Association of Birth Weight with Peripapillary Retinal Nerve Fiber Layer Thickness in Adulthood—Results from a Population-Based Study

Achim Fieß,[1] Stefan Nickels,[1] Michael S. Urschitz,[2] Thomas Münzel,[3] Philipp S. Wild,[4,5,6] Manfred E. Beutel,[7] Karl J. Lackner,[8] Esther M. Hoffmann,[1] Norbert Pfeiffer,[1] and Alexander K. Schuster[1]

[1]Department of Ophthalmology, University Medical Center, Johannes Gutenberg University Mainz, Mainz, Germany
[2]Division of Pediatric Epidemiology, Institute for Medical Biostatistics, Epidemiology and Informatics, University Medical Center, Johannes Gutenberg University Mainz, Mainz, Germany
[3]Center for Cardiology–Cardiology I, University Medical Center, Johannes Gutenberg University Mainz, Mainz, Germany
[4]Preventive Cardiology and Preventive Medicine/Center for Cardiology, University Medical Center, Johannes Gutenberg University Mainz, Mainz, Germany
[5]Center for Thrombosis and Hemostasis, University Medical Center, Johannes Gutenberg University Mainz, Mainz, Germany
[6]German Center for Cardiovascular Research (DZHK), partner site Rhine-Main, Mainz, Germany
[7]Department of Psychosomatic Medicine and Psychotherapy, University Medical Center, Johannes Gutenberg University Mainz, Mainz, Germany
[8]Institute of Clinical Chemistry and Laboratory Medicine, University Medical Center, Johannes Gutenberg University Mainz, Mainz, Germany

Correspondence: Achim Fieß, Department of Ophthalmology, University Medical Center, Johannes Gutenberg University Mainz, Langenbeckstr. 1, 55131 Mainz, Germany; achim.fiess@gmail.com.

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Purpose. Low birth weight is associated with altered retinal development in childhood, including reduced peripapillary retinal nerve fiber layer (pRNFL) thickness. However, to the best of our knowledge, no population-based study has analyzed the relationship of low birth weight to pRNFL thickness in adulthood. The purpose of this study was to investigate whether birth weight has a long-term effect on pRNFL thickness in adulthood.

Methods. In the German population-based Gutenberg Health Study (GHS), participants were examined with spectral-domain optical coherence tomography using a peripapillary scan and automated measurement of pRNFL thickness as a global parameter and in six sectors. The association between self-reported birth weight and the different pRNFL sectors were analyzed with multivariable linear regression, adjusted for potential confounders including sex, age, axial length, self-reported age-related macular degeneration, and glaucoma.

Results. In 3,028 participants, self-reported birth weight was documented and pRNFL measurements were successfully performed (1632 females, ages 54.9 ± 10.0 years). After adjustment for several confounders in the multivariable model, a positive association was observed between birth weight and pRNFL thickness in the global sector (β = 0.13 µm/100 g; 95% CI, 0.08–0.18; $P < 0.001$; $R^2 = 0.007$) and especially in the inferotemporal sector (β = 0.22 µm/100 g; 95% CI, 0.15–0.29; $P < 0.001$; $R^2 = 0.008$) and inferonasal sector (β = 0.28 µm/100 g; 95% CI, 0.17–0.39; $P < 0.001$; $R^2 = 0.005$).

Conclusions. Our data show that there is a weak relationship between birth weight and pRNFL thickness in adulthood. This weak association is particularly present in the inferior part of the optic nerve head. Therefore, low birth weight may have an impact on optic nerve head development and potentially on ocular disease development.

Keywords: birth weight, peripapillary retinal nerve fiber layer, optic nerve, anatomy, epidemiology

During embryologic development, the optic nerve contains approximately 2 million axons at the end of the first trimester, peaks at 4 million, and reaches its final number of about 1 million at the end of the second trimester.[1] Premature birth affects the embryologic development of central nervous tissues[2] and leads to different cortical volumes of the cerebrum of former preterm individuals.[3,4] Adverse development of the immature brain and damage of the optic radiation might lead to a retrograde trans-synaptic degeneration of retinal ganglion cells.[5] Rothman and colleagues[6] observed a correlation between brain structure and peripapillary retinal nerve fiber layer (pRNFL)

thinning in preterm infants (gestational age < 32 weeks). Scarce population-based data exist regarding the association of low birth weight and pRNFL in childhood,[7] whereas to our knowledge no population-based data exist for this relationship in adulthood.

