneal morphology in childhood, so we ask whether perinatal factors have long-term effects on corneal aberrations in adulthood?
- This study shows that treatment for retinopathy of prematurity and lower birth weight percentile are associated with increased higher and lower-order aberrations. Increased corneal aberrations correlated with lower visual acuity and the spherical equivalent refractive error.
- Perinatal factors lead to life-long changes in corneal shape. Particularly low birth weight percentile and retinopathy of prematurity treatment lead to a more irregular corneal shape in adulthood, thereby reducing optical image quality and potentially, lower visual acuity and higher refractive error.

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 in Germany (UMCM). Individuals recruited: (i) were born preterm or at term between 1969 and 2002 and (ii) were between 18 and 52 years of age at study enrolment. According to these design elements, the investigation is a retrospective cohort study with prospective acquisition of follow-up data. For the GPES, every preterm newborn with gestational age at birth (GA) ≤ 32 weeks and every second randomly chosen preterm newborn with GA of 33–36 weeks was contacted and invited to participate. From each month from 1969 to 2002, six (3 males and 3 females) randomly selected full-term subjects with a birth weight between the 10th and 90th percentile were also invited to serve as controls. The study examinations were performed between 2019 and 2021 as reported earlier.[27-35] The flow chart for eligibility and effective recruitment efficacy proportion is displayed in Figure S1. Each recruited participant underwent a detailed ophthalmological examination including Scheimpflug imaging, ocular biometry and a medical history interview.

The study protocol and documents were approved by the local ethics committee of the Medical Chamber of Rhineland-Palatinate, Germany (reference no. 2019-14,161; original vote: 29 May, 2019, latest update: 02 April, 2020). All participants provided written informed consent before

study entry and the GPES complies with Good Clinical Practice (GCP), Good Epidemiological Practice (GEP) and the ethical principles of the Declaration of Helsinki.

Assessment of pre-, peri- and postnatal medical history

The data retrieved from the medical records stored at the UMCM included GA (weeks), birth weight (kg), presence of ROP, stage of ROP, ROP treatment, placental insufficiency, preeclampsia, maternal smoking and maternal breastfeeding. Birth weight percentiles were calculated according to Voigt et al.[36]

Categorisation

For descriptive analysis, participants were grouped into those born full-term (GA ≥ 37 weeks; group 1), preterm with a GA of 33–36 weeks without ROP (group 2), preterm with a GA of 29–32 weeks without ROP (group 3), preterm with a GA ≤ 28 weeks without ROP (group 4), born at GA ≤ 32 weeks with postnatal ROP but not treated (group 5) or treated (group 6) in accordance with the medical literature.[29,37] In the case that only one eye had ROP, the non-ROP eye was excluded from the analysis.

Ophthalmological examination

All participants were examined by Scheimpflug imaging (Pentacam®, pentacam.com) and the corneal shape was described for the total cornea as well as the anterior and posterior surfaces. Objective refraction, best-corrected visual acuity (ARK-1 s, NIDEK, Oculus, oculus.de) and optical biometry (LenStar 900, Haag-Streit, haag-streit.com) were measured in both eyes. The following parameters were assessed with the different devices: visual acuity, spherical equivalent refractive error, axial length, aberration of the total cornea as well as for the anterior and posterior corneal surfaces, separately.

Scheimpflug imaging

Detailed examination of the anterior segment was performed with a Pentacam HR rotating Scheimpflug camera using standardised operating procedures to avoid examiner-dependent variance. Each examination was performed by a trained study employee in a standardised procedure. The Scheimpflug camera captures 25 images of the anterior segment within 2 s to record the following corneal aberrations (analysis including the anterior and posterior surfaces of the cornea): oblique and vertical astigmatism (Z_2^{-2}; Z_2^{2}), corneal vertical and horizontal coma (Z_3^{-1}; Z_3^{1}), corneal vertical and horizontal trefoil (Z_3^{-3}; Z_3^{3}), corneal spherical aberration (Z_4^{0}) and the root-mean-square of corneal higher-order aberrations (RMS HOA; 3rd up to 8th order) and corneal lower-order aberrations (RMS LOA). LOA included 1st and 2nd order aberrations (tilt, astigmatism, defocus). Zernike parameters were calculated on a 6-mm diameter optical zone, and a refractive index of 1.3375 was used to calculate the anterior surface measurements. Within the Pentacam software, ray tracing was applied to calculate aberrations of the total cornea indicating the differences from an ideal (spherical) wavefront, incorporating the shapes of the anterior and posterior corneal surfaces. Each scan was reviewed by a board-certified ophthalmologist with the measurement being excluded in the case of decentration or unsatisfactory quality. The graphical distribution of the corneal parameters was analysed and skewness calculated, with approximately normal distribution assumed for skewness ≤ |1|.

Covariables

The covariables that may affect the main outcome measures were sex (female), age (years), corneal radius (mm), axial length (mm), intraocular pressure (mmHg), GA (weeks), birth weight (kg), birth weight percentile, ROP (yes), ROP treatment (yes), preeclampsia (yes), placental insufficiency (yes), breastfeeding (yes) and maternal smoking in pregnancy (yes).

