Association of Birth Weight With Foveolar Thickness in Adulthood: Results From a Population-Based Study

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Purpose. Low birth weight (BW) is associated with alterations of foveal shape development in childhood—leading to an increased retinal thickness of the fovea. The aim of the present study was to assess whether BW has a long-term effect on foveal retinal thickness (RT) and is still present in adulthood.

Methods. In the German population-based Gutenberg Health Study (GHS), participants were examined with spectral-domain optical coherence tomography. The association between self-reported BW and RT in the foveolar and perifoveal locations was assessed. Multivariable linear regression analyses with adjustment for potential confounders and grading of foveal hypoplasia were performed.

Results. Overall, RT measurements and self-reported BW were available for 2,539 participants (1300 female, mean age 54.5 ± 9.7 years). The absolute foveolar RT was 239.6 ± 25.8 µm, 232.2 ± 20.1 µm and 234.8 ± 21.0 µm, respectively, in the low (<2500 g), normal (2500–4000 g) and high (>4000 g) BW groups ($P < 0.001$). After adjustment for confounders, an association was observed between lower BW and increased foveolar thickness (B = –0.35 [95% confidence interval {CI}: –0.49; –0.20] µm/100 g; $P < 0.001$), whereas only a weak association with RT was observed with the nasal ($P = 0.010$), temporal ($P = 0.011$), and inferior ($P = 0.021$) quadrants in the 1 mm distance, with no association in the 2 mm distance to the fovea. Foveal hypoplasia grade 1 was more frequent in the low BW group (6.8%) compared to the normal (0.9%) and high BW group (1.2%).

Conclusions. This study provides evidence of an association between lower BW and increased foveolar thickness and foveal hypoplasia, indicating that prenatal growth may affect macular morphology, which in turn may persist until adulthood and predispose to retinal disease later in life.

Keywords: birth weight, foveal thickness, macula, anatomy, epidemiology, population-based study

Adverse intrauterine growth and premature birth lead to altered development of various neurologic tissues[1] including disordered retinal layer formation in the macula.[2,3] Initial foveal maturation begins in the twenty-second week of gestational age (GA) whereas the development of foveal depression starts within the twenty-fourth week of GA with a physiological migration of the inner retinal layers to the periphery and the outer retinal layers to the foveal center.[4] Spectral-domain optical coherence tomography (SD-OCT) has shown that premature birth stops retinal migration, leading to an immature foveal shape with an absent or shallow foveal pit and increased inner retinal layers.[2,3,5–7] In the

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Wiesbaden Prematurity Study a foveal photoreceptor layer thinning and a correlation between foveal thickness and visual function was also observed in former extreme preterm children (GA ≤28 weeks) aged four to 10 years independent of the postnatal occurrence of retinopathy of prematurity (ROP)[2].

Former preterm newborns with low birth weight are at increased risk of reduced visual acuity in childhood.[8–11] Furthermore, the population-based Gutenberg Health Study (GHS) demonstrated lower visual acuity in adults with former low birth weight.[12] Consequently, there is the possibility that altered retinal thickness in the fovea might contribute to the increased risk for lower visual acuity in later life, as well as predisposing to retinal disease in adulthood. Recently, we observed that low birth weight is associated with the presence of age-related macular degeneration (AMD).[13]

There are several reports of the effect of extreme prematurity and associated factors on macular thickness in infancy,[14,15] childhood,[2,3,5–7] adolescence,[16–18] and early adulthood,[19–22] but few population-based studies exist investigating the association of low birth weight as proxy for prematurity and adverse neonatal growth with macular thickness.[23] Molnar et al.[23] observed an association between low gestational age and increased macular thickness in preterm children (<27 weeks of GA) aged 6.5 years. However, population-based data on the relationship of low birth weight with macular alterations in adulthood are lacking, especially whether this relationship persists with age. Furthermore, altered macular thickness is associated with several retinal diseases such as AMD in adulthood,[24] one of the main eye diseases leading to visual impairment and blindness in Western countries.[25] Knowledge regarding the factors associated with macular thickening and potentially contributing to an increased risk for AMD is important and may contribute to a better understanding of the risk factors for retinal diseases. Furthermore, currently, every seventh child born worldwide has a low birth weight (<2500 g), with approximately 20.5 million low-birth-weight newborns annually[26]; hence, the long-term effects of low birth weight and associated factors on ocular and retinal development are of importance. This study analyzed the association of birth weight with macular thickness in adults aged 40 to 80 years, hypothesizing that lower birth weight is associated with a thicker foveolar thickness 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).[27] Participants aged between 35 and 74 years of the GHS were recruited between 2007 and 2012 for baseline examination. The participants were selected randomly from the local registry in the city of Mainz and the district of Mainz-Bingen, stratified 1:1 for sex and residence (urban or rural) and in equal strata for decades of age. They were invited to participate by mail, and the second stage was via telephone. The recruitment efficacy proportion was 55.5%.

The present analysis involved participants of the five-year follow-up examination at age 40 to 80 years who had undergone spectral-domain optical coherence tomography (SD-OCT). Of the 15,010 participants at baseline, 12,423 returned for the five-year follow-up (82.8% of all participants). During an extensive general and ophthalmologic examination in the study center, cardiovascular and ophthalmologic parameters were assessed and completed by a computer-assisted personal interview. The macula was imaged by SD-OCT using a 15° × 15° block scan with 37 single scans. All examinations were conducted by certified medical technical assistants and followed standard operating procedures.