Worldwide, every seventh child is born with low birth weight (<2500 g), accounting for about 20.5 million low-birth-weight newborns every year.[8] Because the number of low-birth-weight newborns is increasing,[8] understanding potential long-term effects becomes more important.

Low birth weight is a proxy measure of prenatal growth restriction, preterm birth, and disorders of ocular growth development in childhood, including reduced peripapillary retinal nerve fiber layer thickness. The retinal nerve fiber layer of the optic nerve head is part of the central nervous system and can be non-invasively measured with spectral-domain optical coherence tomography (SD-OCT). Perinatal factors associated with reduced pRNFL thickness in childhood include low birth weight,[9–11] low gestational age at birth,[10,12] and retinopathy of prematurity (ROP).[13] In a recent report, we demonstrated that low birth weight and low gestational age are related to a thinner pRNFL, and postnatal ROP occurrence is linked to an isolated pRNFL increase of the temporal sector in children 4 to 10 years of age. In addition, we found an association between thinner pRNFL and reduced visual acuity.[10] In the population-based Copenhagen Child Cohort 2000 Eye Study, thinner pRNFL thickness was found in former low-birth-weight infants (<2500 g; 11 to 12 years of age at the time of the study) compared to former normal birth weight infants (≥2500 g).[7]

Thinner pRNFL is associated with various optic neuropathies, particularly glaucoma, which is one of the main eye diseases causing visual impairment and blindness in Western countries.[14] Therefore, gaining knowledge about the factors affecting the pRNFL is of importance and may contribute to a better understanding of potential risk factors for glaucoma.

This study analyzed the association of birth weight with pRNFL thickness in adults 40 to 80 years of age. We hypothesized that low birth weight is associated with a thinner pRNFL in adulthood.

Materials and Methods

Study Population

The interdisciplinary Gutenberg Health Study (GHS) is a prospective, population-based, observational, single-center cohort study conducted in the Rhine-Main region of Western Germany (Rhineland-Palatinate).[15] Recruitment of the GHS sample was performed between 2007 and 2012 for baseline examination of participants between 35 and 74 years of age. The sample was randomly drawn from local governmental registry offices, where every resident is mandatorily registered and stratified by sex, residence (urban or rural), and decades of age. Every selected resident was invited by mail with follow-up by telephone. The recruitment efficacy was 55.5%.

The present analysis includes subjects of the 5-year follow-up examination who underwent SD-OCT examination between 2012 and 2017. Overall, 12,423 GHS participants (82.8% of all participants) had a 5-year follow-up examination. These participants had a medical history interview, in addition to a detailed ophthalmological examination, including measurements of peripapillary retinal thickness measurement with SD-OCT.

Written informed consent was obtained from all study participants prior to study participation, and the GHS complied with good clinical practices, good epidemiological practices, and the tenets of the Declaration of Helsinki. The study protocol and study documents were approved by the local ethics committee of the Medical Chamber of Rhineland-Palatinate, Germany (reference no. 837.020.07).

Birth Weight

In this cross-sectional analysis, only subjects with available self-reported birth weights were included. Further inclusion criteria were measurement of objective refraction, corneal curvature, and the pRNFL in at least one eye. The exclusion criterion was a history of ocular injury. The participants were asked to review their records or family albums for documented birth weights; based on this information, they were divided into the following birth weight groups: group 1, low birth weight (<2500 g); group 2, normal birth weight (2500–4000 g); and group 3, high birth weight (>4000 g), as reported earlier.[16–19] Additionally, participants with birth weights below 1000 g and above 6000 g were excluded, as these self-reported data were suspected to be unreliable.

Ophthalmologic Examination

In brief, the ophthalmological examination included measurement of visual acuity and refraction with a Humphrey HARK 599 Autorefractor Keratometer (Carl Zeiss Meditec, Jena, Germany); intraocular pressure measurement with a NT-2000 non-contact tonometer (Nidek, Tokyo, Japan); biometry using a Lenstar LS900 optical biometer (Haag-Streit, Bern, Switzerland); and non-mydriatic fundus photography and imaging of the optic nerve head using the Spectralis SD-OCT system (Heidelberg Engineering, Heidelberg, Germany).[20] The spherical equivalent was calculated by adding the spherical correction value to half the cylinder value.