Inclusion/exclusion criteria

Only participants with successful and valid Scheimpflug imaging of the cornea were included and participants with a history of corneal or cataract surgery, ocular trauma or retinal detachment were excluded as this may have contributed to an altered corneal shape.

Statistical analysis

The primary outcomes were total corneal aberrations as well as corneal HOA and LOA. The secondary outcomes were oblique and vertical astigmatism (Z_2^{-2}; Z_2^{2}), corneal vertical and horizontal coma (Z_3^{-1}; Z_3^{1}), corneal vertical and horizontal trefoil (Z_3^{-3}; Z_3^{3}) and corneal spherical aberration (Z_4^{0}). Descriptive statistics were computed for the main outcome measures stratified by clinical groups. Absolute and relative frequencies of the baseline characteristics were calculated for dichotomous parameters; the mean and standard deviation were calculated for approximately normally distributed variables. Linear regression models with general estimating equations (GEE) were used to assess associations and account for correlations between corresponding eyes. Left eye aberrations in terms of oblique astigmatism, horizontal coma and horizontal trefoil were transformed (multiplied by −1)

before analysis as they were inversely correlated with the right eye findings. First, univariate analyses of the main outcome measures and GA (weeks), birth weight (kg), birth weight percentile, ROP (yes), ROP treatment (yes), placental insufficiency (yes), preeclampsia (yes), breastfeeding (yes) and maternal smoking in pregnancy (yes) were computed. Then, in a multivariable analysis (analysis 1), only parameters associated in the univariate analyses were included with additional adjustment for sex (female), age (years), corneal radius (mm), axial length (mm) and intraocular pressure (mmHg). In a further multivariable analysis (analysis 2), the potential effects of ROP occurrence (yes) and treatment (yes) were analysed. Birth weight was excluded in the multivariable models to avoid collinearity, which was strong between GA and birth weight. Spearman's rank correlation was used to assess the correlation between total corneal aberrations with respect to visual acuity and refractive error. Additional sensitivity analyses were performed, excluding participants wearing contact lenses in the first analysis and including only preterm subjects in the second analysis. Thus, *p*-values are reported only for descriptive purposes and should be interpreted with caution.[38] Calculations were performed using commercial software (IBM SPSS 20.0; SPSS, ibm.com).

RESULTS

Participant characteristics

This study involved 444 eyes of 256 individuals born preterm (mean age [±SD] 28.1 ± 8.4 years, 146 females) and 231 eyes of 132 individuals born full-term (mean age [±SD] 29.8 ± 8.9 years, 77 females). Table 1 presents the participants' descriptive statistics as well as other perinatal and ocular parameters. Within the ROP-treated subjects, four participants (six eyes) underwent laser coagulation and four participants (six eyes) received postnatal cryocoagulation. The recruitment efficacy is presented in Figure S1. Overall, 62 participants were excluded because of previous corneal refractive or cataract surgery or no Scheimpflug imaging was possible, and eight eyes without ROP were excluded as the fellow eye had postnatal ROP.

Corneal aberrations

Table 2 provides the Zernike coefficients for the study groups, showing increased horizontal trefoil ($p = 0.002$) in the preterm participants treated for ROP (group 6) compared to the full-term controls (group 1). Vertical trefoil was decreased in the extremely preterm group without ROP (group 4, GA ≤ 28 weeks; $p = 0.03$). Increased RMS HOA was observed in all participants with ROP (group 5: non-treated ROP, $p = 0.04$ and group 6: treated ROP, $p < 0.001$) compared with the full-term controls (group 1), whereas the RMS LOA was only increased in the treated ROP individuals (group 6) compared to the full-term controls. Total corneal aberrations were also increased in the ROP-treated group compared to the full-term controls, with no difference between preterm groups and the full-term controls for oblique and vertical astigmatism, horizontal and vertical coma, horizontal and vertical trefoil and spherical aberration (Table 2 and Figure 1). Descriptive data for the anterior and posterior corneal surfaces are presented in Tables S1 and S2 showing increased total corneal aberrations, particularly in the ROP-treated group as well as increased RMS LOA and HOA aberrations for the corneal front and back surfaces.

Uni- and multivariable analyses

Total corneal aberrations

In univariable analyses, total corneal aberrations were associated with lower birth weight, birth weight percentile, ROP occurrence and treatment. In model #1, after adjustment for sex, age, corneal radius, axial length and intraocular pressure, low birth weight percentile (B = −0.004 [95%-CI: −0.007; −0.002] $p < 0.001$) remained associated with increased total corneal aberrations. In stepwise analyses after additional inclusion of ROP occurrence and treatment in model #2, lower birth weight percentile (B = −0.004 [95%-CI: −0.006; −0.002] $p < 0.001$) and ROP treatment (B = 0.846 [95%-CI: 0.195; 1.497] $p = 0.01$) were associated with total corneal aberrations.

