Fetal Growth Restriction Leads to an Enlarged Cup-to-Disc Ratio in Adults Born at Full Term

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• PURPOSE: This study explores associations between fetal growth restriction or excessive fetal growth, along with perinatal factors on the optic nerve head morphology in adulthood.

• DESIGN: Retrospective cohort study.

• METHODS: This retrospective cohort study involved a prospective ophthalmological examination of individuals born at full term (with a gestational age of ≥37 weeks) from 1969 to 2002. Each participant underwent nonmydriatic fundus camera photography to capture images of the optic discs, followed by manual measurements. The vertical cup-to-disc ratio (VCDR) and optic disc area were examined and analyzed in relation to the baby's birth weight relative to the gestational age. These categories included those with former moderate (birth weight percentile between the 3rd and <10th), severe SGA (below the third percentile), normal (AGA, 10th-90th percentile), and moderately (birth weight >90th-97th percentile) and severely (birth weight >97th percentile) large for gestational age (LGA) adults within the age range of 18 to 52 years.

• RESULTS: Overall, 535 eyes of 280 individuals (age 29.7 ± 9.2 years, 144 females) born at full term were included. Multivariable analysis showed a significant association between a larger VCDR and the severe SGA group ($B = 0.05$, 95% CI 0.01-0.10; $P = .02$). In the univariable model, placental insufficiency was associated with VCDR ($B = 0.10$, 95% CI 0.01-0.19; $P = .03$). Other perinatal factors did not demonstrate an association with VCDR. Furthermore, there was an indication of an association suggesting a smaller optic disc area in individuals born moderately SGA at full term ($B = -0.17$, 95% CI −0.33 to −0.001; $P = .05$).

• CONCLUSIONS: This study provides evidence that individuals born at-term with severe SGA have an increased VCDR, suggesting that fetal growth restriction has a lasting impact on optic disc morphology independent of prematurity throughout adulthood. (Am J Ophthalmol 2024;262: 170–177.

RESTRICTED FETAL GROWTH IS A MAJOR RISK factor for short- or long-term childhood morbidity.[1,2] Growth restriction at birth is categorized as severely small for gestational age (SGA) when the birth weight falls below the 3rd percentile, and moderately SGA when the birth weight falls between the 3rd and less than the 10th percentile in relation to gestational age.[3,4] It has been demonstrated that up to 50% of stillborn infants were SGA or experienced growth restriction.[5] Further potential consequences may include lower intelligence, below average academic performance, limited social competence, and behavioral issues when compared to individuals born appropriate for gestational age (AGA).[6-8]

Furthermore, there is an association between the retinal nerve fiber layer thickness (RNFL) and fetal growth.[3,9-11] The RNFL thickness is discussed as a measure of central nervous tissue, and is a crucial factor in visual function as the axons located here transmit visual perception. Thus, the question arises, whether parameters of the optic nerve head morphology are different in individuals born SGA. However, there are no data about the influence of adverse fetal growth on optic disc measures in adults born full term. Kandasamy reported data for infants born full term ($n = 35$) finding no association between birth weight and optic disc measures.[12] Furthermore, prior studies have predominantly concentrated on investigating these aspects among preterm infants.[13,14]

Studies among preterm-born participants found no association between the vertical cup-to-disc ratio (VCDR) and fetal growth conditions.[13,14] In contrast, one study showed an association between VCDR and birth weight in 2353 children with a median age of 12 years (individuals born preterm and full term). This association persisted after ex-

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cluding individuals born with a gestational age of <33 weeks.[15] A previous investigation conducted as part of the Gutenberg Prematurity Eye Study (GPES) revealed an association between the lower birth weight percentile and VCDR[16] in adults born preterm and full term but no association between birth weight percentile and optic disc area. However, the long-term effects of adverse fetal growth independent of preterm birth are completely unknown.

Hence, this study examined the relationship between restricted or excessive fetal growth and other perinatal variables with the optic nerve head morphology (VCDR and optic disc size area) in individuals born full term to distinguish the influence of growth restriction independent of prematurity.

MATERIALS AND METHODS

• **STUDY POPULATION:** This single-center, retrospective cohort study was conducted at the University Medical Center Mainz (UMCM) of the Johannes Gutenberg-University Mainz in Germany using acquired prospective data including an ophthalmic examination in adulthood. All participants were born at UMCM between 1969 and 2002, with a gestational age of 37 weeks or more. For each calendar month during this period, 6 randomly chosen full term individuals (3 males and 3 females) with birth weights falling within the 10th and 90th percentiles were invited for examination.[3] In this study, sex was defined according to hospital birth records with only binary outcomes: female/male.

