Received: 20 July 2022 | Accepted: 27 March 2023

DOI: 10.1111/aos.15672

Acta Ophthalmologica

ORIGINAL ARTICLE

Ocular geometry in adults born small, appropriate or large for gestational age at term

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Funding information
Else Kröner-Fresenius-Stiftung; Ernst und Berta Grimmke Stiftung; Stufe 1 Support University Medical Center Mainz

Abstract

Purpose: Intrauterine growth restriction leading to a birth weight (BW) which is too low for gestational age (GA) is a known risk factor for various altered organ morphologies and dysfunction in later life. This study aimed to determine for the first time the effects of being small (SGA) or large for gestational age (LGA) on the ocular geometry of adults born at term.

Methods: All participants were examined with optical biometry (LenStar 900, Haag Streit) to compare the corneal curvature, white-to-white distance, anterior chamber depth, lens thickness and axial length between former moderate (BW percentile 3rd to <10th) and severe (BW <3rd percentile) SGA, controls (BW 10th-90th percentile) and former moderate (BW >90th to 97th percentile) and severe (BW >97th percentile) LGA. Multivariable linear regression was used to analyse associations with GA, BW percentile categories, placental insufficiency, preeclampsia and breastfeeding after adjustment for age and sex.

Results: In total, 589 eyes of 296 individuals born at term (aged 30.0±9.4 years, 156 females) were examined, including 40 severe SGA, 38 moderate SGA, 140 with normal BW, 38 moderate LGA and 40 severe LGA. There was an association between a steeper corneal curvature with moderate (B=−0.201; $p<0.001$) and severe SGA (B=−0.199; $p<0.001$), with extreme SGA associated with smaller white-to-white (B=−0.263; $p=0.001$) and a shorter axial length (B=−0.524; $p=0.031$).

Conclusions: Severe and moderate prenatal growth restriction in adults born at term leads to an altered ocular geometry, namely a steepening of the cornea and a smaller corneal diameter.

KEYWORDS
axial length, birth weight, cornea, epidemiology, large for gestational age, small for gestational age

1 | INTRODUCTION

Birth weight reflects growth in utero due to different maternal, placental and foetal factors and is used as a clinical marker to identify newborns with an increased risk of postnatal complications (Weissmann-Brenner et al., 2012). The Barker hypothesis proposes that restricted foetal growth increases the risk for cardiovascular diseases later in life, (Barker, 1995, 1997; Barker et al., 1990) as insufficient intrauterine nutrition during decisive periods of foetal organ development leads to life-long alterations that may increase the risk of various diseases in later life (Barker, 1997).

Two main groups were identified at risk for adverse postnatal and long-term outcomes, infants born with a low birth weight (SGA) and a high birth weight (LGA) in relation to gestational age depending on the curves for normal foetal growth or birth weight in correlation to GA (Chiavaroli et al., 2014; Weissmann-Brenner et al., 2012). Severe SGA is defined as a birth weight of less than the third percentile and moderate SGA as less than the 10th percentile, while large for gestational age is categorized as either larger than the 90th (moderate) percentile or larger than the 97th percentile in case of severe LGA (Chiavaroli et al., 2016) while AGA (adequate for gestational age) is defined as 10th to 90th birth weight

percentile. This is of particular importance because more than 30 million infants are born SGA worldwide (Lee et al., 2013) and the number of high birth weight infants is increasing due to increased maternal obesity and intrauterine supernutrition (Chiavaroli et al., 2016). In Europe, the prevalence of preterm and full-term infants-born SGA is reported to be 7.6% while about 11.7% are LGA (Chiavaroli et al., 2016).

