Low Birth Weight Is Linked to Age-Related Macular Degeneration: Results From the Population-Based Gutenberg Health Study (GHS)

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Purpose. This study analyzed whether low birth weight is linked to prevalence and incidence of age-related maculopathy (AMD) in adulthood.

Methods. The Gutenberg Health Study (GHS) is a population-based, observational cohort study in Germany. GHS participants at an age from 35 to 74 years were included. An ophthalmologic examination with fundus photography was carried out. Fundus photographs were graded according to the Rotterdam Grading Scheme for AMD at baseline and at the 5-year follow-up examination. Participants were divided into three different birth weight groups (low: <2500 g; normal: 2500–4000 g; and high: >4000 g). Poisson regression analysis with adjustment for several confounders was used to assess associations between birth weight and AMD prevalence (overall, early, late AMD) and 5-year cumulative incidence.

Results. Overall, 6492 participants were included (3538 female, aged 50.7 ± 10.4 years). Prevalence of total AMD was highest in the low birth weight group (11.2%; 40/358) compared to the normal birth weight group (6.5%; 346/5328) and the high birth weight group (8.4%; 68/806). Low birth weight was associated with overall AMD prevalence (prevalence ratio [PR] = 1.54, $P = 0.006$), and in particular with early AMD prevalence (PR = 1.52; $P = 0.01$). No association was observed between low birth weight and cumulative 5-year incidence of AMD.

Conclusions. Our analyses indicate that low birth weight may lead to higher prevalence of retinal diseases in later life, as we observed for AMD. Our results are limited due to missing data and loss to follow-up, but may be a first hint that AMD has one of its origins in early life.

Keywords: birth weight, age-related macular degeneration, age-related maculopathy, epidemiology, population-based study

Age-related macular degeneration (AMD) is one of the leading causes for visual impairment in industrialized countries.[1] In the recent decade, many studies investigated the etiology of AMD and found several risk factors including smoking,[2] nutritional factors,[3] cardiovascular diseases,[4] and genetic markers.[5] Nevertheless, this explains only partially the occurrence of AMD and other factors are suspected to be linked with AMD. One of these factors may be fetal development.

David Barker[6] postulated that low birth weight as surrogate for intrauterine malnutrition is not only a proxy for fetal but also for adult health and increases the risk for disease in adulthood such as coronary artery disease, arterial hypertension, and obesity. He hypothesized that specific developmental

time frames exist when different organs and tissues are sensitive to adverse environmental alterations.[6] This theory was derived from the assumption of "developmental plasticity," which means that one genotype can result in different phenotypes because of adverse intrauterine events to lead to a larger diversity and improve the fit between phenotype and the surrounding environment. This phenomenon was called "programming," indicating that conditions like malnutrition during intrauterine development can cause permanent organ changes potentially lasting lifelong and affecting the occurrence of degenerative disorders in adulthood. Furthermore, as recent reports showed alterations in retinal[7] and choroidal[8] morphology in former low birth weight individuals in childhood, low birth weight may predispose to retinal diseases such as AMD in adulthood.

Only few studies have investigated the relationship between birth weight and AMD. Hall et al.[9] found an association between high birth weight and AMD in a cohort of 392 subjects, although they initially hypothesized that AMD would be associated with reduced fetal growth. Among white study participants, the population-based ARIC study found an increased risk of early AMD with greater birth weight, but not for the total study cohort.[10] Sayer et al.[11] reported on 717 participants born between 1920 and 1930 that birth weight and body weight at 1 year of age as a marker of early growth were not linked with macular degeneration.

However, until now, no study has investigated the relationship between birth weight and incidence of AMD. Hence, this study aimed to analyze whether low birth weight as surrogate of intrauterine malnutrition might be linked to prevalence and incidence of AMD.

Materials and Methods

Study Population and Ethics Approval

The Gutenberg Health Study (GHS) is an observational, population-based single-center cohort study at the University Medical Center of the Johannes Gutenberg-University Mainz in Germany with a total of 15,010 participants examined at baseline between 2007 and 2012. The study had a 5-year follow-up examination between 2012 and 2017.[12] The population sample was sampled for each decade of age containing an equal number of individuals of both sexes and type of residence (urban/rural). The recruitment efficacy proportion was 61.2%. All participants underwent a comprehensive ophthalmologic examination in an interdisciplinary setting including general examinations, psychological tests, and genetic analyses. According to the tenets of the Declaration of Helsinki, written informed consent was obtained from all study participants prior to entering the study, and the GHS complies 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, latest update: 20.10.2015).