Higher-order aberrations

In univariable analyses, GA, BW, BW percentile, ROP occurrence, ROP treatment, placental insufficiency, preeclampsia and breastfeeding were associated with increased RMS HOA. In multivariable analyses (model#1) after adjustment for sex, age, corneal radius, axial length and intraocular pressure, lower GA (B = −0.003 [95%-CI: −0.006; −0.001] $p = 0.01$) and lower BW percentile (B = −0.001 [95%-CI: −0.001; −0.000] $p < 0.001$) were associated with increased higher-order aberrations. In model #2 including ROP occurrence and treatment, BW percentile (B = −0.001 [95%-CI: −0.001; −0.000] $p < 0.001$) and ROP treatment (B = 0.120 [95%-CI: 0.011; 0.229] $p = 0.03$) were associated with increased corneal HOA, while ROP occurrence and the other parameters showed no association (Figure 2, Table 3).

Lower-order aberrations

Root-mean-square of corneal lower-order aberrations was associated in univariable analyses with birth weight, birth weight percentile, ROP occurrence and ROP treatment. After adjusting for sex, age, corneal radius, axial

TABLE 1 Participant characteristics ($n = 388$) stratified by gestational age (GA) and retinopathy of prematurity (ROP)

	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6
Gestational age [weeks]	GA ≥ 37	GA 33–36	GA 29–32	GA ≤ 28	GA ≤ 32	GA ≤ 32
		No ROP	No ROP	No ROP	Non-treated ROP	Treated ROP
Participants/eyes (*n*)	132/231	123/216	77/134	14/27	34/55	8/12
Sex (Female) (%)	77 (58.3%)	74 (60.2%)	42 (54.5%)	8 (57.1%)	19 (55.9%)	3 (37.5%)
Age (y)	29.8 ± 8.9	29.6 ± 9.3	28.1 ± 8.1	24.7 ± 7.9	24.3 ± 3.9	26.3 ± 4.7
Birth weight (g)	3434 ± 388	2070 ± 478	1538 ± 329	928 ± 202	1057 ± 386	751 ± 186
Birth weight < 1500 g (yes)	0 (0%)	13 (10.6%)	34 (44.2%)	14 (100%)	30 (88.2)	8 (100%)
Birth weight < 1000 g (yes)	0 (0%)	0 (0%)	5 (6.5%)	9 (64.3%)	16 (47.1%)	7 (87.5%)
Birth weight percentile	49.4 ± 21.3	25.4 ± 24.3	43.6 ± 24.7	46.1 ± 26	37 ± 26.9	26.5 ± 27.7
Gestational age (weeks)	39.4 ± 1.3	34.3 ± 0.9	30.6 ± 1.2	26.5 ± 1.6	27.9 ± 1.9	26.3 ± 1.8
(min–max)	(37–43)	(33–36)	(29–32)	(23–28)	(25–32)	(24–29)
ROP stage (1/2/3)[a]	0/0/0	0/0/0	0/0/0	0/0/0	21/30/4	0/3/9
Preeclampsia (yes)	11 (8.3%)	22 (17.9%)	8 (10.4%)	3 (21.4%)	7 (20.6%)	2 (25%)
Placental insufficiency (yes)	2 (1.5%)	15 (12.2%)	2 (2.6%)	0 (0%)	1 (2.9%)	0 (0%)
HELLP-syndrome[#]	0 (0%)	6 (4.9%)	1 (1.3%)	0 (0%)	3 (8.8%)	0 (0%)
Maternal smoking (yes)	6 (4.5%)	7 (5.7%)	8 (10.4%)	1 (7.1%)	4 (11.8%)	2 (25%)
Gestational diabetes (yes)	1 (0.8%)	5 (4.1%)	1 (1.3%)	0 (0%)	1 (2.9%)	0 (0%)
Breastfeeding (yes)	73 (55.3%)	66 (53.7%)	40 (51.9%)	5 (35.7%)	16 (47.1%)	3 (37.5%)
Caesarean section	32 (24.2%)	61 (49.6%)	45 (58.4%)	8 (57.1%)	26 (76.5%)	4 (50%)
Vaginal delivery	100 (75.8%)	62 (50.4%)	32 (41.6%)	6 (42.9%)	8 (23.5%)	4 (50%)
Ocular parameters						
Visual acuity (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; 0.0)	0.1 (0.0; 0.3)
Visual acuity (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)	0.1 (0.0; 0.4)
Spherical equivalent (dioptre) OD	−1.08 ± 2.3	−1.1 ± 2.0	−0.9 ± 2.4	−0.3 ± 1.9	−0.8 ± 2.2	−5.4 ± 7.0
Spherical equivalent (dioptre) OS	−0.9 ± 2.1	−1.2 ± 2.3	−0.7 ± 2.2	−0.14 ± 2.2	−1.6 ± 2.8	−3.5 ± 7.8
Axial length (mm) OD	23.8 ± 1.2	23.7 ± 1.0	23.4 ± 1.2	23.1 ± 0.9	23.2 ± 1.1	23.6 ± 1.7
Axial length (mm) OS	23.7 ± 1.2	23.6 ± 1.1	23.4 ± 1.1	22.8 ± 1.0	23.3 ± 1.2	22.8 ± 2.3
Intraocular pressure (mmHg) OD	15.3 ± 2.8	14.9 ± 2.8	14.9 ± 3.2	17.0 ± 3.5	15.3 ± 3.4	17.6 ± 3.4
Intraocular pressure (mmHg) OS	15.1 ± 2.8	14.7 ± 2.98	14.4 ± 2.8	15.1 ± 3.1	15.3 ± 3.5	16.0 ± 1.8

g, gram; mm, millimetre; OD, right eye; OS, left eye; mean and standard deviation were calculated for approximately normally distributed variables, otherwise median and interquartile range.