Several studies have reported that preterm-born subjects with low birth weight are at increased risk of alterations of ocular geometry in infancy (Donzis et al., 1985) and childhood, (Chen et al., 2010; Choi et al., 2000; Fieß, Kolb-Keerl, et al., 2017) showing a steeper corneal curvature, smaller anterior chamber depth, increases lens thickness and smaller axial length. Furthermore, within the Gutenberg Prematurity Eye Study in individuals born preterm and full-term aged 18–52 years, there was evidence that the more preterm the participants were born the steeper the corneal curvature. In the multivariable analyses of all preterm and full-term individuals, a lower birth weight percentile as surrogate for foetal malnutrition was associated with a steeper corneal curvature (Fieß, Nauen, et al., 2022). Scarce data exist showing the influence of adverse foetal growth on ocular dimensions in childhood (Saw et al., 2004; Tideman et al., 2019). However, up-to-now, it is not investigated whether foetal malnutrition leads to persistent ocular changes in later life in adults born on term. In our recent work from the population-based Gutenberg Health Study, we demonstrated an association between low birth weight and increased myopic refractive error (Fieß, Schuster, Nickels, Elflein, et al., 2019) as well as altered ocular geometry that persists into adulthood (Fieß, Schuster, Nickels, Urschitz, et al., 2019). However, these studies only investigated the association between lower birth weight and ocular geometry and did not consider the degree of maturity and did not exclude preterm individuals. Adults with a low birth weight had an increased prevalence of eye diseases such as diabetic retinopathy (Fieß et al., 2020) or age-related macular degeneration (Fieß, Elbaz, Korb, Nickels, et al., 2019). However, the effects on ocular geometry of a low birth weight in correlation to gestational age indicated by an abnormal birth weight percentile as surrogate marker for foetal malnutrition in adults born term are not known.

This study is the first to analyse the long-term effects of being severe and moderate SGA and LGA, respectively, in adults born at term on ocular geometry. It was hypothesized that SGA, particularly severe SGA, is linked to a steeper corneal shape and smaller axial length in subjects born at term.

2 | MATERIALS AND METHODS

2.1 | Study population

This investigation is part of the Gutenberg Prematurity Eye Study (GPES), a single-centre retrospective cohort study at the University Medical Center of the Johannes Gutenberg-University Mainz in Germany (UMCM) with a prospective ophthalmologic examination in adulthood. The GPES recruits individuals that (i) have been born preterm or at term between 1969 and 2002 and (ii) were between 18 and 52 years of age at study enrolment. For each calendar month (from 1969 to 2002), six randomly selected full-term subjects (three males and three females) with a birth weight between the 10th and 90th percentile were invited and examined (Fieß, Nauen, et al., 2022). The control group (group 3) of subjects born AGA (10th–90th percentile) in this study is identical to the control group of the Gutenberg Prematurity Eye Study. Furthermore, for this study, former term newborns of the UMCM were invited age matched according to their birth weight (40 participants in each birth weight percentile category group). They were classified into severely SGA participants (BW <3rd percentile; group 1) (40 persons), moderately SGA (BW percentile 3rd–<10th; group 2) (40 persons), AGA (BW percentile 10th–90th; group 3) (140 persons, GPES control group), moderately LGA (BW percentile >90th–97th; group 4) (40 persons) and severely LGA (BW percentile >97th percentile; group 5) (40 persons). All study participants had a gestational age ≥37 weeks and were born at the UMCM between 1969 and 2002. An ophthalmologic examination including ocular biometry was conducted between 2019 and 2021. In addition, all participants completed a questionnaire and medical birth records were reviewed to obtain relevant data.

Written informed consent was obtained from all participants before they entered into the study and this study complied 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. 2019–14 161; original vote: 29.05.2019, latest update: 02.04.2020).

2.2 | Assessment of pre-, peri- and postnatal history

Medical birth records were reviewed including pre-, peri- and postnatal birth history (birth weight in kg, gestational age in weeks, pre-eclampsia, placental insufficiency, maternal smoking, gestational diabetes and breastfeeding).