Furthermore, 40 participants of the different SGA and large for gestational age (LGA) groups were examined, all with a gestational age ≥37 weeks and 133 individuals born full term with a birth weight percentile within the 10th and 90th percentiles were examined and served as the control group.[3] The age-matched participants were invited to take part in the study. Participants with no VCDR measurements were excluded. There were 37 individuals born severe SGA (BW percentile < 3rd), 35 moderate SGA (3rd to <10th percentile), 38 severe LGA (BW percentile > 97th), 37 moderate LGA (BW percentile > 90th to 97th), and 133 AGA (BW percentile between 10th and 90th). The measurements were obtained between 2019 and 2021, as well as a review of the children's and their mothers' birth records.

Each participant underwent a comprehensive ophthalmological assessment, including fundus photography and a medical history interview. Additionally, their medical records containing their perinatal and postnatal history were reviewed.

All participants provided written informed consent before they entered the study complying 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).

• **ASSESSMENT OF PRE- AND POSTNATAL HISTORY:** The participants' medical histories from their records archived at the UMCM contained various parameters such as gestational age (in weeks), birth weight (in kilograms), placental insufficiency, maternal smoking, preeclampsia, breastfeeding, and perinatal adverse events. Their birth-weight percentiles were calculated according to the methodology outlined by Voigt et al.[17]

• **EXPOSURE: BIRTH WEIGHT PERCENTILE:** Birth weight percentile was determined by considering birth weight relative to gestational age[17] to categorize individuals into 5 groups: severe SGA (BW percentile < 3; group 1), moderate SGA (BW percentile 3rd to <10th; group 2), AGA (BW percentile 10—90th; group 3), moderate LGA (BW percentile > 90-97th; group 4), and severe LGA (BW percentile > 97th percentile; group 5). All individuals were born full-term (gestational age ≥37 weeks).

• **OPHTHALMOLOGIC EXAMINATION:** Every study participant underwent a thorough ophthalmologic examination involving assessments of the objective refraction using an ARK-1s instrument (NIDEK/OCULUS). The refractive error was determined, and the spherical equivalent was calculated by adding the sphere and half of the cylindrical value. Nonmydriatic fundus photography (VisucamPRO NM; Zeiss) was conducted in a darkened room with neutral pupils, capturing images of the optic nerve head at 30° and 45° angles. The imaging process began with the right eye, and regular data quality checks were performed. The VCDR and optic disc area were measured in optic nerve head-centered images and corrected for optical magnification according to Garway-Heath et al.[18] The VCDR measurement was conducted using 30° images with measurements of the macula-disc angle, optic disc size in an elliptical shape, and its angle relative to the macula-disc line were taken from 45° images. Photographs of the optic disc were taken and subsequently measured manually by one investigator (AS) who was masked to the study details. The intra-rater reliability for VCDR measurements was high, as indicated by an intraclass correlation coefficient (ICC) of 0.96 (95% CI 0.94-0.98). A subset was measured by a second investigator (AH) showing high inter-rater reliability (ICC = 0.89 (95% CI 0.83-0.93).The torsion angle was calculated using the discrepancy between the vertical angle of the macula-disc line and the long optic disc diameter.[16] Overall, the following optic disc parameters were assessed in this study: vertical disc length (mm), vertical cup length (mm), VCDR (mm), optic disc area (mm²), macula disc length (mm²), macula disc angle (degrees), and torsion angle (absolute).

TABLE 1. Characteristics of the Study Sample ($n = 280$) of the Gutenberg Prematurity Study Stratified by Severe and Moderate SGA and LGA Groups