Written informed consent was obtained from all study participants before study entry, and the GHS complied with Good Clinical Practice (GCP), Good Epidemiological Practice (GEP), and the ethical principles 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; original vote: 22.3.2007).

Inclusion and Exclusion Criteria

In this analysis, only subjects with available self-reported birth weight and retinal thickness in the macula measurements were included. Further inclusion criteria were measurement of objective refraction, corneal curvature and axial length in at least one eye. Subjects with vitreoretinal lesions (i.e., epiretinal membranes, retinal vein occlusion, diabetic maculopathy, myopic degeneration, macular edema) were excluded. Age-related macular degeneration (AMD) was not a criteria for exclusion.

Birth Weight

Every participant was asked together with study invitation to the GHS study center to review personal records and family albums for their documented birth weight, then classified according to birth weight into groups: low birth weight group <2500 g (group 1); normal birth weight group 2500–4000 g (group 2); and high birth weight group >4000 g (group 3) as reported previously.[12,13,28–33] Furthermore, participants with birth weight <1000 g and >6000 g were excluded becasue these self-reported data were deemed unreliable. The self-reported birth weight was validated through comparison the medical literature and data of the German Federal Statistical Office as reported previously.[12]

Ophthalmologic Examination

Briefly, ophthalmological examination included the measurement of visual acuity and refraction with a Humphrey Automated refractor/Keratometer (HARK) 599, intraocular pressure measurement with a noncontact tonometer, (NT 2000, Nidek Co./Japan), biometry (Lenstar LS900, Haag-Streit, Bern, Switzerland), non-mydriatic fundus photography, and imaging of the macula via SD-OCT (Spectralis-OCT; Heidelberg Engineering, Heidelberg, Germany).[34]

Optical Coherence Tomography

The macula was imaged using SD-OCT with a block scan 15 × 15° in EDI-modus and a standard 7.7 mm corneal curvature. The Heidelberg Eye Explorer Software tool (HEYEX, version 1.9.14.0, Heidelberg Engineering,

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Heidelberg, Germany) was used for automatic segmentation of the total retinal thickness of the macula and retinal thickness calculation in the fovea and perifoveal region in an ETDRS grid with 1 mm, 2 mm, and 3 mm distance circles in the four quadrants. The deepest foveal depression was assumed to be the foveal center. Furthermore, an automatic segmentation of the outer nuclear layer (ONL) was performed, with each scan reviewed by an investigator and invalid scans with decentration, reduced image quality or segmentation errors were excluded.

SD-OCT imaging was conducted in nonmydriatic eyes. Each scan was checked by a board-certified ophthalmologist for decentration or layer segmentation errors and eyes with such errors were excluded. Consequently, the present study only includes high-quality images with ideal centration, a high signal strength >15 dB (and accurate automated delineation). Furthermore, foveal scans of the right eye were evaluated by two independent graders (F.M.W., S.G.) for the presence of foveal hypoplasia, which was defined according to a previous report.[35] In the case of deviating gradings, the grading was determined by the senior grader (A.K.S.). Foveal hypoplasia was categorized into four different grades: grade 1 was defined as a shallow foveal pit, the presence of wider ONL and OS lengthening; grade 2 as grade 1 but absence of foveal pit; grade 3 was defined as grade 2 but with the absence of OS lengthening; grade 4 was defined as grade 3 but with the absence of ONL widening.[35]

Covariates

Based on a literature search, the following parameters were considered to be associated with macular thickness[36–38] and potentially associated with birth weight,[13,33] therefore included in the multivariable models: sex, age, axial length, AMD, corneal radius, intraocular pressure, smoking, high-density lipoprotein, low-density lipoprotein, triglycerides, and HbA1c.

Ocular biometry was performed using a LenStar 900 (Haag Streit, Köniz, Switzerland) as described previously.[33] Fundus photographs were graded by an experienced ophthalmologist under supervision of an experienced senior grader according to the classification system of the Rotterdam Eye Study[39] for AMD as described previously.[13] In accordance with the classification of the International AMD Epidemiology Study Group small, hard drusen were not judged to be an AMD diagnosis.[40]

Statistical Analysis

The main outcomes were total retinal thickness in the foveolar (thinnest position in the fovea), foveal and in the eight perifoveal locations (superior, inferior, nasal and temporal of the fovea in 1 to 2 mm and 2 to 3 mm distance). A nonresponder analysis was conducted with respect to information on birth weight. Descriptive statistics included absolute and relative frequencies for dichotomous parameters and mean and standard deviation for approximately normally distributed data, otherwise the median and interquartile range were calculated.