2.3 | Categorization

BW percentile was calculated according to Voigt et al. (2006) for this analysis. All subjects were born full-term (GA ≥37 weeks) and were grouped into severe SGA participants (BW <3rd percentile; group 1), moderate SGA (BW percentile 3rd–<10th; group 2), AGA (BW percentile 10th–90th; group 3), moderate LGA (BW percentile >90th–97th; group 4) and severe LGA (BW percentile >97th percentile; group 5). The control group (group 3) of subjects born AGA (10th–90th percentile) was the same control group of the Gutenberg Prematurity Eye Study (Fieß, Nauen, et al., 2022).

2.4 | Ophthalmologic examination

The objective refraction and distance-corrected visual acuity were measured (ARK-1s, NIDEK; Oculus) in each participant and the spherical equivalent was calculated by adding the sphere and half of the cylindric value (Fieß et al. 2022). Ocular geometry was measured with LenStar 900 (Haag Streit). Within one examination procedure, three different measurements were conducted, and the mean value was computed. For this study, the following measurements were recorded: corneal radius as the arithmetic mean between the steeper and flatter corneal radius, white-to-white distance as a surrogate marker 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 checked for outliers and participants who had previous corneal refractive surgery were excluded from the analysis.

2.5 | Statistical analysis

Descriptive statistics were computed. Absolute and relative frequencies were calculated for dichotomous parameters, the mean and standard deviation for approximately normally distributed data, otherwise median and interquartile range. The main outcome measures were corneal radius, white-to-white distance, anterior chamber depth, lens thickness, axial length and spherical equivalent. Linear regression models with generalized estimating equations (GEE) were used to assess associations and account for correlations between both eyes of one subject. In model #1, the main outcome measures were tested in univariable analysis. In model #2, associations of age (years), sex (female), GA (weeks), birth weight percentile (categories), placental insufficiency (yes), preeclampsia (yes) and breastfeeding (yes) were assessed in a multivariable model. Birth weight was not incorporated into this model due to the high correlation between birth weight and gestational age. This is an explorative study and no adjustment for multiple testing was carried out. Calculations were performed using commercial statistical software (IBM SPSS 20.0; SPSS, Inc.).

3 | RESULTS

3.1 | Participant characteristics

In this study, 589 eyes of 296 individuals born at term were included (aged 30.0±9.4 years, 156 females). There were 40 subjects with a BW < 3rd percentile, 38 with 3rd to <10th BW percentile, 140 with BW percentile 10th–90th, 38 with BW percentile >90th to 97th and 40 with BW percentile >97th. The recruitment efficacy proportion was 52.6% in all SGA and LGA individuals and 48.3% in AGA study participants. Three participants were excluded because of corneal refractive surgery and one due to missing LenStar data. Furthermore, in three participants, LenStar data were only measurable in one eye. Table 1 presents the characteristics of the study sample including peri- and postnatal data. Both eyes were processed separately.

3.2 | SGA, AGA and LGA groups

Participants with severe SGA had the steepest corneal radius, followed by moderate SGA subjects. The corneal radius of LGA subjects did not differ from AGA subjects. A smaller white-to-white distance and a shorter axial length were observed in severe SGA subjects. Severe LGA subjects did not show any different ocular geometry compared to AGA subjects. Anterior chamber depth and lens thickness were similar between the five groups (Table 2). Scatterplots of birth weight percentile with corneal radius indicate that there is a linear relationship up to 75th percentile of BW (Figure 1).

TABLE 1 Characteristics of the study sample (n = 296) of individuals born at term stratified by moderate and severe SGA and LGA groups.