BW Percentile	Severe SGA <3	Moderate SGA 3 to <10	AGA 10-90	Moderate LGA >90 to 97	Severe LGA >97
Number of participants/eyes	37/68	35/68	133/256	37/70	38/73
Sex (women)	20 (54.1%)	17 (48.6%)	75 (56.4%)	15 (40.5%)	17 (44.7%)
Age (y)	29.1 ± 9.7	30.1 ± 9.6	29.8 ± 9.1	29.7 ± 9.4	31.7 ± 10.2
Birth weight	2053 ± 330	2704 ± 354	3425 ± 396	4283 ± 293	4743 ± 606
Gestational age (weeks)	37.7 ± 1.1	38.5 ± 1.4	39.3 ± 1.3	39.9 ± 1.3	40.3 ± 1.2
(min-max)	(37-41)	(37-42)	(37-43)	(37-43)	(37-43)
Preeclampsia	9 (24.3%)	2 (5.7%)	11 (8.3%)	1 (2.7%)	5 (13.2%)
Placental insufficiency (yes)	11 (29.7%)	0 (0%)	2 (1.5%)	0 (0%)	0 (%)
HELLP syndrome (yes)	1 (2.7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Maternal smoking (yes)	4 (10.8%)	0 (0%)	7 (5.3%)	0 (0%)	1 (2.6%)
Maternal alcohol consumption (yes)	0 (0%)	2 (5.7%)	1 (0.8%)	0 (0%)	1 (2.6%)
Gestational diabetes (yes)	1 (2.7%)	0 (0%)	1 (0.8%)	1 (2.7%)	2 (5.3%)
Breastfeeding (yes)	14 (37.8%)	17 (48.6%)	76 (57.1%)	26 (70.3%)	29 (76.3%)
Ocular parameters					
Spherical equivalent (diopter) OD	−0.8 ± 1.6	−1.8 ± 2.5	−1.0 ± 2.2	−1. 1 ± 2.0	−0.6 ± 1.7
Spherical equivalent (diopter) OS	−1.00 ± 2.0	−2.1 ± 2.8	−1.0 ± 2.1	−1.1 ± 2.0	−0.6 ± 1.7
Intraocular pressure (mmHg) OD	16.0 ± 2.4	15.7 ± 2.4	15.2 ± 2.9	15.8 ± 3.0	14.9 ± 2.9
Intraocular pressure (mmHg) OS	16.2 ± 2.6	15.6 ± 2.3	15.2 ± 2.9	15.7 ± 3.6	14.9 ± 3.3

AGA = appropriate for gestational age; HELLP syndrome = hemolysis, elevated liver enzymes, and low platelet count syndrome; LGA = large for gestational age; SGA = small for gestational age.

• **COVARIATES:** The following covariates were considered as potential factors that could affect the main outcome measures: sex (female), age, optic disc size (mm²), gestational age (weeks), preeclampsia (yes), maternal smoking (yes), placental insufficiency (yes), and breastfeeding (yes).

• **STATISTICAL ANALYSIS:** The primary focus of this study were the various parameters related to optic disc morphology and they were descriptively analyzed based on the clinical group. Absolute and relative frequencies were calculated for dichotomous parameters, while the mean and standard deviation were calculated for variables that approximated a normal distribution. ANOVA was performed to compare normally distributed ocular parameters among the different birth weight groups, and global *P*-values were computed. Linear regression models with generalized estimating equations were employed to examine associations and address correlations between corresponding eyes.

Univariable analysis to assess the primary outcome measures was conducted in model #1. The variables tested included gestational age (in weeks), birth weight percentile (categorized), smoking during pregnancy (yes), breastfeeding (yes), preeclampsia (yes), and placental insufficiency (yes). These regression analyses were adjusted for age and sex. In model #2, further adjustment was conducted for age, sex and spherical equivalent, and the optic disc area was also included as an adjustment variable in the VCDR analysis.

This is an explorative study so no adjustment for multiple testing was performed. The statistical analysis was performed using commercial software (IBM SPSS 20.0; SPSS, Inc., Chicago, IL, USA).

RESULTS

• **PARTICIPANT CHARACTERISTICS:** In this study, a total of 535 eyes from 280 individuals who were born full term were examined, with an average age of 29.7 ± 9.2 years, including 144 females. The recruitment efficacy proportion was 52.6% for individuals in the SGA and LGA groups, and 48.3% for those in the AGA group. Descriptive characteristics and peri– and postnatal parameters are presented in Table 1. The age at examination was not significantly different between the various SGA, LGA, and AGA groups.