Both eyes of an individual were included in the analyses, if OCT data were available, and linear regression models with general estimating equations (GEE) were used to assess associations and to account for correlations between both eyes of an individual. In model 1, birth weight was included as an independent variable, with model 2 including adjustments for sex, age, axial length, AMD, corneal radius, intraocular pressure, smoking, high-density lipoprotein, low-density lipoprotein, triglycerides, and HbA1c. The prevalence of foveal hypoplasia was compared between the different study groups using χ^2 test. Furthermore, the correlation between distant-corrected visual acuity and retinal layer thickness was calculated by Spearman correlation. In addition, various sensitivity analyses were performed. First, a sensitivity analysis including only subjects with an axial length of 23.00 mm (twenty-fifth percentile) to 24.4 mm (seventy-fifth percentile) was performed. Second, an analysis with equal proportions of subjects in each birth weight group was conducted to investigate the disproportion of subjects between the three birth weight groups. Third, another sensitivity analysis was performed with all participants with self-reported birth weight including those with <1000 g and >6000 g. Fourth, another sensitivity analysis was conducted excluding eyes with foveal hypoplasia. Fifth, a sensitivity analysis was performed with additional inclusion of a linear and quadratic term for birth weight in the univariate and multivariable model assessing the relationship with foveolar thickness. All models were computed in the first step including birth weight as a continuous variable and in a second step including birth weight as a categorical variable (birth weight <2500 g, birth weight 2500–4000 g, a birth weight >4000 g). In another sensitivity analysis the relationship of birth weight with foveal retinal thickness stratified for sex was assessed. Because this is an explorative study, a significance level was not defined; thus P values are reported only for descriptive purposes and should be interpreted with caution.[41]

The data were analyzed with R version 3.6.1 (2019-07-05) R Core Team (2019); R: A language and environment for statistical computing; R Foundation for Statistical Computing, Vienna, Austria.[42]

Results

Participant Characteristics

Of the 15,010 participants at baseline 12,423 were examined at the five-year follow-up. Correctly segmented SD-OCT scans of at least one eye were possible in 4190 persons, with missing scans mainly due to organizational reasons. Self-reported birth weight was documented in 2550 of these participants with 11 individuals excluded because of their birth weight >6000 g (10 subjects) or <1000 g (one subjects), leading to a study sample of 2539 individuals.

The participants' characteristics are presented in Table 1 with a mean age of 54.5 ± 9.7 years and 51.2% (n = 1300) were female. Overall, a low birth weight (<2500 g) was reported for 151 participants, normal birth weight (2500–4000 g) by 2058 participants and high birth weight (>4000 g) by 330 participants (Table 1). The prevalence of foveal hypoplasia grade 1 was 6.8% (95% CI: 3.4%-12.4%) in the low-birth-weight group, 0.9% (95% CI: 0.6%–1.5%) in the normal birth weight group and 1.2% (95% CI: 0.4%–3.3%) in the high birth weight group. No eye had foveal hypoplasia grade 2 or higher. There was a significant difference in the prevalence of foveal hypoplasia between the low and normal birth weight group ($P < 0.001$) but not between the normal and high birth weight group ($P = 0.8$) (Fig. 1).

Table 1. Characteristics of the Study Sample (n = 2539)

Variable	All	Female	Male
Number of participants	2539	1300	1239
Number (percentage) of woman	1300 (51.2%)	1300 (100%)	0 (0%)
Age (y)	54.5 ± 9.7	54.2 ± 9.6	54.8 ± 9.8
Birth weight (g)	3414 ± 660	3288 ± 620	3546 ± 677
Low birth weight (percentage)	151 (5.9%)	94 (7.2%)	57 (4.6%)
Normal birth weight (percentage)	2058 (81.1%)	1098 (84.5%)	960 (77.5%)
High birth weight (percentage)	330 (13.0%)	108 (8.3%)	222 (17.9%)
BMI (kg/m^2)	27.2 ± 5.0	26.5 ± 5.5	27.9 ± 4.3
Arterial hypertension (yes)	1063 (41.9%)	456 (35.1%)	607 (49.0%)
Diabetes mellitus (yes)	166 (6.5%)	59 (4.5%)	107 (8.6%)
Smoking (yes)	454 (17.9%)	212 (16.3%)	242 (19.5%)
logMAR OD	0.0 (0.0; 0.1)	0.0 (0.0; 0.1)	0.0 (0.0; 0.1)
logMAR OS	0.0 (0.0; 0.1)	0.0 (0.0; 0.1)	0.0 (0.0; 0.1)
IOP OD (mm Hg)	14.7 ± 2.9	14.5 ± 2.7	14.9 ± 3.1
IOP OS (mm Hg)	14.8 ± 2.9	14.6 ± 2.8	15.0 ± 3.1
Spherical equivalent OD (Diopter)	−0.4 (−1.5; 0.5)	−0.4 (−1.5; 0.5)	−0.4 (−1.4; 0.5)
Spherical equivalent OS (Diopter)	−0.4 (−1.5; 0.5)	−0.4 (−1.5; 0.5)	−0.25 (−1.4; 0.5)
Axial length OD (mm)	23.8 ± 1.2	23.5 ± 1.1	24.1 ± 1.1
Axial length OS (mm)	23.8 ± 1.2	23.5 ± 1.1	24.0 ± 1.2
Corneal radius OD (mm)	7.8 ± 0.3	7.7 ± 0.3	7.9 ± 0.3
Corneal radius OS (mm)	7.8 ± 0.3	7.7 ± 0.3	7.8 ± 0.3
Eye diseases			
No AMD OD	2124 (94.9%)	1093 (94.8%)	1031 (95.0%)
Early AMD OD (yes)	111 (5.0%)	58 (4.9%)	53 (5.0%)
Late AMD OD (yes)	3 (0.1%)	2 (0.2%)	1 (0.1%)
No AMD OS	2084 (94.9%)	1084 (95.6%)	1000 (94.3%)
Early AMD OS (yes)	108 (4.9%)	50 (4.4%)	58 (5.5%)
Late AMD OS (yes)	3 (0.1%)	0 (0.0%)	3 (0.3%)
Pseudophakia OD (yes)	103 (4.1%)	49 (3.8%)	54 (4.4%)
Pseudophakia OS (yes)	104 (4.1%)	47 (3.6%)	57 (4.6%)
Glaucoma (yes)	16 (0.7%)	7 (0.6%)	9 (0.8%)