[#]HELLP-syndrome – maternal haemolysis, elevated liver enzymes and low platelet count.

[a]Number of eyes with ROP stage 1/2/3.

length and intraocular pressure in multivariable model #1, birth weight percentile remained associated (B = −0.004 [95%-CI: −0.006; −0.002] $p < 0.001$). The inclusion of ROP occurrence and treatment in model #2 revealed a significant association with lower birth weight percentile (B = −0.004 [95%-CI: −0.006; −0.002] $p = 0.001$) and ROP treatment (B = 0.838 [95%-CI: 0.173; 1.504] $p = 0.01$) (Figure 2, Table 3).

Total corneal aberrations, visual acuity and refractive error

Spearman's rank correlation revealed an association between total corneal aberrations and distance corrected visual acuity ($r = 0.38$; $p < 0.001$), as well as with refractive error ($r = -0.15$; $p < 0.001$).

Sensitivity analyses

The sensitivity analyses excluding contact lens wearers and only including preterm subjects revealed similar results.

DISCUSSION

This study evaluated the long-term effects of different degrees of prematurity, ROP and other perinatal factors on the corneal shape in adults, providing new data that

TABLE 2 Total corneal aberration parameters of the study groups ($n = 388$)

	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6
Gestational age [weeks]	GA ≥ 37	GA 33–36	GA 29–32	GA ≤ 28	GA ≤ 32	GA ≤ 32
		No ROP	No ROP	No ROP	Non-treated ROP	Treated ROP
Participants/eyes (*n*)	132/231	123/216	77/134	14/27	34/55	8/12
Total Cornea						
Astigmatism						
Oblique (Z_2^{-2}) OD	−0.03 ± 0.55	−0.6 ± 0.80	0.10 ± 0.88	−0.7 ± 0.41	0.10 ± 0.40	0.13 ± 0.30
Oblique (Z_2^{-2}) OS	0.16 ± 0.41	−0.11 ± 0.51*	−0.02 ± 0.57	0.04 ± 0.81	0.19 ± 0.82	0.16 ± 0.94
Vertical (Z_2^{2}) OD	−0.70 ± 0.65	−0.78 ± 1.12	−0.57 ± 0.74	−0.44 ± 0.53	−1.08 ± 1.24	−0.43 ± 0.81
Vertical (Z_2^{2}) OS	−0.69 ± 0.72	−0.67 ± 0.94	−0.73 ± 1.20	−0.74 ± 0.59	−0.70 ± 0.93	−0.26 ± 0.86
Coma						
Horizontal (Z_3^{1}) OD	0.01 ± 0.17	0.02 ± 0.23	−0.01 ± 0.26	−0.00 ± 0.18	0.06 ± 0.37	0.05 ± 0.05
Horizontal (Z_3^{1}) OS	0.02 ± 0.17	−0.12 ± 0.22	0.04 ± 0.22	−0.06 ± 0.23	−0.28 ± 0.22	0.01 ± 0.13
Vertical (Z_3^{-1}) OD	−0.00 ± 0.21	0.01 ± 0.18	−0.01 ± 0.25	−0.02 ± 0.19	−0.03 ± 0.26	−0.04 ± 0.09
Vertical (Z_3^{-1}) OS	0.00 ± 0.21	0.03 ± 0.22	0.01 ± 0.32	0.13 ± 0.18*	−0.05 ± 0.25	−0.00 ± 0.15
Trefoil						
Horizontal (Z_3^{3}) OD	0.00 ± 0.13	0.02 ± 0.25	0.02 ± 0.15	0.03 ± 0.14	0.02 ± 0.10	0.04 ± 0.06
Horizontal (Z_3^{3}) OS	0.00 ± 0.12	0.02 ± 0.39	0.04 ± 0.36	0.06 ± 0.28	−0.09 ± 0.21*	0.09 ± 0.12*
Vertical (Z_3^{-3}) OD	−0.08 ± 0.12	0.00 ± 0.70	0.03 ± 0.57	−0.12 ± 0.14	−0.07 ± 0.11	0.01 ± 0.09*
Vertical (Z_3^{-3}) OS	−0.05 ± 0.14	−0.09 ± 0.14	−0.08 ± 0.19	−0.30 ± 0.39*	−0.15 ± 0.24*	−0.07 ± 0.12
Spherical aberration (Z_4^{0}) OD	0.20 ± 0.19	0.19 ± 0.08	0.23 ± 0.13	0.19 ± 0.12	0.21 ± 0.13	0.14 ± 0.04*
Spherical aberration (Z_4^{0}) OS	0.21 ± 0.12	0.20 ± 0.12	0.21 ± 0.09	0.22 ± 0.13	0.23 ± 0.11	0.24 ± 0.09
Corneal aberrations (RMS)						
Total OD	1.41 ± 0.58	1.42 ± 0.55	1.41 ± 0.65	1.27 ± 0.47	1.48 ± 0.73	2.98 ± 1.24*
Total OS	1.40 ± 0.54	1.45 ± 0.58	1.38 ± 0.57	1.15 ± 0.35*	1.47 ± 0.68	2.25 ± 0.6**
Higher-order aberrations (HOA) OD	0.37 ± 0.11	0.40 ± 0.12	0.41 ± 0.13	0.37 ± 0.10	0.42 ± 0.13	0.54 ± 0.17*
Higher-order aberrations (HOA) OS	0.38 ± 0.11	0.40 ± 0.12	0.40 ± 0.16	0.36 ± 0.10	0.44 ± 0.11*	0.61 ± 0.21*
Lower-order aberrations (LOA) OD	1.35 ± 0.59	1.40 ± 0.55	1.35 ± 0.65	1.20 ± 0.47	1.41 ± 0.74	2.92 ± 1.24*
Lower-order aberrations (LOA) OS	1.33 ± 0.54	1.40 ± 0.59	1.31 ± 0.56	1.08 ± 0.35*	1.51 ± 0.68	2.16 ± 0.65**