Ocular biometry was performed with the Lenstar 900 optical biometer, as described earlier.[18] Furthermore, age-related macular degeneration (AMD) was surveyed. Glaucoma was defined according to the definition proposed by Foster et al.,[21] the International Society of Geographical and Epidemiological Ophthalmology (ISGEO) definition, with a few adjustments with regard to visual field testing (using frequency doubling technology perimetry), as described before.[22] In brief, the vertical cup-to-disc ratio (vCDR) was determined in each eye, and individual cutoff values with respect to optic disc size were computed. Eyes with a vCDR ≥ 97.5th percentile (of a normal population without visual field defect) with a visual field defect, eyes with a vCDR above the 99.5th percentile, or eyes with a rim width ≤ 0.1 were defined as glaucoma, if there was no other explanation for these measurements investigated by two masked glaucoma specialists.

Optical Coherence Tomography

With SD-OCT, a non-invasive and non-contact device uses light reflection of the various retinal tissues to generate cross-sectional two- and three-dimensional images of the retina. For the present study, a circular peripapillary scan of 12° diameter centered on the optic disc with eye tracking

was conducted with a standard 7.7-mm corneal curvature and ametropia of 0 diopter (dpt). Heidelberg Eye Explorer (HEYEX) software was used for automatic segmentation of pRNFL thickness. Software algorithms calculated global and sectorial pRNFL thickness (global, superonasal, nasal, inferonasal, inferotemporal, temporal, superotemporal) from the data provided by the circle scans. We adjusted the pRNFL measures for ocular magnification by incorporating corneal curvature and spherical equivalent, the same parameters used in the HEYEX software for adjustment of ocular magnification (personal communication with Heidelberg Engineering).

All SD-OCTs were performed in non-mydriatic eyes. Also, all scans were checked by an experienced investigator and were excluded in case of decentralization or layer segmentation errors. In addition, scan quality was checked and only high-quality images with ideal centration and a high signal strength of >15 dB (ranging from 0 for no signal to 40 for an excellent signal) were selected for this study.

Covariates

The following parameters were included in the multivariable model because they were considered to be associated with the pRNFL based on the medical literature[23–25] and were judged as being potentially associated with birth weight: (1) age, (2) sex, (3) axial length, (4) age-related macular degeneration, and (5) glaucoma (ISGEO definition).

Statistical Analysis

The main outcome measures were pRNFL thickness in the global sector and in the six subsectors (superonasal, nasal, inferonasal, inferotemporal, temporal, and superotemporal). A comparison of characteristics of participants with available self-reported birth weights versus participants without self-report birth weights was conducted. The distribution of low, normal, and high birth weights in our cohort was compared to reported birth weight data in the medical literature and to data of the German Federal Statistical Office, as reported earlier.[16,26] Descriptive statistics were computed for the main outcome measures. Absolute and relative frequencies were calculated for dichotomous parameters. The mean and standard deviation were calculated for approximately normally distributed data; otherwise, the median and interquartile range were used.

Both eyes of an individual were included into our analyses, if sufficient peripapillary OCT imaging was available, and linear regression models with general estimating equations were used to assess associations and to account for correlations between both eyes of an individual. In model 1, the main outcome measures were related to birth weight as independent variable; in model 2, the associations were adjusted for age, sex, axial length, age-related macular degeneration, and glaucoma (ISGEO definition). Furthermore, a sensitivity analysis was carried out including only subjects with an axial length between 23.00 mm (25th percentile) and 24.4 mm (75th percentile). To investigate the disproportion of subjects between the three birth weight groups, we performed a subanalysis with equal proportions of subjects in each birth weight group. Another sensitivity analysis was performed on all participants with self-reported birth weights, including those reporting birth weights < 1000 g and > 6000 g, as well.

All models were computed in a first step that included birth weight as a continuous variable and in a second step that included birth weight as a categorical variable (birth weight < 2500 g, birth weight 2500–4000 g, and birth weight > 4000 g).

The data were analyzed with R version 3.5.2.[27] This was an explorative study, and no adjustment for multiple testing was carried out.