dpt, diopter; AMD, age-related macular degeneration; IOP, intraocular pressure; OD, right eye; OS, left eye.

Data from the population-based Gutenberg Health Study (2012–2017) by birth weight groups. Mean ± Standard Deviation or Median and 25%/75% Quantiles.

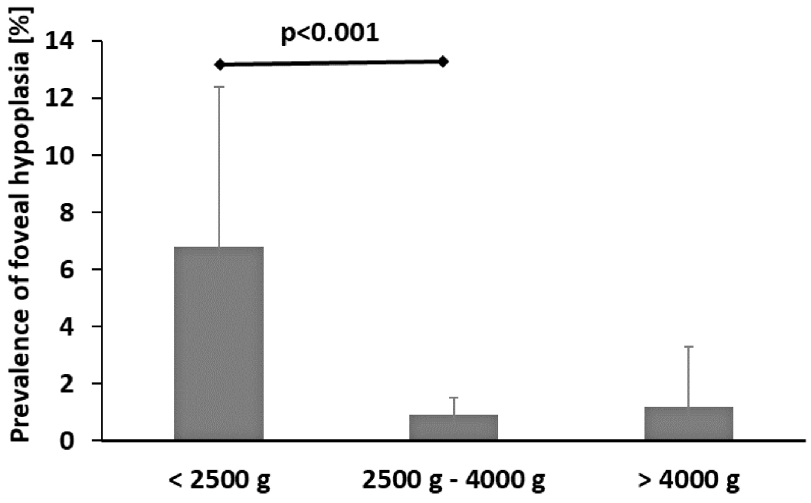

Figure 1. Prevalence of foveal hypoplasia in relation to birth weight group. Data from the German Gutenberg Health Study 2012–2017. The *error bars* indicate the 95% confidence interval of the prevalence estimates.

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Item Nonresponse Analysis

We compared those subjects included in the analysis with those attending the 5-year follow-up examination. The subjects in our analysis were about 6 years younger and more often female (51.2% vs. 48.2%), with no difference in birth weight. The included subjects were less likely to have arterial hypertension and diabetes, but more often smoked. Similar foveolar thickness was observed in participants with and without birth weight information.

Birth Weight Categorized Into Low, Normal and High Birth Weight

Descriptive data for macular retinal thickness is reported in Table 2. The low-birth-weight group showed considerable thicker foveolar thickness whereas the retina in a distance of 1 and 2 mm showed no statistical differences between the different birth weight groups.

When analyzing birth weight categorized into low, normal, and high birth weight, the foveolar thickness was higher in the low birth weight group compared to the normal birth weight group in the univariate analysis (model 1: B = 9.53 µm [95% CI: 5.32; 13.73], P < 0.001) and after adjusting for several confounders (model 2: B = 10.18 µm [95% CI: 6.05; 14.31], P < 0.001). The high birth weight group showed a weak association with an increased foveolar thickness compared to the normal birth weight group in the univariate analysis (model 1: B = 2.44 µm [95% CI: 0.00; 4.88], P = 0.05) although no association was observed in the multivariable analysis (model #2: B = 0.67 µm [95% CI: −1.70; 3.04], P = 0.58).

After excluding eyes with foveal hypoplasia as sensitivity analysis, an increased foveolar thickness was associated with the low-birth-weight group (B = 4.21 µm, P = 0.03) and high birth weight (B = 2.67 µm, P = 0.05) compared to normal birth weight in the univariate analysis. No differences were observed between the low and high birth weight group compared to the normal birth weight group in the different perifoveal locations (Table 3).

Birth Weight as a Continuous Variable

In the univariate analysis, lower birth weight was associated with increased foveolar thickness (B = −0.20 [−0.35; −0.06] µm per 100 g; P = 0.007) (Fig. 2 and Table 4). This association was still present after adjusting for several confounders (B = −0.35 [−0.49; −0.20] µm per 100 g; P < 0.001). No association was observed in the univariate analysis between birth weight and retinal thickness in the different quadrants in the 1- to 2-mm distance to the fovea. In contrast, the multivariable analysis revealed that lower birth weight showed a weak association with retinal thickness in the 1- to 2-mm distance to the fovea in the nasal quadrant (B = −0.13 [−0.23; −0.03] µm per 100 g; P = 0.010), inferior quadrant (B = −0.11 [−0.21; −0.02] µm per 100 g; P = 0.021) and temporal quadrant (B = – 0.12 [–0.22; –0.03] µm per 100 g; P = 0.011), as well as the mean value of all four quadrants