Note: Linear regression analysis was applied to compare the different groups with the full-term control group (reference).

Abbreviations: GA, gestational age; ROP, Retinopathy of Prematurity; mm, millimetre; OD, right eye; OS, left eye.

*Statistical difference ($p < 0.05$) compared to the control group.; **Statistical difference ($p < 0.001$) compared to the control group.

low birth weight percentile and ROP treatment increase corneal HOA and LOA in adults. The clinical significance of these findings is indicated by the correlation between total corneal aberrations and visual acuity and refractive error, indicating that perinatal origins lead to life-long alterations in corneal shape, thereby reducing optical image quality and possibly deteriorating visual acuity in affected individuals.

There is a lack of data regarding the effects of prematurity on corneal aberrations. Two previous studies analysed the impact of prematurity on corneal aberrations in childhood using Scheimpflug imaging. In the Wiesbaden Prematurity Study (WPS) of 259 children born full-term and 226 children born preterm with a mean age of 7.2 ± 2.0 years, increased HOAs and LOAs were observed in participants born extremely preterm (GA ≤28 weeks), with no association with ROP after adjusting for gestational age.[4] Ecsedy and colleagues examined 27 (50 eyes) children born preterm and 34 (68 eyes) children born full-term aged 7–14 years in a prospective case-control study, reporting increased HOAs in preterm children, although the study group was heterogeneous in terms of ROP occurrence and treatment.[3] In a recent report of the population-based Gutenberg Health Study of 5628 participants, low BW (<2500 g) was associated with increased corneal HOAs and LOAs and increased spherical aberration, but these results were limited by missing data on gestational age and postnatal ROP occurrence.[23] Consequently, this study provides the first data about the long-term effects taking into account various perinatal factors and determining their influence on corneal shape. This analysis revealed that ROP

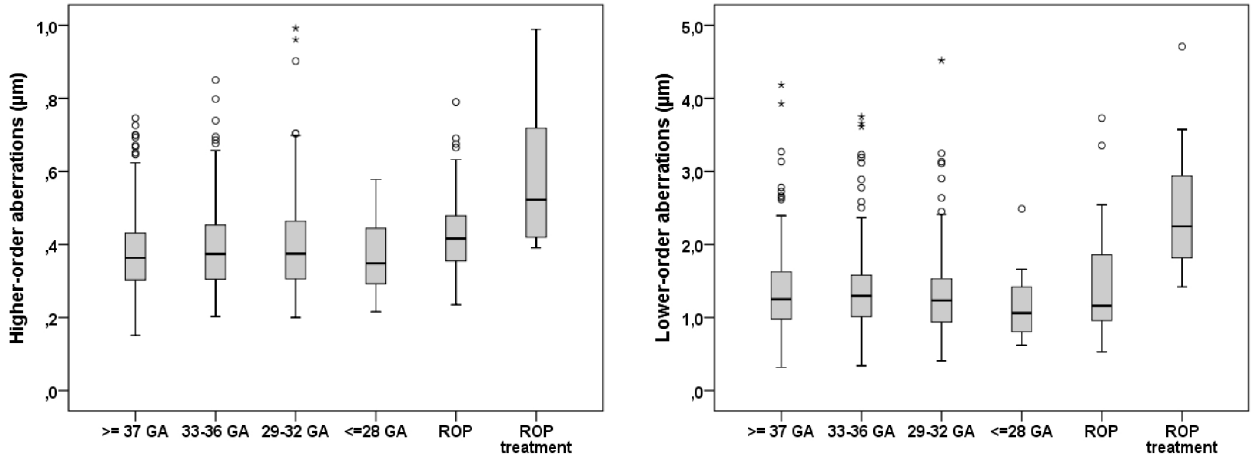

FIGURE 1 Higher order (left) and lower order (right) aberrations of the different study groups. The ROP-treated individuals (group 6) had increased higher- and lower-order aberrations of the total cornea. GA, gestational age in weeks; ROP, retinopathy of prematurity.