Results

Participant Characteristics

Of the 15,010 participants at baseline, 12,423 were examined at the 5-year follow-up. Of these, 6140 had successful SD-OCT measurements of at least one eye. Missing measurements were attributed to organizational issues. Of these, in turn, 3679 had documented self-reported birth weight data. Eighteen participants were excluded due to implausible birth weight data (>6000 g or <1000 g), and 633 participants were excluded due to missing data on corneal curvature or spherical equivalent measurement or due to medical history of eye injury.

The participants' characteristics are presented in Table 1. Participants mean age was 54.9 ± 10.0 years, and 53.9% (n = 1632) were female. Birth weight below 2500 g (group 1) was reported by 173 participants, birth weight between 2500 g and 4000 g (group 2) was reported by 2499 participants, and a birth weight above 4000 g (group 3) was reported by 356 participants (Table 1). Descriptive data on global pRNFL and for each sector are presented in Table 2. The low-birth-weight group showed the lowest pRNFL measures in the various sectors compared to the normal-weight and high-birth-weight groups.

Item Non-Responder Analysis

Out of the 12,423 participants who attended the follow-up examination, 9,395 did not provide birth weight data, had no pRNFL measurement, or did not meet the inclusion criteria. Participants with available information were younger and more likely to be female compared to participants with missing information. In addition, they were less likely to have hypertension and diabetes and their ocular parameters were similar. In particular, global pRNFL thickness was similar between participants with and without birth weight information. Participants without OCT data were slightly younger and had similar birth weights.

Birth Weight as Continuous Variable

Global pRNFL was thinner in adults with low birth weight in unadjusted analyses (model 1: β = 0.12 µm/100 g; 95% CI, 0.07–0.17; P < 0.001) and in adjusted analyses after consideration of age, sex, axial length, age-related macular degeneration, and glaucoma (model 2: β = 0.13 µm/100 g; 95% CI, 0.08–0.18; P < 0.001). Furthermore, low birth weight was associated with thinner pRNFL in the inferotemporal sector (model 2: β = 0.22 µm/100 g; 95% CI, 0.15–0.29; P < 0.001) and inferonasal sector (model 2: β = 0.28 µm/100 g; 95% CI, 0.17–0.39; P < 0.001). The superotemporal sector (model 2: β = 0.09 µm/100 g; 95% CI, 0.01–0.19; P = 0.024), the superonasal sector (model 2: β = 0.15 µm/100 g; 95% CI, 0.05–0.25; P = 0.004), and the nasal sector (model 2: β

Table 1. Characteristics of the Study Sample ($N = 3028$)

Variable	Birth Weight		
	<2500 g	2500–4000 g	>4000 g
Participants, *n*	173	2499	356
Female, *n* (%)	115 (66.5%)	1389 (55.6%)	128 (36.0%)
Age (y), mean ± SD	56.1 ± 11.0	54.6 ± 9.9	56.1 ± 9.7
Birth weight (g), mean ± SD	2042 ± 356	3343 ± 396	4495 ± 438
Body mass index (kg/m^2), mean ± SD	27.1 ± 5.3	26.9 ± 5.0	28.2 ± 4.89
Presence of arterial hypertension, *n* (%)	79 (45.7)	1042 (41.7)	170 (47.8)
logMAR OD, median (25%, 75% percentiles)	0.1 (0.0, 0.2)	0.1 (0.0, 0.1)	0.1 (0.0, 0.2)
logMAR OS, median (25%, 75% percentiles)	0.1 (0.0, 0.2)	0.1 (0.0, 0.1)	0.1 (0.0, 0.2)
IOP OD (mm Hg), mean ± SD	14.8 ± 3.1	14.6 ± 2.9	15.1 ± 2.9
IOP OS (mm Hg), mean ± SD	15.0 ± 3.1	14.7 ± 2.8	15.2 ± 3.0
Spherical equivalent OD (dpt), median (25%, 75% percentiles)	–0.38 (–1.88, 0.75)	–0.25 (–1.38, 0.50)	–0.12 (–1.25, 0.88)
Spherical equivalent OS (dpt), median (25%, 75% percentiles)	–0.25 (–1.75, 0.75)	–0.25 (–1.38, 0.62)	–0.12 (–1.12, 0.75)
Axial length OD (mm), mean ± SD	23.6 ± 1.3	23.8 ± 1.2	23.9 ± 1.2
Axial length OS (mm), mean ± SD	23.5 ± 1.2	23.7 ± 1.2	23.9 ± 1.2
Corneal radius OD (mm), mean ± SD	7.68 ± 0.25	7.77 ± 0.28	7.86 ± 0.26
Corneal radius OS (mm), mean ± SD	7.68 ± 0.26	7.77 ± 0.28	7.85± 0.27
Eye disease present			
AMD, *n* (%)	5 (2.9)	31 (1.2)	4 (1.1)
Glaucoma, *n* (%)	3 (1.9)	20 (0.9)	1 (0.3)

Data are from the population-based Gutenberg Health Study (2012–2017). IOP, intraocular pressure.