Table 2. Measurements of Macula Thickness by Birth Weight Groups

Retinal Thickness (µm)	<2.5 kg (n = 151)	2.5–4.0 kg (n = 2058)	>4.0 kg (n = 330)	*P* Value
Right eye (N = 1982)				
Foveolar (µm)	239.6 ± 25.8	232.2 ± 20.1	234.8 ± 21.0	<0.001
Foveal (µm)	285.4 ± 23.1	281.7 ± 20.3	284.5 ± 20.9	0.032
Inner locations (1–2 mm distance)				
Superior (µm)	343.5 ± 17.0	344.8 ± 15.8	345.4 ± 17.3	0.54
Inferior (µm)	341.4 ± 17.3	342.3 ± 16.1	343.0 ± 17.6	0.64
Nasal (µm)	340.3 ± 18.2	341.1 ± 17.0	341.9 ± 18.2	0.67
Temporal (µm)	330.5 ± 17.4	331.2 ± 15.9	331.7 ± 17.6	0.78
Inner location mean (µm)	338.9 ± 16.9	339.8 ± 11.6	340.5 ± 17.0	0.65
Outer locations (2–3 mm distance)				
Superior (µm)	341.9 ± 16.2	342.8 ± 15.5	342.7 ± 16.9	0.80
Inferior (µm)	338.5 ± 16.7	340..6 ± 15.3	340.3 ± 16.4	0.37
Nasal (µm)	348.4 ± 16.3	349.9 ± 15.2	349.2 ± 15.9	0.53
Temporal (µm)	333.5 ± 16.0	335.0 ± 14.3	335.6 ± 16.0	0.44
Outer location mean (µm)	340.6 ± 15.8	342.1 ± 14.5	342.0 ± 15.7	0.56
Left eye (N = 1458)				
Foveolar (µm)	240.1 ± 23.9	232.8 ± 20.8	233.1 ± 21.9	0.023
Foveal (µm)	287.0 ± 21.2	282.4 ± 20.8	284.0 ± 20.7	0.16
Inner locations (1–2 mm distance)				
Superior (µm)	344.8 ± 17.3	345.7 ± 16.2	345.4 ± 17.3	0.89
Inferior (µm)	342.8 ± 16.4	341.6 ± 16.3	341.4 ± 17.1	0.81
Nasal (µm)	343.2 ± 17.7	342.7 ± 17.4	342.8 ± 18.0	0.96
Temporal (µm)	330.5 ± 17.1	330.2 ± 16.5	330.7 ±16.8	0.91
Inner location mean (µm)	340.4 ± 16.6	340.0 ± 16.0	340.1 ± 16.8	0.99
Outer locations (2–3 mm distance)				
Superior (µm)	343.8 ± 17.8	344.3 ± 15.9	342.4 ± 15.8	0.27
Inferior (µm)	340.4 ± 16.7	340.9 ± 15.5	339.5 ± 15.8	0.50
Nasal (µm)	349.4 ± 17.0	350.2 ± 15.8	348.5 ± 16.0	0.33
Temporal (µm)	334.1 ± 16.1	334.8 ± 14.7	334.6 ± 15.1	0.90
Outer Location Mean (µm)	341.9 ± 16.4	342.6 ± 14.8	341.2 ± 15.1	0.48

Data from the population-based Gutenberg Health Study (2012–2017). Mean ± SD.

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Table 3. Associations of Retinal Thickness in the Fovea and Perifoveal Locations With Birth Weight Groups in the Gutenberg Health Study (2012–2017)