Inclusion Criteria

All GHS study participants with available AMD grading at baseline and with self-reported birth weight data were included in the prevalence analysis. With respect to cumulative incidence of AMD, those subjects with additional fundus photographs gradable for AMD lesions at 5-year follow-up were included in the incidence analysis sample (Supplementary Fig. S1).

Birth Weight

In the present analysis, we included participants with self-reported birth weight. Every participant was asked at the invitation to the study examination to review his or her records and family album for documentation of birth weight as reported earlier.[13,14] Participants were divided into the three birth weight groups: low birth weight <2500 g (group 1); normal birth weight with birth weight between 2500 and 4000 g (group 2); and high birth weight >4000 g (group 3) in accordance with medical literature.[15,16] Additionally, participants with birth weight below 1000 g and above 6000 g were excluded, as these self-reported data were suspected to be unreliable.

Ophthalmologic Examination

A detailed description of the ophthalmologic examinations was reported elsewhere.[17] All subjects were examined in a 5-hour standardized baseline examination with assessment of the following ophthalmologic data: ophthalmologic history, objective refraction (HARK) 599 (Carl Zeiss AG, Jena, Germany), distance-corrected visual acuity, intraocular pressure (Nidek NT-2000; Nidek Co., Gamagori, Japan), and nonmydriatic fundus photography (Visucam PRO NM; Carl Zeiss Meditec AG) performed by a qualified ophthalmologist.

Fundus Photography

Fundus photography was performed in a darkened room with nonpharmacologically dilated pupils, including a 30° image of the macula. The right eye was imaged first. Regular data quality control was conducted.[18]

Photographic Grading of Age-Related Maculopathy

All fundus photographs were graded by an experienced ophthalmologist (H.E.) under supervision of an experienced senior grader (T.P.) according to the classification system of the Rotterdam Eye Study.[19] Fundus photographs were graded regarding presence or absence of AMD within a radius of two disc diameters distance from the fovea (Supplementary Table S1). Absence of AMD was graded as stage 0. AMD-associated changes in the macula were classified as early and late maculopathy. Early AMD included stage 1 (soft, distinct drusen [≥63 μm] only or pigmentary abnormalities only, no soft drusen [≥63 μm]); stage 2 (soft, indistinct drusen [≥125 μm] or reticular drusen only or soft, distinct drusen [≥63 μm] with pigmentary abnormalities); and stage 3 (soft, indistinct [≥125 μm] or reticular drusen with pigmentary abnormalities).[18] Late AMD comprises neovascular or atrophic changes (stage 4) of AMD. Other lesions that were suspected not to be the result of AMD but of other generalized or vascular diseases like retinal vein occlusion, diabetic maculopathy, myopic degeneration, trauma, macular pucker, or chorioretinitis were classified separately (stage 5) and excluded from AMD analysis. In accordance with the classification of the International AMD Epidemiology Study Group, small, hard drusen are not judged to be an AMD diagnosis.[20] Prevalence data were determined per participant. If different stages of AMD were detected between the right and left eye, the worse stage defined the classification. If a nonspecific maculopathy was observed only in one eye, this was classified as being unrelated to AMD.[18] Incident AMD was defined as newly detected AMD in at least

one eye at the 5-year follow-up period with AMD stage 0 at baseline in both eyes.

Covariates

Several covariates were investigated that were reported to be linked to AMD in medical literature.[2–4] Arterial hypertension was diagnosed in cases of one of the following: intake of antihypertensive drugs, mean systolic blood pressure ≥140 mm Hg or mean diastolic blood pressure ≥90 mm Hg on three consecutive measurements at rest, or diagnosis of arterial hypertension by a physician. Obesity was defined by a body mass index (BMI) ≥30 kg/m^2. Self-reported smoking status was dichotomized into current smoking and nonsmoking (including former smoking).