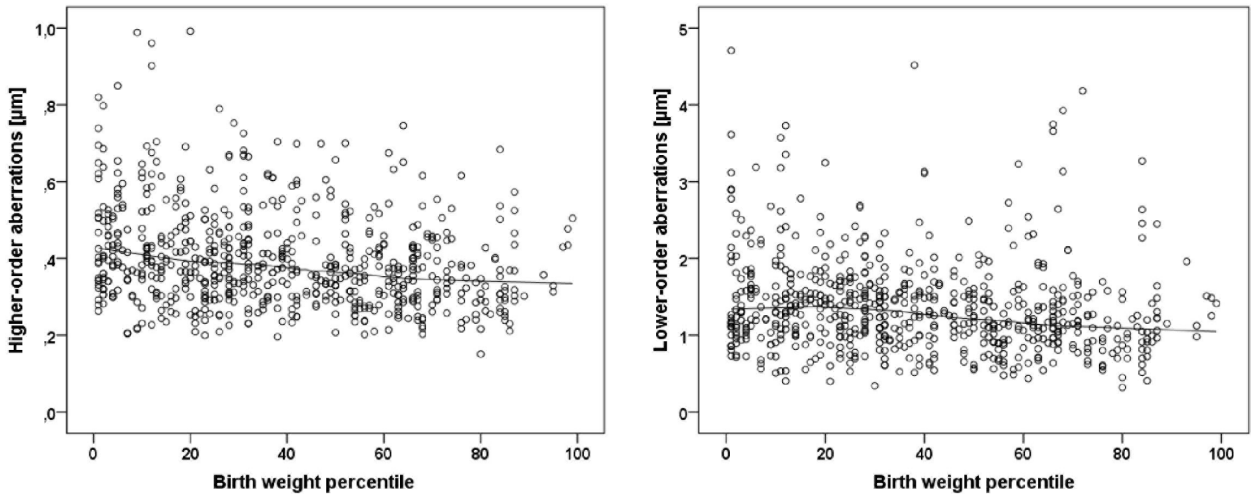

FIGURE 2 Relationship between birth weight percentile and higher-order aberrations (left) and lower-order aberrations (right) in the Gutenberg prematurity eye study (n = 388). The line presents the Loess (Locally Weighted Scatterplot Smoothing) curve.

treatment contributes to increased HOAs and LOAs, while ROP occurrence was not associated with corneal aberrations in multivariable analyses. Interestingly, the low birth weight percentile showed a strong association with HOAs and LOAs after adjusting for several confounders in multivariable analyses, indicating that adverse prenatal growth indicated by low birth weight percentile contributes to an altered corneal shape in adulthood. Furthermore, the anterior and posterior corneal surfaces were analysed separately, showing an association between ROP treatment and increased HOAs and LOAs. The posterior surface of the cornea is rarely analysed separately, but it should also be considered as it is responsible for a considerable amount of corneal astigmatism.[39]

The pathophysiological origins leading to an altered corneal shape are unclear, although there is evidence that preterm birth and associated factors are linked to altered ocular geometry in childhood, such as a steeper corneal shape, thicker lens, smaller anterior chamber depth and shorter axial length,[5,6,12] and that these alterations persist into adulthood.[18,32] Fielder et al.[16] postulated that temperature differences between the intra- and extrauterine environments after preterm birth may cause reduced flattening of the cornea. The association between low birth weight percentile as a proxy for prenatal and intrauterine adverse growth and increased corneal aberrations suggests that adverse intrauterine growth may play an important role in the development of corneal shape in preterm individuals. This is in congruence to the Baker theory hypothesising that intrauterine malnutrition leads to alterations in organ development resulting in abnormal organ morphology and dysfunction in later life.[40] We can only speculate about potential pathological mechanisms leading to altered corneal aberrations. One reason might be changes in corneal remodelling processes and ultrastructural alterations in collagen fibre development, as well as an altered duration of corneal

TABLE 3 Linear associations of corneal aberration parameters with perinatal parameters ($n = 388$)