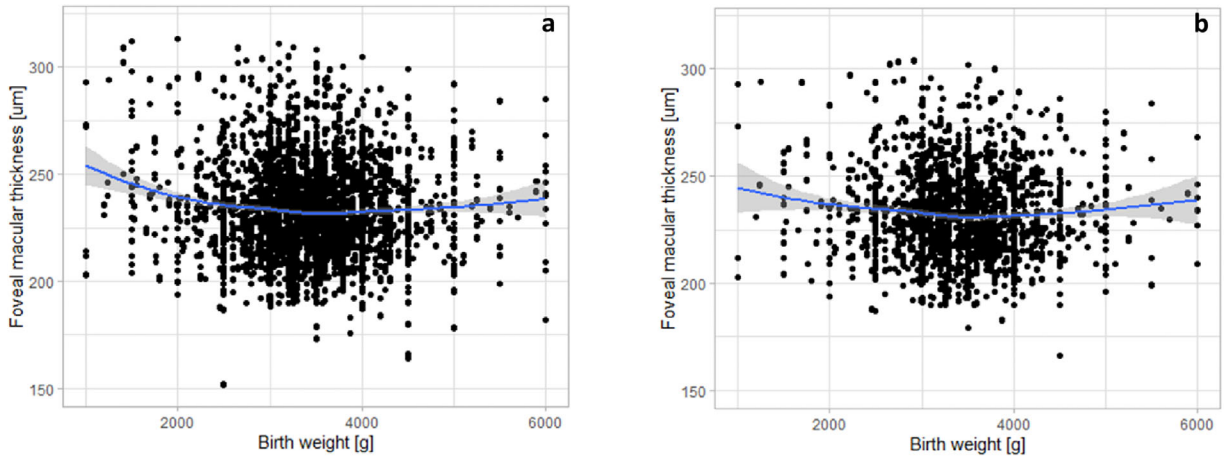
	Model 1*		Model 2†	
	β (95% CI)	P	β (95% CI)	P
RT foveolar (µm)				
Birth weight < 2500 g	9.53 (5.32; 13.73)	<0.001	10.18 (6.05; 14.31)	<0.001
Birth weight 2500 g–4000 g	Reference		Reference	
Birth weight > 4000 g	2.44 (0.00; 4.88)	0.05	0.67 (−1.70; 3.04)	0.58
RT in the fovea (µm)				
Birth weight < 2500 g	6.07 (2.41; 9.74)	0.001	7.09 (3.57; 10.61)	<0.001
Birth weight 2500 g–4000 g	Reference		Reference	
Birth weight > 4000 g	2.57 (0.16; 4.98)	0.038	−0.36 (−2.65; 1.94)	0.76
RT 1–2 mm superior (µm)				
Birth weight < 2500 g	0.20 (−2.54; 2.94)	0.88	0.92 (−1.34; 4.15)	0.50
Birth weight 2500 g–4000 g	Reference		Reference	
Birth weight > 4000 g	−0.01 (−1.94; 1.91)	0.99	−1.04 (−2.88; 0.79)	0.27
RT 1–2 mm inferior (µm)				
Birth weight < 2500 g	0.73 (−2.01; 3.46)	0.60	1.48 (−1.17; 4.13)	0.27
Birth weight 2500 g–4000 g	Reference		Reference	
Birth weight > 4000 g	−0.17 (−2.12; 1.79)	0.87	−1.58 (−3.43; 0.28)	0.096
RT 1–2 mm nasal (µm)				
Birth weight < 2500 g	0.57 (−2.33; 3.48)	0.70	1.40 (−1.41; 4.20)	0.33
Birth weight 2500 g–4000 g	Reference		Reference	
Birth weight > 4000 g	−0.07 (−2.14; 1.99)	0.94	−1.77 (−3.73; 0.19)	0.077
RT 1–2 mm temporal (µm)				
Birth weight < 2500 g	1.22 (−1.54; 3.98)	0.39	2.05 (−0.60; 4.70)	0.13
Birth weight 2500 g–4000 g	Reference		Reference	
Birth weight > 4000 g	0.44 (−1.50; 2.37)	0.54	−1.39 (−3.24; 0.47)	0.14
RT 1–2 mm mean (µm)				
Birth weight < 2500 g	0.68 (−2.00; 3.36)	0.62	1.46 (−1.12; 4.04)	0.27
Birth weight 2500 g–4000 g	Reference		Reference	
Birth weight > 4000 g	0.05 (−1.86; 1.95)	0.96	−1.44 (−3.25; 0.36)	0.12
RT 2–3 mm superior (µm)				
Birth weight < 2500 g	−0.86 (−3.69; 1.97)	0.55	−0.70 (−3.44; 2.04)	0.62
Birth weight 2500 g–4000 g	Reference		Reference	
Birth weight > 4000 g	−1.24 (−3.11; 0.63)	0.19	−0.39 (−2.13; 1.34)	0.66
RT 2–3 mm inferior (µm)				
Birth weight < 2500 g	−0.82 (−3.61; 1.97)	0.56	−0.53 (−3.20; 2.15)	0.70
Birth weight 2500 g–4000 g	Reference		Reference	
Birth weight > 4000 g	−1.10 (−3.16; 0.45)	0.14	−0.91 (−2.60; 0.77)	0.29
RT 2–3 mm nasal (µm)				
Birth weight < 2500 g	−0.69 (−3.44; 2.05)	0.62	−0.03 (−2.70; 2.64)	0.98
Birth weight 2500 g–4000 g	Reference		Reference	
Birth weight > 4000 g	−1.30 (−3.18; 0.59)	0.18	−1.29 (−3.09; 0.52)	0.16
RT 2–3 mm temporal (µm)				
Birth weight < 2500 g	−0.15 (−2.79; 2.48)	0.91	0.26 (−2.24; 2.77)	0.84
Birth weight 2500 g–4000 g	Reference		Reference	
Birth weight > 4000 g	−0.08 (−1.82; 1.66)	0.93	−0.40 (−2.05; 1.25)	0.64
RT 2–3 mm mean (µm)				
Birth weight < 2500 g	−0.70 (−3.33; 1.96)	0.61	−0.40 (−2.93; 2.14)	0.76
Birth weight 2500 g–4000 g	Reference		Reference	
Birth weight > 4000 g	−1.07 (−2.81; 0.67)	0.23	−0.77 (−2.39; 0.86)	0.36

CI, confidence interval.
Linear regression analysis using generalized estimating equations to control for correlations between right and left eyes.
* Crude model without adjustment.
† Adjusted for sex, age, axial length, AMD, corneal radius, intraocular pressure, smoking, high-density lipoprotein, low-density lipoprotein, triglycerides, and HbA1c.