Table 2. Measurements of pRNFL Thickness by Birth Weight Groups

pRNFL	pRNFL Thickness (µm), Mean ± SD		
	Birth Weight < 2500 g ($n = 173$)	Birth Weight 2500–4000 g ($n = 2499$)	Birth Weight > 4000 g ($n = 356$)
Right eye			
Global	95.9 ± 9.7	97.8 ± 9.7	98.3 ± 9.4
Superotemporal	133.4 ± 17.7	135.9 ± 18.3	136.3 ± 17.9
Temporal	70.6 ± 11.3	72.6 ± 13.6	71.4 ± 13.4
Inferotemporal	142.5 ± 19.5	146.3 ± 20.0	144.9 ± 20.7
Inferonasal	109.7 ± 24.3	110.9 ± 23.8	112.8 ± 24.2
Nasal	71.0 ± 13.9	73.1 ± 14.6	74.5 ± 14.7
Superonasal	98.3 ± 21.6	97.8 ± 19.1	99.8 ± 19.6
Left eye			
Global	94.4 ± 10.7	97.7 ± 9.4	98.7 ± 10.0
Superotemporal	133.2 ± 19.0	134.7 ± 18.5	134.3 ± 18.1
Temporal	67.7 ± 12.1	68.8 ± 12.7	67.5 ± 12.1
Inferotemporal	138.5 ± 19.9	144.4 ± 20.7	143.7 ± 20.7
Inferonasal	107.1 ± 26.2	112.3 ± 23.5	116.2 ± 25.0
Nasal	67.2 ± 16.1	71.8 ± 14.5	74.2 ± 14.6
Superonasal	106.0 ± 21.2	108.2 ± 20.5	111.9 ± 22.1

Data are from the population-based Gutenberg Health Study (2012–2017).

= 0.18 µm/100 g; 95% CI, 0.00–0.35; $P = 0.048$) revealed a weaker association, and the other sectors showed no association in the adjusted model (Table 3). Scatterplots of birth weight with pRNFL thickness of the global sector, nasal inferior sector, and temporal inferior sector are displayed in the Figure. Pearson's correlation coefficients of global and sectoral pRNFL with birth weight as the continuous variable for the right and left eye are presented in the Supplementary Table.

Birth Weight Categorized into Low, Normal, and High Birth Weight

When analyzing birth weights categorized as low, normal, or high, the global pRNFL thickness was smaller in the low-birth-weight group compared to the normal-birth-weight group in the adjusted analysis (model 2: $\beta = -2.20$ µm; 95% CI, –3.47 to –0.92; $P < 0.001$), whereas the pRNFL was thicker in the high-birth-weight group compared to the normal-birth-weight group (model 2: $\beta = 1.06$ µm; 95% CI, 0.21–1.91; $P = 0.015$) (Table 4).

In adjusted analyses, the low-birth-weight group showed a thinner pRNFL in the inferotemporal sector ($\beta = -3.44$ µm; 95% CI, –5.26 to –1.61; $P < 0.001$), but the other sectors showed no association.

Among the high-birth-weight participants, a thicker pRNFL was observed in the inferotemporal (model 2: $\beta = 2.43$ µm; 95% CI, 1.13–3.72; $P < 0.001$), inferonasal (model 2: $\beta = 3.98$ µm; 95% CI, 1.85–6.11; $P < 0.001$), and superonasal (model 2: $\beta = 2.73$ µm; 95% CI, 0.80–4.66; $P = 0.006$) sectors compared to normal-birth-weight subjects. No relationship was observed in the other sectors.