• **DESCRIPTIVE ANALYSIS OF OPTIC DISC PARAMETERS:** Optic disc parameters with respect to vertical cup length, optic disc area, macular disc length, macular disc angle and torsion angle (absolute value) were not different between groups. Macula-disc angle was 8.66° ± 3.40° in the severe SGA group (<3), 10.41° ± 3.85° in group 2 (moderate SGA, 3 to <10), 9.79° ± 3.54° in group 3 (AGA, 10-90), 9.74° ± 3.74° (Moderate LGA, >90 to 97) and 9.49° ± 3.48° in group 5 (Severe LGA, >97) (Table 2). There were differences between the groups in the vertical disc length

TABLE 2. Optic Nerve Head Morphology of the Gutenberg Prematurity Eye Study (GPES) Sample (n = 280) for Each Study Group

	Severe SGA	Moderate SGA	AGA	Moderate LGA	Severe LGA	
OD, No. of Eyes	35	34	129	35	35	*P*-Value
Vertical disc length, mm	1.73 ± 0.15	1.69 ± 0.15	1.77 ± 0.16	1.81 ± 0.21	1.75 ± 0.14	.02
Vertical cup length, mm	0.58 ± 0.28	0.46 ± 0.25	0.53 ± 0.28	0.50 ± 0.28	0.48 ± 0.31	.38
VCDR (IQR)	0.32 (0.20, 0.45)	0.28 (0.16, 0.36)	0.30 (0.17, 0.40)	0.28 (0.17, 0.40)	0.26 (0.12, 0.37)	.32
Optic disc area, mm²	2.25 ± 0.47	2.17 ± 0.42	2.36 ± 0.42	2.40 ± 0.56	2.35 ± 0.49	.15
Macula disc length, mm²	4.58 ± 0.25	4.52 ± 0.33	4.60 ± 0.31	4.66 ± 0.43	4.64 ± 0.29	.38
Macular disc angle, degrees	8.66 ± 3.40	10.41 ± 3.85	9.79 ± 3.54	9.74 ± 3.74	9.49 ± 3.48	.34
Torsion angle (absolute), degrees (IQR)	17.00 (5.00, 24.00)	19.50 (7.50, 29.25)	17.00 (4.00, 35.00)	12.00 (6.00, 27.00)	11.00 (3.00, 27.00)	.77
OS, No. of Eyes	33	34	127	35	38	
Vertical disc length, mm	1.74 ± 0.34	1.72 ± 0.18	1.76 ± 0.16	1.76 ± 0.19	1.78 ± 0.16	.54
Vertical cup length, mm	0.65 ± 0.27	0.53 ± 0.25	0.55 ± 0.29	0.50 ± 0.27	0.50 ± 0.34	.18
VCDR (IQR)	0.38 (0.25, 0.51)	0.33 (0.19, 0.40)	0.31 (0.20, 0.42)	0.31 (0.17, 0.35)	0.23 (0.14, 0.39)	.05
Optic disc area, mm²	2.20 ± 0.36	2.21 ± 0.50	2.27 ± 0.45	2.30 ± 0.52	2.34 ± 0.50	.66
Macula disc length, mm²	4.55 ± 0.30	4.57 ± 0.35	4.57 ± 0.34	4.58 ± 0.36	4.62 ± 0.36	.93
Macular disc angle, degrees	3.15 ± 4.23	4.41 ± 3.53	4.06 ± 3.91	4.20 ± 2.99	3.58 ± 3.48	.61
Torsion angle (absolute), degrees (IQR)	14.00 (7.50, 35.00)	18.00 (7.75, 34.00)	22.00 (9.00, 35.00)	22.00 (10.00, 36.00)	19.00 (14.00, 30.00)	.94

AGA = appropriate for gestational age; LGA = large for gestational age; OD = right eye; OS = left eye; SGA = small for gestational age; VCDR = vertical cup-to-disc ratio.

Global *P*-values were calculated for group comparisons using ANOVA analyses.

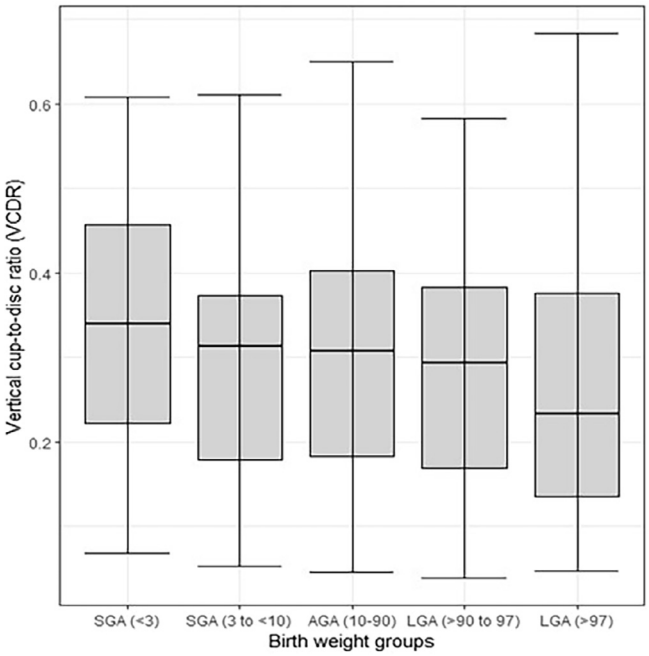

FIGURE. Boxplot of the vertical cup-to-disc ratio (VCDR) stratified by birth weight percentile groups in individuals born at term (n = 280). Participants who were born severely small-for-gestational age (SGA) showed an increased VCDR. AGA = appropriate for gestational age; LGA = large for gestational age; SGA = small for gestational age; VCDR = vertical cup-to-disc ratio.