	Univariate		Model 1		Model 2	
	B [95% CI]	*p*	B [95% CI]	*p*	B [95% CI]	*p*
Total corneal aberrations [µm]						
Gestational age (weeks)	−0.010 (−0.023; 0.004)	0.17	-		-	
Birth weight (kg)	−0.066 (−0.128; −0.005)	0.04	*		*	
Birth weight percentile	−0.004 (−0.006; −0.001)	0.003	−0.004 (−0.007; −0.002)	<0.001	−0.004 (−0.006; −0.002)	<0.001
ROP (yes)	0.263 (0.024; 0.502)	0.03	-		0.152 (−0.070; 0.375)	0.18
ROP treatment (yes)	1.036 (0.509; 1.564)	<0.001	-		0.846 (0.195; 1.497)	0.01
Placental insufficiency (yes)	0.258 (−0.055; 0.572)	0.11	-		-	
Preeclampsia (yes)	0.042 (−0.104; 0.188)	0.58	-		-	
Breastfeeding (yes)	0.095 (−0.208; 0.018)	0.10	-		-	
Smoking pregnancy (yes)	0.070 (−0.245; 0.105)	0.44	-		-	
Higher-order aberrations (HOA) [µm]						
Gestational age (weeks)	−0.003 (−0.006; −0.001)	0.008	−0.003 (−0.006; −0.001)	0.01	−0.001 (−0.004; 0.001)	0.35
Birth weight (kg)	−0.023 (−0.035; −0.012)	<0.001	*		*	
Birth weight percentile	−0.001 (−0.002; −0.001)	<0.001	−0.001 (−0.001; −0.000)	<0.001	−0.001 (−0.001; −0.000)	<0.001
ROP (yes)	0.064 (0.019; 0.109)	0.005	-		0.032 (−0.009; 0.072)	0.12
ROP treatment (yes)	0.216 (0.092; 0.341)	0.001	-		0.120 (0.011; 0.229)	0.03
Placental insufficiency (yes)	0.070 (0.008; 0.133)	0.03	0.047 (−0.021; 0.115)	0.18	0.053 (−0.014; 0.121)	0.12
Preeclampsia (yes)	0.042 (0.003; 0.082)	0.04	−0.002 (−0.037; 0.033)	0.91	−0.002 (−0.038; 0.033)	0.90
Breastfeeding (yes)	−0.029 (−0.053; −0.005)	0.02	−0.011 (−0.032; 0.011)	0.34	−0.010 (−0.031; 0.011)	0.37
Smoking pregnancy (yes)	0.022 (−0.029; 0.073)	0.40	-		-	
Lower-order aberrations (LOA) [µm]						
Gestational age (weeks)	−0.011 (−0.025; 0.003)	0.12	-		-	
Birth weight (kg)	−0.074 (−0.136; −0.011)	0.02	*		*	
Birth weight percentile	−0.004 (−0.006; −0.001)	0.002	−0.004 (−0.006; −0.002)	<0.001	−0.004 (−0.006; −0.002)	0.001
ROP (yes)	0.27 (0.03; 0.511)	0.03	-		0.145 (−0.080; 0.370)	0.21
ROP treatment (yes)	1.049 (0.561; 1.538)	<0.001	-		0.838 (0.173; 1.504)	0.01
Placental insufficiency (yes)	0.232 (−0.081; 0.545)	0.15	-		-	
Preeclampsia (yes)	0.056 (−0.095; 0.208)	0.47	-		-	
Breastfeeding (yes)	−0.098 (−0.212; 0.017)	0.09	-		-	
Smoking pregnancy (yes)	−0.037 (−0.227; 0.152)	0.70	-		-	

Note: Linear regression analysis using generalised estimating equations to control for correlations between right and left eyes.

Model 1 inclusion of parameters associated in the univariate analyses ($p < 0.05$) and adjustment for sex, age, corneal radius, axial length and intraocular pressure.
*Birth weight (kg) was not included in this model due to the high correlation with gestational age.

Model 2 inclusion of parameters associated in the univariate analyses ($p < 0.05$) and adjustment for sex, age, corneal radius, axial length and intraocular pressure, as well as the inclusion of ROP occurrence and treatment.

Total corneal aberrations: model 1: $r^2 = 0.06$; model 2: $r^2 = 0.11$.

Corneal HOA aberrations: model 1: $r^2 = 0.17$; model 2: $r^2 = 0.17$.

Corneal LOA aberrations: model 1: $r^2 = 0.05$; model 2: $r^2 = 0.10$.

Abbreviations: B, Beta; CI, Confidence interval; mm, millimetre.

hydration, evaporation and remodelling processes due to adverse perinatal nutrition. Furthermore, absorbed energy during ROP treatment might be another factor contributing to altered corneal aberrations in those subjects.[21] Thus, we assume that preterm birth together with intrauterine malnutrition play an important role in the development of corneal shape.

Corneal aberrations are an important parameter in determining retinal image quality, and may play a significant role in the process of emmetropisation.[41] Spherical aberration at the corneal periphery may contribute to myopia development,[42] and associations between myopia and ocular fourth-order aberrations have been reported.[43] In this context, we observed a significant association between total corneal aberrations and the spherical equivalent refractive error. This might indicate that increased corneal aberrations contribute, together with other factors, to the well-known increased risk for refractive error in individuals treated for ROP.

Previous authors have reported that the influence of corneal aberrations on visual perception is small compared with myopia and astigmatism.[44] The Wiesbaden Prematurity Study found no significant correlation between corneal aberrations and visual acuity,[4] while the Gutenberg Health Study observed only a small effect size between low BW and corneal aberrations in adulthood, hypothesising that altered corneal aberrations in adults born with low BW are of subclinical importance.[23] This study showed an association between total corneal aberrations and lower visual acuity indicating that altered corneal aberrations contribute, together with other factors such as foveal alterations and foveal developmental delay,[9,22] to an increased risk of lower visual acuity in adults born preterm, particularly those treated postnatally for ROP.