	Severe SGA	Moderate SGA	AGA	Moderate LGA	Severe LGA
BW percentile	<3	3 to < 10	10–90	>90 to 97	>97
Number of participants/eyes	40 / 80	38 / 74	140 / 280	38 / 76	40 / 79
Gender (Women) (%)	23 (58%)	19 (50%)	81 (58%)	15 (40%)	18 (45%)
Age (years)	29.0±9.3	29.8±9.6	29.9±9.2	30.2±9.6	31.6±10.2
Birth weight (g)	2073±334	2690±353	3420±392	4300±289	4740±591
Gestational age (weeks)	37.8±1.2	38.5±1.4	39.3±1.3	40.0±1.4	40.3±1.2
(Min–max)	(37–41)	(37–42)	(37–43)	(37–43)	(37–43)
Pre-eclampsia (yes)	10 (25%)	1 (2.6%)	11 (7.9%)	2 (5.3%)	7 (17.5%)
Placental insufficiency (yes)	11 (27.5%)	0 (0%)	2 (1.4%)	0 (0%)	0 (0%)
Maternal smoking (yes)	4 (10%)	0 (0%)	7 (5%)	0 (0%)	2 (5%)
Gestational diabetes (yes)	1 (2.5%)	0 (0%)	1 (0.7%)	1 (2.6%)	2 (5%)
Breastfeeding (yes)	17 (42.5%)	18 (47.4%)	79 (56.4%)	25 (65.8%)	31 (77.5%)
Ocular parameters					
Intraocular pressure (mmHg) OD	14.0±2.7	14.2±2.8	15.2±2.8	14.3±3.0	13.9±2.5
Intraocular pressure (mmHg) OS	14.1±2.8	14.3±2.9	15.1±2.8	14.29±3.0	13.9±2.6

Abbreviations: g, gram; mm, millimetre; dpt, diopter; AGA, adequate for gestational age; SGA, small for gestational age; LGA, large for gestational age; BW, birth weight.

3.3 | Uni- and multivariable analyses

There was an association between a steeper corneal curvature and severe SGA (B=−0.199 [95%-CI: −0.301; −0.097] mm; $p<0.001$) and moderate SGA (B=−0.201 [95%-CI: −0.292; −0.111] mm; $p<0.001$). Furthermore, severe SGA was associated with a smaller white-to-white distance (B=−0.263 [95%-CI: −0.419; −0.107] mm; $p=0.001$), while moderate LGA was associated with a larger white-to-white distance (B=0.158 [95%-CI: 0.040; 0.277] mm; $p=0.009$). No significant associated perinatal factors were observed in multivariable analyses for anterior chamber depth and lens thickness. Axial length was smaller in severe SGA (B=−0.524 [95%-CI: −0.999; −0.048] mm; $p=0.031$) participants in multivariable analysis. Increased myopic refractive error was observed in the moderate SGA group (B=−1.198 [95%-CI: −2.080; −0.316] mm; $p=0.008$) but not in the other groups (Table 3).

4 | DISCUSSION

This study provides new data about the effects of restricted and excessive growth on ocular geometric long-term outcomes in adults born at term now aged between 18 and 52 years. A low birth weight percentile as a proxy for restricted intrauterine growth in individuals born at term is associated with a steeper corneal curvature and smaller white-to-white distance as a surrogate for corneal diameter, while severe SGA showed shorter axial length. There are several reports assessing the association between prematurity and low birth weight with corneal shape and ocular geometry, however, there has been no data regarding the association of low birth weight percentile as surrogate marker for adverse foetal growth in adults born at term.

In previous reports assessing corneal geometry within the first 40 weeks of post-gestational age, low birth weight and preterm birth were both associated with a steeper

TABLE 2 Ocular geometric parameters of the full-term study sample ($n=296$) for each study group.