TABLE 3. Association Analyses of the Vertical Cup-to-Disc Ratio and the Optic Nerve Head Area for Adults Born Full Term ($n = 280$) for the Sample of the Gutenberg Prematurity Eye Study (GPES)

	Univariable Model Adjusted for Age and Sex		Multivariable Model Adjusted for Age, Sex, Spherical Equivalent, Optic Disc Size Area	
Vertical Cup-To-Disc ratio, mm	Estimate for Median (95% CI)	*P*-Value	Estimate for Median (95% CI)	*P*-Value
Severe SGA (<3)	0.057 (0.008 to 0.105)	.02	0.053 (0.008 to 0.099)	.02
Moderate SGA (3 to <10)	−0.016 (−0.063 to 0.031)	.50	−0.011 (−0.059 to 0.037)	.65
Moderate LGA (>90 to 97)	−0.027 (−0.073 to 0.019)	.25	−0.033 (−0.078 to 0.012)	.15
Severe LGA (>97)	−0.039 (−0.092 to 0.014)	.15	−0.041 (−0.089 to 0.007)	.09
Preeclampsia	0.003 (−0.062 to 0.067)	.93	_____	_____
Placental Insufficiency	0.098 (0.008 to 0.188)	.03	_____	_____
Smoking during Pregnancy (yes)	0.015 (−0.059 to 0.090)	.68	_____	_____
Breastfeeding (yes)	−0.024 (−0.059 to 0.020)	.17	_____	_____
Optic disc area, mm²				
Severe SGA (<3)	−0.101 (−0.244 to 0.042)	.17	−0.096 (−0.231 to 0.039)	.16
Moderate SGA (3 to <10)	−0.130 (−0.250 to −0.011)	.03	−0.165 (−0.330 to −0.001)	.05
Moderate LGA (>90 to 97)	0.028 (−0.145 to 0.202)	.75	0.022 (−0.141 to 0.185)	.79
Severe LGA (>97)	0.021 (−0.143 to 0.185)	.81	0.036 (−0.132 to 0.204)	.67
Preeclampsia	−0.086 (−0.257 to 0.085)	.33	_____	_____
Placental Insufficiency	−0.006 (−0.293 to 0.281)	.97	_____	_____
Smoking during Pregnancy (yes)	−0.067 (−0.272 to 0.138)	.71	_____	_____
Breastfeeding (yes)	0.005 (−0.099 to 0.109)	.92	_____	_____

Vertical cup-to-disc ratio (VCDR) and optic disc area: Linear regression analysis using generalized estimating equations to control for correlations between both eyes. Model 1: Univariable model with adjustment for age and sex; model 2: Multivariable model with adjustment for sex, age, spherical equivalent. The optic disc area was included in the VCDR analysis.

in the right eye ($P = .02$) and the VCDR in the left eye ($P = .05$).

• **ASSOCIATION ANALYSES:** After adjusting for age, sex, spherical equivalent and optic disc area, VCDR was positively associated with severe SGA ($B = 0.053$, 95% CI 0.008-0.099; $P = .02$) (Figure, Table 3). In the univariable analysis, placental insufficiency was the only perinatal factor associated with VCDR ($B = 0.098$, 95% CI 0.008-0.188; $P = .03$), but it was not included in the multivariable analysis due to its high prevalence in the severe SGA group.

The optic disc area showed a negative association with moderate SGA in the multivariable model ($B = -0.165$, 95% CI −0.330 to −0.001; $P = .05$).

DISCUSSION

The present study provides data examining optic nerve head morphology among individuals born at full term, investigating restricted or excessive fetal growth. To our knowledge, this is the first study examining the VCDR with

a focus solely on participants born full term and the impact of abnormal fetal growth as previous analyses were primarily conducted on preterm infants.