Various factors have been suggested to regulate the development of corneal shape. Refractive error and axial length may be determined by genetic factors, while it is often assumed that corneal shape is particularly influenced by non-genetic factors.[45] There is evidence that corneal aberrations are influenced by intraocular pressure,[46] lid movements, a narrower palpebral position and aperture and narrower palpebral angle.[47-49] This study extends these previous reports, highlighting for the first time that in preterm newborns, abnormal nutritional status and postnatal ROP have long-lasting effects on corneal aberrations in adulthood.

Overall, changes in corneal aberrations may be of clinical importance because imaging errors lead to lower optical resolution at the retina, and influence refractive error development.[5,42] However, the effects of corneal HOAs are small compared to the effects of myopia and astigmatism.[42]

Optical image formation in the human eye is determined by several components, one of which is the cornea. It is possible that corneal aberrations may be compensated by internal optical components, therefore not affecting image quality and visual perception. On the other hand, increased aberrations may affect the quality of the retinal image because we observed an association between increased corneal aberration, decreased visual acuity and increased refractive error, potentially indicating the clinical importance of corneal irregularity.

This study has some limitations. It was a single-centre design and several former newborns could not be contacted or declined to take part; thus, there is the risk of selection bias. Furthermore, Scheimpflug imaging was not possible in some participants or the measurements were of low quality, particularly in those having low visual acuity and difficulty fixating, which could be another reason for bias. The small number of participants treated for ROP with a GA ≤28 weeks must also be considered when interpreting the results. No ocular wavefront analysis was performed; thus, no statement about optical quality and internal aberrations is possible and we cannot differentiate whether this leads to decreased image quality on the retina in preterm human eyes. The findings may also be affected by the presence of corneal ectasia and corneal dystrophy, as well as other ocular conditions except cataract and corneal refractive surgery, which were excluded from the present analysis. Another bias could be caused by the inclusion of contact lens wearers, as rigid gas permeable contact lenses users may have some degree of corneal warpage which could potentially affect corneal aberrations. However, the sensitivity analysis excluding contact lens wearers revealed comparable results.

Of note, this is the largest ophthalmologic cohort of adults born preterm with different degrees of prematurity with and without ROP worldwide from a database of over 40,000 infants. The comprehensive data collection of perinatal history enabled a detailed analysis of the separate effects of GA, ROP occurrence and treatment and several other perinatal factors on corneal shape. Furthermore, all investigators were blinded as to the participants' birth characteristics, and all measurements were conducted according to strict standardised operating procedures to reduce examiner-dependent bias.

CONCLUSION

In conclusion, this study highlights the life-long effects of preterm birth together with prenatal growth restriction and postnatal ROP treatment on corneal shape irregularity in adulthood. The altered corneal shape may contribute to reduced optical image quality and impact visual function and refractive error development in affected individuals.

AUTHOR CONTRIBUTIONS

Achim Fieß: Conceptualization (lead); data curation (lead); formal analysis (lead); funding acquisition (lead); investigation (lead); methodology (lead); project administration (lead); resources (lead); software (lead); supervision (lead); validation (lead); visualization (lead); writing – original draft (lead); writing – review and editing (lead). **Lina Amalia Berger:** Conceptualization (equal); data curation (equal); formal analysis (equal); investigation (equal); methodology (equal); software (equal); validation (equal); visualization (equal); writing – review and editing (equal). **Jana C Riedl:** Data curation (equal); investigation (equal); methodology (equal); validation (equal); writing – review and editing (equal). **Eva Mildenberger:** Data curation (equal); investigation (equal); methodology (equal); supervision (equal); validation (equal); writing – review and editing (equal). **Michael S Urschitz:** Data curation (equal); formal analysis (equal); investigation (equal); methodology (equal); validation (equal); writing – review and editing (equal). **Ulrike Hampel:** Formal analysis (equal); methodology (equal); validation (equal); visualization (equal); writing – review and editing (equal). **Joanna Wasielica-Poslednik:** Formal analysis (equal); investigation (equal); methodology (equal); visualization (equal); writing – review and editing (equal). **Fred Zepp:** Investigation (equal); methodology (equal); validation (equal); writing – review

and editing (equal). **Bernhard Stoffelns:** Formal analysis (equal); methodology (equal); validation (equal); writing – review and editing (equal). **Norbert Pfeiffer:** Formal analysis (equal); funding acquisition (equal); investigation (equal); methodology (equal); resources (equal); validation (equal); writing – review and editing (equal). **Alexander K Schuster:** Conceptualization (equal); data curation (equal); formal analysis (equal); funding acquisition (equal); investigation (equal); methodology (equal); resources (equal); software (equal); supervision (equal); validation (equal); visualization (equal); writing – review and editing (equal).

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CONFLICT OF INTEREST

The authors report no conflict of interest.

DATA AVAILABILITY STATEMENT

AF 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 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 on 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 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 UM (www.unimedizin-mainz.de).

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