	Severe SGA <3	Moderate SGA 3 to<10	AGA 10–90	Moderate LGA >90 to 93	Severe LGA >97
Number of participants/eyes	40 / 80	38 / 74	140 / 280	38 / 76	40 / 79
Right eye					
Mean corneal radius [mm]	7.67±0.22**	7.68±0.24**	7.89±0.30	7.96±0.27	7.93±0.29
White-to-white distance [mm]	11.92±0.43**	12.14±0.50	12.23±0.35	12.45±0.34#	12.35±0.54
Anterior chamber depth [mm]	2.94±0.35	3.05±0.35	2.93±0.32	3.05±0.36	3.00±0.29
Lens thickness [mm]	3.74±0.31	3.74±0.35	3.78±0.33	3.76±0.31	3.79±0.34
Axial length [mm]	23.22±1.19#	23.84±1.21	23.74±1.19	24.19±1.09#	23.87±0.91
Spherical equivalent [diopter]	−0.94±1.93	−1.93±2.51#	−0.98±2.18	−1.08±1.88	−0.64±1.78
Left eye					
Mean corneal radius [mm]	7.67±0.21**	7.68±0.25**	7.88±0.32	7.95±0.28	7.93±0.29
White-to-white distance [mm]	11.93±0.42**	12.16±0.41	12.24±0.6	12.45±0.36#	12.32±0.47
Anterior chamber depth [mm]	2.95±0.34	3.05±0.37	2.94±0.33	3.06±0.38	3.02±0.27
Lens thickness [mm]	3.72±0.32	3.73±0.36	3.76±0.34	3.71±0.32	3.73±0.32
Axial length [mm]	23.26±1.26#	23.85±1.26	23.69±1.17	24.11±1.05#	23.80±0.96
Spherical equivalent [diopter]	−1.14±2.17	−2.14±2.65#	−0.97±2.09	−1.09±1.97	−0.70±1.78

Note: Ocular geometry was compared including the different SGA and LGA groups in comparison to the AGA group (reference) using linear regression analysis.
Abbreviations: AGA, adequate for gestational age; SGA, small for gestational age; LGA, large for gestational age; BW, birth weight and mm, millimetre.
#Statistical difference ($p<0.05$) compared to the AGA group.
**Statistical difference ($p<0.001$) compared to the AGA group.

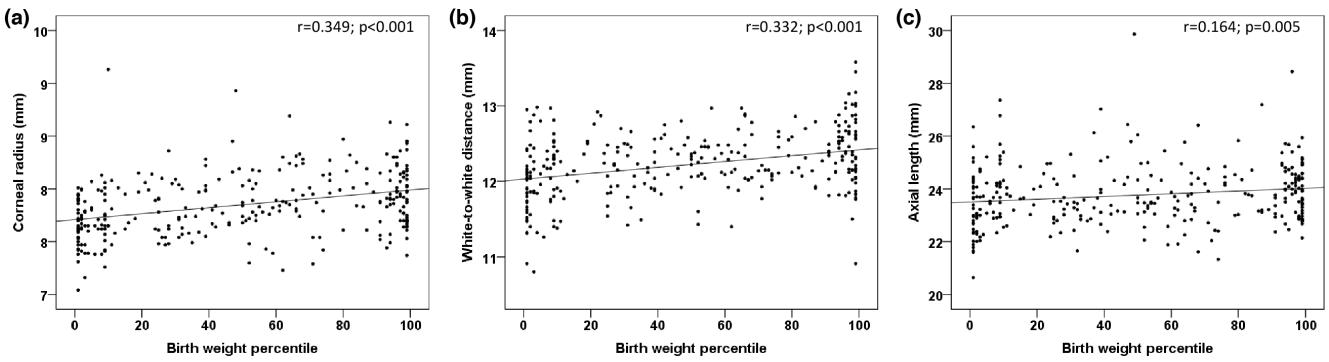

FIGURE 1 Scatterplot of birth weight percentile with (a) corneal radius, (b) white-to-white distance (c) and axial length in former full-term individuals ($n=296$). Participants with lower birth weight percentiles showed a slightly steeper corneal curvature and a smaller white-to-white distance.

TABLE 3 Linear associations of ocular geometric parameters with different perinatal parameters ($n = 296$) of individuals born at term (37–42 weeks).