The results highlight that the VCDR increases in individuals born with severe SGA at-term, while the optic disc area was independent of fetal growth restriction. Moreover, placental insufficiency was associated with a larger VCDR. In line with this association between severe SGA with VCDR, a multicenter study examining 2353 primarily 12-year-old children born full term and preterm, found that the VCDR was lower (0.0136 reduction in mean cup/disc ratio; $P = .002$) with each additional kilogram of birth weight.[15] The authors postulated that this is due to disturbed maturation of ganglion cells, whose axons run in the neuronal rim of the optic disc, potentially leading to an increase in neuroretinal rim tissue and a decrease in the cup-to-disc ratio.[15] Fledelius et al. reported that individuals born preterm with low birth weights (below 2000 g) show a significantly greater cup-disc ratio.[19] Other studies examining the association between birth weight and VCDR found no association[13,14] but they did not exclude preterm individuals.

Large optic cups in severe SGA cases might also be attributed to periventricular leukomalacia (PVL), a condition linked to late intrauterine or early post-natal intracerebral hemorrhages, which can cause optic disc changes resembling glaucomatous neuropathy.[20,21] While our study focuses on full-term births and abnormal fetal growth's effects on optic nerve head morphology, it is plausible that undiagnosed hemorrhages could explain some of our observations. However, due to the retrospective nature of our study dating back to 1969, confirming such hemorrhages is not possible.

Current research has shown that smoking during pregnancy results in a thinner RNFL, with no observed impact on other optic nerve head parameters.[22,23] There is a limited body of available research to assess the impact of perinatal parameters on VCDR, making it challenging to compare our findings. One prior study of the Gutenberg Prematurity Eye Study investigating prematurity and optic nerve head morphology showed an association between VCDR and smoking during pregnancy or placental insufficiency in individuals born preterm.[16] Our findings imply that placental insufficiency may influence VCDR in individuals born full term, whereas other perinatal parameters showed no association.

In comparison to our finding of a smaller optic disc area in cases of moderate SGA, Samarawickrama et al. demonstrated that lower birth weight is associated with a larger vertical optic disc diameter.[15] However, no studies have established a direct correlation between lower birth weight for gestational age and optic disc area.[12,24] To date, it has been mainly demonstrated that prematurity is associated with a smaller optic disc.[25]

• **STRENGTH AND LIMITATIONS:** The present study has several limitations. One limitation is its single-center, hospital-based design. Additionally, due to the unavailability of contact information for some individuals and the refusal of others to participate in the study examination, our sample may not be entirely representative, although the effective recruitment efficiency proportion was relatively high. It is worth noting that most GPES participants were of white ethnicity, therefore the conclusions should primarily pertain to this group. Furthermore, this was an exploratory study, and no adjustment for multiple testing was conducted, which should also be taken into account when interpreting the study data.

Nonetheless, this study has several strengths. Notably, the substantial sample size, and, to the best of our knowledge, this is the first study exclusively dedicated to investigating optic nerve characteristics in full-term individuals with abnormal fetal growth. Additionally, the comprehensive analysis of perinatal data extracted from medical charts of mothers and newborns allowed for a thorough examination of perinatal parameters. Moreover, each measurement was conducted in strict accordance with standardized operating procedures to minimize interrater variability.

CONCLUSION

In conclusion, our findings provide novel insights into the impacts of fetal growth restriction on the optic nerve head morphology in full-term born individuals, revealing that the VCDR increases in individuals born severely SGA at-term. These findings indicate that fetal growth restriction has a lasting impact on the optic nerve head morphology until adulthood and may indicate a lower neuronal reserve for degenerative optic disc diseases.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

Achim Fieß: Writing – review & editing, Writing – original draft, Visualization, Supervision, Formal analysis, Data curation, Conceptualization. **Sandra Gißler:** Writing – review & editing, Writing – original draft, Visualization, Formal analysis, Data curation. **Eva Mildenberger:** Writing – review & editing, Validation, Data curation. **Esther M. Hoffmann:** Writing – review & editing, Validation, Data curation. **Panagiotis Laspas:** Writing – review & editing, Validation, Data curation. **Bernhard Stoffelns:** Writing – review & editing, Validation, Data curation. **Norbert Pfeiffer:** Writing – review & editing, Validation, Data curation. **Alica Hartmann:** Writing – review & editing, Visualization, Validation, Formal analysis, Data curation. **Alexander K. Schuster:** Writing – review & editing, Visualization, Validation, Supervision, Formal analysis, Data curation, Conceptualization.

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