Standard laboratory measurements were carried out at the Institute of Clinical Chemistry and Laboratory Medicine, University Medical Center of the Johannes Gutenberg University Mainz. Venous blood sampling was performed according to standard operating procedures while the subject was in fasting state (i.e., overnight fast if the subject was examined before 12 AM and 5-hour fast if the subject was examined after 12 AM). Laboratory measurements were performed of low-density lipoproteins (mg/dL), high-density lipoproteins (mg/dL), and triglycerides (mg/dL). Family history as a proxy for genetic susceptibility was assessed with the questionnaire item "Do you know of any AMD cases among your parents or siblings?" The socioeconomic status (SES) was defined according to the SES-index as used within the German Health Update 2009 (GEDA) with a range from 3 to 21 (3 indicates the lowest SES and 21 the highest SES).[21]

Statistical Analysis

All data were quality controlled by a central data management unit and checked for completeness and correctness. A predefined statistical analysis plan was developed. The primary outcome measures of this analysis were the prevalence of AMD: (a) any type of AMD, (b) early stage of AMD, (c) late stages of AMD, and (d) 5-year cumulative incidence of AMD.

Descriptive statistics included absolute and relative frequencies for dichotomous parameters, mean and standard deviations for approximately normally distributed data, and otherwise median and interquartile ranges. Regarding nonresponder analysis, we analyzed the difference between subjects reporting birth weight and having AMD grading and subjects with missing data. The birth weight data distribution of our cohort was compared to distributions reported in medical literature and governmental data.[14,22] Poisson regression analysis was performed assessing the association of the different birth weight groups (birth weight <2500 g, birth weight between 2500 and 4000 g, birth weight >4000 g) with the binary variables AMD, early AMD, late AMD, and incident AMD. In model 1, the main outcome measures were tested in a univariate analysis with birth weight as independent variable; in model 2 these measures were adjusted for age (years) and sex (female); in model 3 adjustments for age (years), sex (female), SES, smoking (yes), arterial hypertension (yes), BMI (kg/m^2), refraction (spherical equivalent in diopter), low-density lipoprotein (mg/dL), high-density lipoprotein (mg/dL), and triglycerides (mg/dL) were performed, as reported in medical literature.[2–4] These associations are described as prevalence ratios (PRs) and respective risk ratios (RRs) with 95% confidence intervals (CIs). In addition, a potential association of birth weight as continuous variable with AMD using a quadratic term for birth weight was tested, as initial descriptive analysis showed a higher prevalence for low and high birth weight. This led to 24 initially planned models. A sensitivity analysis was performed using logistic regression analysis instead of Poison regression. As this was an explorative study, *P* values should be regarded as a continuous parameter reflecting the level of evidence and are therefore reported exactly. Data were analyzed with R version 3.3.1 (R Core Team (2016), R: A language and environment for statistical computing, R Foundation for Statistical Computing, Vienna, Austria; https://www.R-project.org/; in the public domain).

Results

Participant Characteristics

The analysis sample included 6492/15,010 study participants with data on birth weight and AMD grading at baseline. Of these, 4144/6492 had additional AMD grading at 5-year follow-up and were included in the incidence analysis sample (Supplementary Fig. S1). Participant characteristics such as sex, age, birth weight, SES, smoking, arterial hypertension, and cardiovascular parameters are presented in Table 1. Mean age of all study participants was 50.7 ± 10.4 years, and 54.5% (3538) were female. Most of the participants were white (98.6%). Overall, 358 of all participants reported a birth weight below 2500 g (group 1), 5328 participants reported a birth weight between 2500 g and 4000 g (group 2), and 806 participants reported a birth weight above 4000 g (group 3).

Nonresponder Analysis

Overall, 6588/15,010 (43.9%) GHS participants did not report birth weight. Consequently, for 8422/15,010 (56.1%) participants, self-reported birth weight data were available, and for 6532/15,010 (43.5%), birth weight data and AMD grading were documented at baseline. Furthermore, 40/15,010 (0.3%) were excluded because of birth weight <1000 g or >6000 g. Of the 6492/15,010 (43.3%) participants included at baseline, 4144/15,010 (27.6%) had successful AMD grading at 5-year follow-up (Supplementary Fig. S1). The nonresponder analysis showed that study participants with self-reported birth weight were rather younger, with a slightly lower AMD prevalence and incidence being sex- and age-related (Supplementary Table S2). Furthermore, study participants in the analysis sample (having data on birth weight and AMD grading) were slightly younger than participants with self-reported birth weight and missing AMD grading (Supplementary Table S3). With respect to the incidence analysis sample, study participants without 5-year follow-up were slightly older and more often female compared to participants with 5-year follow-up (Supplementary Table S4).