	Unadjusted[a]		Multivariable[b]	
	B [95% CI]	*p*	B [95% CI]	*p*
Mean corneal radius [mm]				
Gestational age (weeks)	0.019 (0.021; 0.068)	<0.001	0.018 (−0.008; 0.044)	0.2
Birth weight (kg)	0.129 (0.095; 0.163)	<0.001	[c]	[c]
Birth weight percentile (<3rd)	−0.200 (−0.273; −0.127)	<0.001	−0.199 (−0.301; −0.097)	<0.001
Birth weight percentile (3rd–<10th)	−0.187 (−0.272; −0.103)	<0.001	−0.201 (−0.292; −0.111)	<0.001
Birth weight percentile (10th–90th; ref.)	Ref.	Ref.	Ref.	Ref.
Birth weight percentile (>90th–97th)	0.133 (0.041; 0.225)	0.005	0.057 (−0.037; 0.152)	0.2
Birth weight percentile (>97th)	0.098 (0.002; 0.193)	0.045	0.040 (−0.062; 0.143)	0.4
Placental insufficiency (yes)	−0.104 (−0.318; 0.110)	0.3	0.046 (−0.184; 0.275)	0.7
Pre-eclampsia (yes)	−0.072 (−0.159; 0.016)	0.1	−0.039 (−0.136; 0.058)	0.4
Breastfeeding (yes)	−0.016 (−0.087; 0.054)	0.7	−0.061 (−0.127; 0.005)	0.068
White-to-white distance [mm]				
Gestational age (weeks)	0.058 (0.027; 0.090)	<0.001	0.009 (−0.024; 0.042)	0.6
Birth weight (kg)	0.193 (0.138; 0.248)	<0.001	[c]	[c]
Birth weight percentile (<3rd)	−0.347 (−0.482; −0.212)	<0.001	−0.263 (−0.419; −0.107)	0.001
Birth weight percentile (3rd–<10th)	−0.083 (−0.227; 0.062)	0.3	−0.095 (−0.237; 0.046)	0.2
Birth weight percentile (10th–90th; ref.)	Ref.	Ref.	Ref.	Ref.
Birth weight percentile (>90th–97th)	0.254 (0.136; 9.372)	<0.001	0.158 (0.040; 0.277)	0.009
Birth weight percentile (>97th)	0.129 (−0.032; 0.290)	0.1	0.055 (−0.105; 0.215)	0.5
Placental insufficiency (yes)	−0.351 (−0.615; −0.087)	0.009	−0.095 (−0.385; 0.194)	0.5
Pre-eclampsia (yes)	−0.117 (−0.266; 0.033)	0.1	−0.027 (−0.181; 0.126)	0.7
Breastfeeding (yes)	0.113 (−0.021; 0.205)	0.2	0.057 (−0.030; 0.144)	0.2
Axial length [mm]				
Gestational age (weeks)	0.103 (0.007; 0.198)	0.035	0.054 (−0.058; 0.165)	0.4
Birth weight (kg)	0.266 (0.121; 0.411)	<0.001	[c]	[c]
Birth weight percentile (<3rd)	−0.582 (−0.979; −0.185)	0.004	−0.524 (−0.999; −0.048)	0.031
Birth weight percentile (3rd–<10th)	0.123 (−0.293; 0.538)	0.6	0.135 (−0.287; 0.559)	0.5
Birth weight percentile (10th–90th; ref.)	Ref.	Ref.	Ref.	Ref.
Birth weight percentile (>90th–97th)	0.47 (0.11; 0.84)	0.011	0.320 (−0.066; 0.706)	0.1
Birth weight percentile (>97th)	0.099 (−0.224; 0.421)	0.6	−0.012 (−0.383; 0.360)	0.9
Placental insufficiency (yes)	−0.091 (−0.917; 0.735)	0.8	0.476 (−0.393; 1.345)	0.3
Pre-eclampsia (yes)	−0.151 (−0.459; 0.157)	0.3	−0.012 (−0.370; 0.346)	0.9
Breastfeeding (yes)	0.134 (−0.142; 0.409)	0.3	0.093 (−0.183; 0.370)	0.5
Spherical equivalent [diopter]				
Gestational age (weeks)	−0.020 (−0.191; 0.150)	0.8	−0.107 (−0.317; 0.104)	0.3
Birth weight (kg)	0.196 (−0.049; 0.440)	0.1	[c]	[c]
Birth weight percentile (<3rd)	0.057 (−0.606; 0.720)	0.9	−0.185 (−0.983; 0.614)	0.7
Birth weight percentile (3rd–<10th)	−1.084 (−1.935; −0.233)	0.013	−1.198 (−2.080; −0.316)	0.008
Birth weight percentile (10th–90th; ref.)	Ref.	Ref.	Ref.	Ref.
Birth weight percentile (>90th–97th)	0.007 (−0.644; 0.657)	0.9	−0.061 (−0.799; 0.677)	0.9
Birth weight percentile (>97th)	0.484 (−0.108; 1.075)	0.1	0.432 (−0.247; 1.110)	0.2
Placental insufficiency (yes)	−0.131 (−0.014; 0.751)	0.8	−0.405 (−1.400; 0.591)	0.4
Pre-eclampsia (yes)	0.123 (−0.462; 0.709)	0.7	0.087 (−0.511; 0.684)	0.8
Breastfeeding (yes)	−0.214 (−0.705; 0.277)	0.4	−0.312 (−0.830; 0.206)	0.2