($B = -0.11$ [−0.20; −0.02] µm per 100 g; $P = 0.018$). At the 2- to 3-mm distance, none of the different quadrants showed a significant association with birth weight (Table 4). The sensitivity analysis excluding eyes with foveal hypoplasia showed no significant association with birth weight as continuous variable in the univariate and multivariable model.

Sensitivity Analyses

Participants with birth weight <1000 g and >6000 g were not excluded in sensitivity analysis resulting in similar results. The same was observed when only subjects with an axial length between 23.00 and 24.4 were included.



The blue line presents the loess (Locally Weighted Scatterplot Smoothing) curve. Legend: µm – micrometer; g — gram; 2a all eyes 2b right eyes without foveal hypoplasia.

Figure 2. Scatterplots of birth weight with foveal retinal thickness in the Gutenberg Health Study. (a) All participants and (b) only participants without hypoplasia. Participants with low birth weights showed increased foveal retinal thickness, although there was a trend for increased foveal thickness in high birth weight subjects.

Table 4. Associations of Retinal Thickness in the Fovea and Perifoveal Locations With Birth Weight (As Continuous Variable) (n = 2539) in the Gutenberg Health Study (2007–2012)

	Model 1*		Model 2†	
Birth Weight (100 g)	**β (95% CI)**	***P* Value**	**β (95% CI)**	***P* Value**
RT foveolar (µm)	−0.20 (−0.35; −0.06)	0.007	−0.35 (−0.49; −0.20)	<0.001
RT foveal (µm)	−0.03 (−0.16; 0.10)	0.69	−0.25 (−0.38; −0.12)	<0.001
Inner locations (1-2 mm distance)				
RT superior (µm)	0.02 (−0.08; 0.12)	0.68	−0.08 (−0.18; 0.01)	0.097
RT inferior (µm)	0.01 (−0.08; 0.11)	0.78	−0.11 (−0.21; −0.02)	0.021
RT nasal (µm)	0.01 (−0.09; 0.11)	0.83	−0.13 (−0.23; −0.03)	0.010
RT temporal (µm)	0.03 (−0.07; 0.12)	0.52	−0.12 (−0.22; −0.03)	0.011
RT inner location mean (µm)	0.02 (−0.08; 0.11)	0.72	−0.11 (−0.20; −0.02)	0.018
Outer locations (2-3 mm distance)				
RT superior (µm)	−0.03 (−0.13; 0.07)	0.57	−0.00 (−0.10; 0.09)	0.96
RT inferior (µm)	−0.01 (−0.10; 0.09)	0.87	−0.01 (−0.10; 0.08)	0.84
RT nasal (µm)	−0.05 (−0.14; 0.05)	0.33	−0.06 (−0.15; 0.03)	0.19
RT temporal (µm)	0.02 (−0.07; 0.11)	0.66	−0.03 (−0.12; 0.06)	0.53
RT outer location mean (µm)	−0.02 (−0.11; 0.08)	0.74	−0.03 (−0.11; 0.06)	0.57

RT, retinal thickness; CI, confidence interval.
Linear regression analysis using generalized estimating equations to control for correlations between right and left eyes was applied.
* Crude model without adjustment.
† Adjusted for sex, age, axial length and age-related macular degeneration, corneal radius, intraocular pressure, smoking, high-density lipoprotein, low-density lipoprotein, triglycerides, and HbA1c.

No association was observed between foveolar thickness of ONL and birth weight in the different models, or between total foveolar retinal thickness and ONL thickness with distant corrected visual acuity. Furthermore, scatterplots of birth weight with foveal retinal thickness stratified for sex are displayed in Supplementary Figure S1. Both groups showed that low birth weight participants revealed increased foveal retinal thickness. In the univariable and multivariable models assessing the association of foveolar thickness with a linear and quadratic birth weight term there was a quadratic relationship ($P < 0.001$) in addition to the linear relationship ($P < 0.001$).

Discussion

The present study demonstrates that low birth weight is related to an increased foveolar thickness and a higher rate of foveal hypoplasia grade 1 of the retina in adulthood. Our data provide new insights regarding the effects of prenatal growth on the macular region, demonstrating that an altered macular morphology particular in the fovea is evident in middle and late adulthood for low birth weight individuals. This finding may be of importance because an altered foveal thickness is associated with retinal diseases such as AMD.

Our data are in line with previous studies in infancy[14,15] childhood,[2,3,5–7] adolescence,[16–18] and early adulthood,[19–22] expanding this knowledge into middle and late adulthood with population-based data. These previous studies reported that the main factors influencing macular morphology were low birth weight, low gestational age, and postnatal ROP occurrence and treatment. Hammer and colleagues[22] showed that the increase in inner retinal layer thickness in prematurity was relatively uniform across 3° whereas there was a distinct increase in ONL thickness in the central 1°