Table 3. Associations of Global and Sectoral pRNFLs with Birth Weight as Continuous Variable ($N = 3028$)

	Model 1*			Model 2†		
pRNFL	**β (95% CI)**	***P***	***R*²**	**β (95% CI)**	***P***	***R*²‡**
Global	0.12 (0.07, 0.17)	<0.001	0.006	0.13 (0.08, 0.18)	<0.001	0.007
Superotemporal	0.12 (0.04, 0.21)	0.005	0.002	0.09 (0.01, 0.19)	0.024	0.001
Temporal	0.00 (–0.06, 0.06)	1.0	0.000	–0.02 (–0.08, 0.04)	0.469	0.000
Inferotemporal	0.19 (0.12, 0.26)	<0.001	0.007	0.22 (0.15, 0.29)	<0.001	0.008
Inferonasal	0.22 (0.10, 0.33)	<0.001	0.003	0.28 (0.17, 0.39)	<0.001	0.005
Nasal	0.14 (−0.03, 0.31)	0.11	0.001	0.18 (0.00, 0.35)	0.048	0.001
Superonasal	0.14 (0.04, 0.24)	0.005	0.002	0.15 (0.05, 0.25)	0.004	0.002

Data are from the population-based Gutenberg Health Study (2012–2017). Linear regression analysis using generalized estimating equations to control for correlations between right and left eyes was applied.

* Model 1 is crude model without adjustment.

† Model 2 is adjusted for sex, age, axial length, age-related macular degeneration, and glaucoma (ISGEO definition).

‡ Change of R^2 when including birth weight as an additional parameter in the multivariable model.

Table 4. Associations of Global and Sectorial pRNFL with Birth Weight Groups ($N = 3028$)

	Model 1*			Model 2†		
pRNFL	**β (95% CI)**	***P***	***R2***	**β (95% CI)**	***P***	***R2*‡**
Global						
Birth weight < 2500 g	–2.57 (–3.88, –1.25)	<0.001		–2.20 (–3.47, –0.92)	<0.001	
Birth weight 2500–4000 g	Reference	—	0.005	Reference	—	0.004
Birth weight > 4000 g	0.66 (–0.20, 1.51)	0.135		1.06 (0.21, 1.91)	0.015	
Superotemporal						
Birth weight < 2500 g	–2.42 (–4.71, –0.13)	0.038		–1.70 (–3.92, 0.51)	0.13	
Birth weight 2500–4000 g	Reference	—	0.001	Reference	—	0.000
Birth weight > 4000 g	–0.35 (–1.95, 1.25)	0.668		–0.17 (–1.77, 1.43)	0.83	
Temporal						
Birth weight < 2500 g	–0.90 (–2.40, 0.60)	0.24		–0.74 (–2.18, 0.71)	0.318	
Birth weight 2500–4000 g	Reference	—	0.001	Reference	—	0.001
Birth weight > 4000 g	–1.11 (–2.29, 0.07)	0.064		–1.11 (–2.23, 0.01)	0.053	
Inferotemporal						
Birth weight < 2500 g	–3.63 (–5.54, –1.73)	<0.001		–3.44 (–5.26, –1.61)	<0.001	
Birth weight 2500–4000 g	Reference	—	0.006	Reference	—	0.006
Birth weight > 4000 g	2.03 (0.72, 3.33)	0.002		2.43 (1.13, 3.72)	<0.001	
Inferonasal						
Birth weight < 2500 g	–3.17 (–6.39, 0.06)	0.054		–2.83 (–5.92, 0.26)	0.073	
Birth weight 2500–4000 g	Reference	—	0.003	Reference	—	0.004
Birth weight > 4000 g	2.92 (0.71, 5.13)	0.010		3.98 (1.85, 6.11)	<0.001	
Nasal						
Birth weight < 2500 g	–4.38 (–9.16, 0.39)	0.072		–4.06 (–8.84, 0.72)	0.096	
Birth weight 2500–4000 g	Reference	—	0.001	Reference	—	0.001
Birth weight > 4000 g	–0.22 (–3.69, 3.24)	0.90		0.61 (–2.87, 4.08)	0.733	
Superonasal						
Birth weight < 2500 g	–1.42 (–4.19, 1.34)	0.314		–0.95 (–3.64, 1.75)	0.49	
Birth weight 2500–4000 g	Reference	—	0.002	Reference	—	0.002
Birth weight > 4000 g	2.45 (0.55, 4.36)	0.012		2.73 (0.80, 4.66)	0.006	

Data are from the population-based Gutenberg Health Study (2012–2017). Linear regression analysis using generalized estimating equations to control for correlations between right and left eyes.