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

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

[a]Crude model without adjustment.

[b]Model with the inclusion of sex (female), age (years), gestational age (weeks), birth weight percentile (<3rd), birth weight percentile (3rd–<10th), birth weight percentile (10th–90th; reference), birth weight percentile (>90th–97th), birth weight percentile (>97th), placental insufficiency (yes), pre-eclampsia (yes) and breastfeeding (yes).

[c]Birth weight (kg) was not included in this model due to the high correlation with gestational age.

cornea (Friling et al., 2004). A rapid corneal flattening was observed immediately after preterm birth in postnatal weeks 2–4 which slowed down after the first 8 weeks of life (Inagaki, 1986). In line with these reports, other groups observed a steeper ocular geometry in preterm children with a low birth weight (Choi et al., 2000; Fieß, Kolb-Keerl, et al., 2017), and school-aged children (Chen et al., 2010).

Similar findings were observed in adolescents and adults. In the population-based 'National Health and Nutrition Examination Survey' in the United States, a steeper cornea was associated with low birth weight in adolescents (Fieß, Schuster, et al., 2017). There are few data available for the effects of low birth weight in adults, while no data exist assessing the long-term effects of growth restriction irrespective of prematurity on ocular shape. Sun and colleagues showed in subjects between 5 and 80 years that low birth weight is correlated with a steeper cornea (Sun et al., 2010), which is in line with the data from the Gutenberg Health Study with participants aged 40–80 years (Fieß, Schuster, Nickels, Urschitz, et al., 2019). However, these studies only investigated the association between lower birth weight and ocular geometry and did not consider the degree of maturity. Fieß et al. investigated 438 former preterm and full-term individuals and found that the more preterm the participants were born the steeper corneal curvature (Fieß, Nauen, et al., 2022). Further, the authors reported that a lower birth weight percentile was linked to a steeper cornea. Nevertheless, the effects of preterm birth and malnutrition was difficult to differentiate in this report, as preterm birth and malnutrition show a correlation. Consequently, we established a cohort of term-born subjects and examined the effect of foetal malnutrition in this study design revealing that a low birth weight in correlation to gestational age in term subjects also leads to a steepening of the corneal curvature. Our data are in contrast to the hypothesis of Fielder et al., 1986 explaining the alteration of the anterior segment by lower extrauterine temperature on the corneal surface after preterm birth leading to less flattening of the cornea. In contrast to the corneal shape, we observed no associations with respect to the anterior chamber depth and perinatal factors in term subjects and when investigating lens thickness. This is in line with data reported in children (Fieß, Kolb-Keerl, et al., 2017; Ojaimi et al., 2005; Saw et al., 2004) and low birth weight adults (Fieß, Schuster, Nickels, Elflein, et al., 2019; Sun et al., 2010).