Description of AMD Prevalence and Incidence

The prevalence of AMD (overall) was descriptively highest in the low birth weight group 11.2% (40/358) compared to 6.5% (346/5328) in the normal birth weight group and 8.4% (68/806) in the high birth weight group.

Early AMD was also descriptively highest in the low birth weight group 10.7% (38/358) compared to 6.2% (331/5328) in the normal birth weight group and 8.1% (65/806) in the high birth weight group (Table 1). Late AMD prevalence was low in all three groups, with a prevalence in the low birth weight group of 0.6% (2/358) compared to 0.3% (15/5328) in the normal birth weight group and 0.4% (3/806) in the high birth weight group.

Five-year cumulative incidence of AMD was 3.8% (8/358) in the low birth weight group, 1.5% (52/5328) in the normal birth weight group, and 1.8% (9/806) in the high birth weight group.

Table 1. Characteristics of the Gutenberg Health Study Sample. Study Participants With Birth Weight Data and AMD Grading ($n = 6492$) for the Total Cohort and Separated on Birth Weight Group. Mean ± Standard Deviation

Variable	All, 6492	<2.5 kg, 358	2.5–4.0 kg, 5328	>4.0 kg, 806
Sex (women)	54.5% (3538)	69.8% (250)	56.2% (2995)	36.4% (293)
Age, y	50.7 ± 10.4	52.5 ± 10.9	50.4 ± 10.3	52.3 ± 10.4
SES[A]	13.7 ± 4.3	13.0 ± 4.1	13.7 ± 4.3	13.5 ± 4.5
Obesity (yes)	23.3% (1514)	24.0% (86)	22.4% (1191)	29.4% (237)
Body mass index, kg/m^2	26.2 (23.4/29.7)	26.0 (22.9/29.7)	26.0 (23.3/29.5)	27.4 (24.7/30.7)
Smoking (yes)	21.0% (1363)	19.3% (69)	20.7% (1103)	23.7% (191)
Hypertension (yes)	40.7% (2640)	42.7% (153)	40.0% (2128)	44.5% (359)
Low-density lipoprotein, mg/dL	138.1 ± 35.3	139.6 ± 34.1	137.9 ± 35.5	138.4 ± 34.4
High-density lipoprotein, mg/dL	57.9 ± 15.6	59.7 ± 16.4	58.3 ± 15.7	54.7 ± 14.1
Triglycerides, mg/dL	100.0 (74.0/141.0)	102.0 (74.0/145.0)	99.0 (74.0/139.0)	106.4 (76.0/152.3)
Birth weight				
Birth weight, g	3401 ± 646	2014 ± 380	3329 ± 400	4490 ± 404
Low birth weight <1500 g (yes)	0.5% (31)	8.7% (31)	0% (0)	0% (0)
High birth weight >5000 g (yes)	0.8% (54)	0% (0)	0% (0)	6.7% (54)
Ophthalmologic parameters				
Visual acuity (logMAR)	0 (0/0.10)	0 (0/0.10)	0 (0/0.10)	0 (0/0.10)
Spherical equivalent (diopter)	−0.12 (−1.12/0.75)	−0.12 (−1.62/0.75)	−0.12 (−1.25/0.62)	0.12 (−0.75/0.88)
Intraocular pressure, mm Hg	14.2 ± 2.8	14.2 ± 3.0	14.2 ± 2.7	14.2 ± 2.9
Age-related macular degeneration				
Family history of AMD (yes)	5.0% (322)	4.5% (16)	4.9% (262)	5.5% (44)
AMD, OD (yes)	5.1% (332)	8.4% (30)	4.7% (249)	6.6% (53)
AMD, OS (yes)	4.7% (302)	6.4% (23)	4.4% (237)	5.2% (42)
Early AMD, OD (yes)	4.9% (317)	7.9% (28)	4.5% (238)	6.3% (51)
Early AMD, OS (yes)	4.4% (287)	6.2% (22)	4.2% (225)	5.0% (40)
Late AMD, OD (yes)	0.2% (15)	0.6% (2)	0.2% (11)	0.3% (2)
Late AMD, OS (yes)	0.2% (15)	0.3% (1)	0.2% (12)	0.3% (2)
AMD incidence (yes)	1.7% (69)	3.8% (8)	1.5% (52)	1.8% (9)

OD, right eye; OS, left eye; SES[A], socioeconomic status, calculated using the German Health Update 2009,[21] which ranges from 3 (lowest SES) to 21 (highest SES).