* Model 1 is crude model without adjustment.

† Model 2 is adjusted for sex, age, axial length, age-related macular degeneration, and glaucoma (ISGEO definition).

‡ Change of R^2 when including birth weight as an additional parameter in the multivariable model.

Sensitivity Analyses

Equal proportions of subjects in each group revealed comparable results. Similar associations were observed when study participants with birth weights < 1000 g or > 6000 g were included, as well, and when analyzing subjects with an axial length of 23.00 to 24.4 mm.

Discussion

In this study, low birth weight was associated with a thinner pRNFL in adulthood. These results provide new insights into the long-term effects of low birth weight on optic nerve morphology, indicating that pre- and perinatal growth restrictions are connected to altered optic nerve morphology

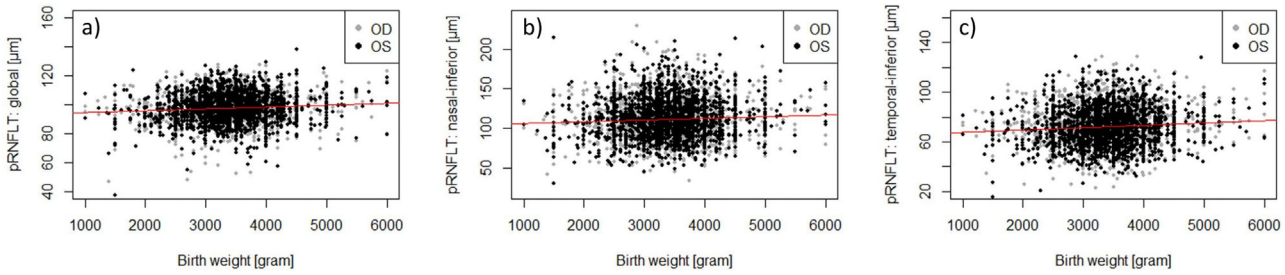

Figure. Scatterplot of birth weight with pRNFL thickness of the (**A**) global sector, (**B**) nasal inferior sector, and (**C**) temporal inferior sector in the Gutenberg Health Study ($N = 3028$). Participants with lower birth weights showed a thinner pRNFL in the global measurement and in the nasal inferior and temporal inferior sectors.

beyond childhood and adolescence, with particular impact on the inferior part of the optic disc. This may be of clinical relevance, as early signs of glaucoma include an alteration of the ISNT (inferior ≥ superior ≥ nasal ≥ temporal) rule,[28] and low birth weight might be linked to optic neuropathies such as glaucoma.

Our results are in line with previous reports on former preterm and/or low-birth-weight infants[7,9,10,12,13] and expand previous knowledge into adulthood. The Wiesbaden Prematurity Study found that a thinner pRNFL was related to low birth weight and low gestational age, whereas ROP was linked to isolated thickening of the temporal sector. The authors concluded that the more preterm the infants, the greater the alteration in the pRNFL.[10]

However, other authors have observed that the pRNFL is thinner even in former late-preterm[29] and full-term[30] infants when they had a birth weight below the 10th percentile, which agrees with the data of Pueyo et al.[11] Akerblom et al.[31] and colleagues also demonstrated that low birth weight was linked to a thinner pRNFL in a sample of former preterm infants.

In a large population-based study of 1323 children 11 to 12 years of age (Copenhagen Child Cohort 2000 Eye Study), the pRNFL was 3.5 µm thinner in low-birth-weight children (<2500 g) compared to normal-birth-weight children (≥2500 g),[7] a finding comparable to the pRNFL differences found in the present study.

In agreement with the data of Ashina et al.,[7] we observed a correlation of higher birth weight with thicker pRNFL in the superonasal, inferonasal, and inferotemporal sectors. However, it is still unclear whether higher pRNFL thickness has a protective effect against nerve diseases involving the optic nerve head, such as glaucoma, as well as retinal ganglion cell loss with resulting visual field defects.

Pueyo et al.[11] hypothesized that possible causes for a thinner pRNFL in former preterm subjects may be postnatal hypoxic events leading, via different pathways, to neuronal apoptosis in ganglion cells and inner nuclear layers. In addition, an association of intraventricular hemorrhage with optic nerve head morphology was observed in an earlier report,[32] which could also contribute to pRNFL alterations, particularly in low-birth-weight individuals with an increased risk for such adverse cerebral events.