to 2° of the fovea, with both contributing to the increased thickness. Furthermore, some authors reported that macular thickness decreased particularly in former preterm and full-term children with prenatal growth restriction indicated by a birth weight below the tenth percentile. In a study in the Swedish population, Molnar et al.[23] investigated the effects of extreme prematurity in 6.5-year-old children, observing an increased central macula thickness in 134 extreme preterm children (GA<27 weeks) compared to 145 control individuals. They found a decrease in macular thickness of 3.9 µm per gestational week and identified gestational age, ROP, and male gender as the main risk factors. In our study, we observed that a decrease in birth weight (per 100 g) was related to an increase in foveolar retinal thickness of 0.35 µm. Furthermore, Molnar and colleagues[23] observed a difference of about 34 µm in foveal thickness between 6.5-year-old extreme preterm children and full-term children compared to 7 µm in the present population-based study. This discrepancy may be due to the different groups (extreme preterm subjects vs. low-birth-weight individuals in the general population), but it is also possible that changes continue to occur in adolescence as the eye grows. Perifoveal macular thickness was slightly thinner in the study by Molnar et al.[23] These differences may be caused by the different study designs analyzing rather the effects of low birth weight in a population-based setting in adults in the present study than the effects of extreme prematurity and ROP on foveal thickness in early life. Furthermore, this study provides novel data analyzing retinal morphology in adults, showing that the increased rate of foveal hypoplasia grade 1 in subjects is associated with low birth weight, similar to previous reports in preterm children of an increased prevalence of foveal hypoplasia.[17,43,44] However, it is notable that the association between low birth weight and increased foveolar retinal thickness was still present in our sensitivity analysis excluding participants with foveal hypoplasia.

Overall, our findings support the hypothesis that the increased foveolar thickness in former preterm low-birth-weight subjects is due to a disordered migration of the inner retinal layers away from the fovea. The retinal thickness of the ONL in the fovea did not differ between the study groups further reporting that a migration disorder of the inner retinal layers contributes to a thicker foveal shape than altered ONL development. To our knowledge, this is the first study to indicate that retinal alterations caused by low birth weight persist into late adulthood.

The present study may have clinical significance for both children and adults: In previous reports in children,[2] adolescents and early adulthood,[45] as well as the EPICure@19Study[21] investigating subjects up to 19 years of age, a correlation between retinal layer thickness in the macula region with best corrected visual acuity was observed. Consequently, one may speculate that an altered foveal shape may lead to an increased risk for reduced visual acuity in life, or that this is not necessarily associated with reduced visual acuity, as increased foveolar thickness in former preterm newborns only indicates former prematurity or prenatal growth restriction.[17] In line with this, we found no association between retinal thickness and visual acuity in our study. Furthermore, our finding of increased foveolar thickness may be of clinical relevance as different retinal diseases are associate with altered macular thickness, such as AMD.[24] This is of particular importance as we previously observed an increased AMD prevalence of about 70% in the low birth weight group within the GHS. The prevalence of AMD was with 11.2% in the low birth weight group compared to 6.5% in the normal birth weight group and 8.4% in the high birth weight group,[24] indicating that low birth weight accompanied by increased foveal thickness might be a risk factor for AMD. Future studies should explore this relationship, possibly demonstrating that there are "fetal origins of adult eye diseases" as hypothesized previously.[13] However, the present statistical analyses may only explain a small amount of the variability in retinal thickness; thus it is still unclear whether our findings are of clinical or merely subclinical importance.

Strengths and Limitations

The main limitation of the present study is that 44% of participants did not provide self-reported birth weight data. In our item nonresponse analysis subjects with missing birth weight data were younger and more likely female. These parameters were included in our statistical models, the results cannot be generalized to the German population. Another major limitation of our study is that birth weight could not be validated by reviewing medical birth files of all participants. To ensure correct birth weight reports, every participant was requested to review personal records and family albums about birth weight data before study entry. For a subgroup of participants born in the University Medical Center Mainz (UMCM), self-reported birth weight data were compared to documented birth weight data in medical charts and birth registries of the UMCM, revealing a high intraclass correlation coefficient of 0.89 (CI 0.83; 0.92), thus the self-reported birth weight was assumed to be highly valid. However, we cannot guarantee the integrity of self-reported birth weight data for all participants. In a previous Australian Twin Study a high external validity was also observed when comparing self-reported birth weight data with documented birth weight data in medical files. Furthermore, the proportion of persons with low, normal and high birth weight in our sample was comparable to the data of the German Federal Statistical Office of the early 1970s and medical records as reported previously.[12] Further restrictions of the present analysis are the lack of data concerning gestational age and postnatal occurrence and treatment of ROP. It seems that mechanistically, individuals born prematurely may have different developmental effects than those born at term with lower birth weight. However, because gestational age was not surveyed, we cannot differentiate between the effects of preterm delivery and low birth weight in our participants. Furthermore, because of the high correlation between birth weight and preterm birth, the association between birth weight and foveal thickness may be due to preterm birth; this should be considered when interpreting the results. Also, OCT-imaging was not available for all study participants primarily because of organizational reasons, and all retinal thickness segmentations were reviewed by a board-certified ophthalmologist to minimize the risk of segmentation errors.

Summary

Overall, the present study provides new results concerning the long-term sequelae of low birth weight on macular morphology in middle and late adulthood. Increased foveolar thickness is related to low birth weight and this relationship persists until later life. Our results indicate that macular, particularly foveal shape, may have origins—among others—

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in early life, possibly contributing to an increased risk of macular diseases, which are associated with an altered foveal shape.

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