In the multivariable analysis, there was an association between severe SGA and shorter axial length. The association between low gestational age and low birth weight with a smaller axial length is well known in children born preterm (Cook et al., 2003; Ecsedy et al., 2014; Fieß, Kolb-Keerl, et al., 2017; Hirano et al., 1979). However, some of the authors did not consider the strong correlation between birth weight and gestational age. Fledelius and colleagues reported that postnatal ocular growth is affected by a low BW percentile in infants born preterm (Fledelius & Fledelius, 2012), while the effects of restricted growth on ocular long-term outcome in subjects born at term is unknown and our data can fill this gap showing that particularly restricted and not excessive growth affects axial length. Two reports exist assessing the association of low birth weight with a shorter axial length in adulthood (Fieß, Schuster, Nickels, Urschitz, et al., 2019; Sun et al., 2010), however, gestational age was not surveyed in either study.

4.1 | Strengths and limitations

This study has several limitations. First, its design is a single-centre hospital-based study. Second, not all identified former newborns of the UMCM could be contacted, while others declined to participate. Furthermore, data about spherical equivalent is restricted because it could be influenced by other non-adjusted factors such as family history of myopia or hyperopia. Furthermore, it has to be considered that no cycloplegia was performed which could bias the results particularly in younger individuals with a hyperopic refractive error. In addition, it has to be reflected that the influence of foetal malnutrition on ocular dimensions may be studied at an earlier stage of life as done by Saw et al. (2004) and Tideman et al. (2019), before the possible development of myopia due to environmental factors. As the development of the corneal curvature generally ends before myopia formation, our study highlights the persistent influence of foetal malnutrition on corneal curvature characteristics. Furthermore, because perinatal diagnostics improved significantly in the last five decades, we cannot fully exclude that the determination of gestational age might be more exactly measured today.

However, there are several strengths of this analysis. We included subjects born at term in different birth weight percentiles groups to investigate the effect of low and high birth weight in a relatively homogeneous group with respect to gestational age and assessed their perinatal medical history.

4.2 | Conclusion

Severe and moderately small for gestational age is associated with a steeper corneal curvature in subjects born at term, indicating that corneal development is also influenced by foetal malnutrition irrespective of prematurity leading to life-long alterations in ocular geometry.

AUTHOR CONTRIBUTIONS

Conceived and designed the study: AF and AKS; analysed the data: AF, AS, EM, MSU and AKS; wrote the article: AF; critically revised the article: AF, AS, EM, MSU, BS, NP and AKS; all authors read and approved the final article. This article contains parts of the thesis of Anna Schultheis.

ACKNOWLEDGEMENTS

The whole study team thank all participants who took part in this study. Open Access funding enabled and organized by Projekt DEAL.

FUNDING/SUPPORT

All authors: Dr. Fieß is supported by the Intramural Research Funding (Stufe I) of the University Medical Center of Johannes Gutenberg University Mainz. This study was supported by the Ernst- und Berta-Grimmke Stiftung 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 article. 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'.

FINANCIAL DISCLOSURE/CONFLICT OF INTEREST

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 Novartis.

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no competing interests.

ACCESS TO DATA, RESPONSIBILITY AND ANALYSIS

AF had full access to all the data in this study and took 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 make their requests to the coordinating PI (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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How to cite this article: Fieß, A., Schultheis, A., Mildenberger, E., Urschitz, M.S., Stoffelns, B., Pfeiffer, N. et al. (2024) Ocular geometry in adults born small, appropriate or large for gestational age at term. *Acta Ophthalmologica*, 102, e86–e93. Available from: https://doi.org/10.1111/aos.15672