Our findings might have relevance for both children and adults. Rothman et al.[6] observed that a thinner pRNFL in former preterm low-birth-weight infants is connected with altered brain structure and impaired neurologic development. Other studies reported an association of pRNFL damage with reduced visual acuity[10] and impaired neurodevelopmental outcome[33] in former low-birth-weight individuals. To our knowledge, no data exist regarding whether these associations are long lasting and persist into adulthood. Our study offers a first hint that the pRNFL is altered in adulthood due to low birth weight. Furthermore, our finding of a thinner pRNFL, particularly in the inferior sector, may be relevant, as in glaucoma patients pRNFL changes manifest in the inferior sectors first[34] with a conspicuous ISNT rule,[35] leading to initial superior Bjerrum scotoma.[36] Additionally, progression of glaucoma is most frequently located in the inferotemporal sector of the pRNFL,[34] and pRNFL thinning is linked to several optic neuropathies.[34,37–39] Consequently, low birth weight may be a previously unknown risk factor, among others, predisposing for these diseases, including glaucoma. This suggestion should be explored further to identify fetal origins of important adult eye diseases. However, it has to be mentioned that our statistical model explained only small amounts of the variance in the pRNFL ($R^2 = 0.007$, weak association), and it is unclear whether our findings have a clinical impact or whether the changes we observed are of only subclinical importance.

Strengths and Limitations

Forty-four percent of the study participants did not provide self-reported birth weight data. Participants with missing birth weight information were generally younger and more often female. When participants with self-reported birth weight data were compared to participants without birth weight data, only small differences were observed in ocular parameters after adjusting for sex and age. Consequently, we assume that our results can be generalized to the underlying German population.

A major restriction is that self-reported birth weight data could not be validated by reviewing birth records. To ensure the validity of the self-reported birth weight data, every subject was requested to look for documented birth weight data in their personal records or family albums; however, it has to be considered that birth weight data may be limited, and misclassification cannot be excluded. An earlier Australian twin study found a high reliability between self-reported and documented birth weight data in birth records, with an intraclass correlation coefficient of 0.978 (95% CI, 0.972–0.982).[40] In addition, the distribution of the participants' birth weight data was comparable to that of governmental data from the German Federal Statistical Office for the early 1970s, as reported earlier.[16,26]

We do not have any information about gestational age and postnatal ROP occurrence and ROP treatment, which would

allow further stratification of the analyses. Previous studies in children have particularly recruited former extreme-low-birth-weight infants,[10] which is in contrast to the population-based approach of the GHS study. As a result, our data reflect the influence of low birth weight on the pRNFL in the general population, rather than the effect of prematurity, which may differ from our findings. Analyses of our model fits show that only a small amount of the pRNFL variation can be explained by our statistical models, including birth weight data. Furthermore, the disproportionality in subjects among the birth weight groups could lead to a distortion, so we performed sensitivity analyses.

Strengths of the study are the population-based design and the large sample size. In addition, study investigators were blinded to birth weight data, and examinations were carried out with strict standard operating procedures.

Summary

In summary, our results highlight the long-term effects of low birth weight on optic nerve morphology beyond childhood, indicating that low birth weight is a risk factor for a thinner pRNFL in adulthood. Our results suggest that adult pRNFL morphology has its origin in early life; thus, there is the possibility that low birth weight may predispose for optic neuropathies accompanied by pRNFL alteration.

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This analysis presents clinical data regarding a large-scale, population-based cohort with ongoing follow-up examinations. This project represents a major scientific effort that maintained high methodological standards and followed detailed guidelines for analysis and publication to ensure sound scientific analyses at the highest level. The data are not available to the scientific community outside the established and controlled workflows and algorithms. To meet the general principle of verification and reproducibility of scientific findings, we offer access to our data through a local database at any time upon request, in accordance with the ethics vote. The GHS steering committee, which includes a member of each involved department and the coordinating principal investigator of the Gutenberg Health Study (P.S.W.), convenes once a month. The steering committee decides on internal and external access by researchers and use of the data and biomaterials based on a research proposals supplied by the researchers. Interested researchers can make their requests to the coordinating PI of the Gutenberg Health Study (philipp.wild@unimedizin-mainz.de). More detailed contact information is available at the homepage of the GHS (www.gutenberghealthstudy.org).

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