Analysis for Birth Weight Categorized Into Low, Normal, and High Birth Weight

Prevalence of Any Type of AMD. The low birth weight group showed a higher AMD prevalence at baseline (model 1 [univariate]: birth weight <2500 g: PR = 1.72 [95% CI: 1.26–2.34] $P = 0.001$) and after adjustment for age and sex (model 2: birth weight <2500 g: PR = 1.52 [95% CI: 1.13–2.06] $P = 0.006$) and after adjustment for additional potential confounders (model 3: birth weight <2500 g: PR = 1.54 [95% CI: 1.13–2.09] $P = 0.006$). A univariate association was observed between high birth weight and AMD prevalence (model 1: birth weight >4000 g: PR = 1.30 [95% CI: 1.01–1.67] $P = 0.040$), but this association was not observed after adjusting for age and sex (model 2) or other potential confounders (model 3) (Table 2).

Prevalence of Early AMD. Study participants with low birth weight showed a higher prevalence of early AMD than those with normal birth weight in univariate analysis (model 1: birth weight <2500 g: PR = 1.71 [95% CI: 1.25–2.36] $P < 0.001$) and after adjustment for age and sex (model 2: birth weight <2500 g: PR = 1.51 [95% CI: 1.11–2.07] $P = 0.009$) and other potential confounders (model 3: birth weight <2500 g: PR = 1.52 [95% CI: 1.11–2.08] $P = 0.010$) (Table 2).

A univariate association was observed between high birth weight and prevalence of early AMD (model 1: birth weight >4000 g: PR = 1.30 [95% CI: 1.01–1.68] $P = 0.044$), but this association was not observed after adjusting for age and sex (model 2) or other potential confounders (model 3) (Table 2).

Prevalence of Late AMD. Low birth weight was not significantly associated with the prevalence of late AMD (models 1–3). Similarly, high birth weight was not significantly associated with the prevalence of late AMD (models 1–3) (Table 3) either.

Five-Year Cumulative Incidence of AMD. Study participants with low birth weight showed a higher risk for AMD at 5-year follow-up compared to normal birth weight in univariate analysis (model 1: birth weight <2500 g: RR = 2.43 [95% CI: 1.17–5.05] $P = 0.017$). After adjustment for potential confounders in model 2 and model 3, no significant association was observed. Furthermore, study participants with high birth weight did not have an altered risk for AMD (Table 3).

Birth Weight as a Continuous Variable

No association of birth weight as continuous variable with AMD prevalence (overall, early AMD, late AMD) and with 5-year cumulative incidence was observed, either in the univariate analysis (model 1) or in the multivariable models 2 and 3 (Supplementary Tables S5, S6). When including an additional quadratic term for birth weight (continuously), the analysis showed that overall and early prevalence of AMD was inversely related to the linear term and positively to the quadratic term, but no association was observed for late AMD and 5-year cumulative incidence in the multivariable models (Supplementary Tables S7, S8). In the Figure, the association of birth weight and the predicted probability for AMD is displayed.

Sensitivity Analysis

Sensitivity analysis with logistic regression analysis instead of Poison regression showed similar results.

Table 2. Associations of Overall and Substages of AMD Prevalence With Birth Weight Groups in the Gutenberg Health Study†

	Model 1		Model 2		Model 3	
	PR (95% CI)‡	*P*	PR (95% CI)§	*P*	PR (95% CI)||	*P*
Overall AMD						
Birth weight <2500 g*	1.72 (1.26–2.34)	0.001	1.52 (1.13–2.06)	0.006	1.54 (1.13–2.09)	0.006
Birth weight 2500–4000 g*	Reference		Reference		Reference	
Birth weight >4000 g*	1.30 (1.01–1.67)	0.040	1.11 (0.87–1.42)	0.42	1.15 (0.89–1.48)	0.28
Early AMD						
Birth weight <2500 g*	1.71 (1.25–2.36)	<0.001	1.51 (1.11–2.07)	0.009	1.52 (1.11–2.08)	0.010
Birth weight 2500–4000 g*	Reference		Reference		Reference	
Birth weight >4000 g*	1.30 (1.01–1.68)	0.044	1.11 (0.86–1.43)	0.42	1.15 (0.89–1.48)	0.29
Late AMD						
Birth weight <2500 g*	2.08 (0.48–9.07)	0.33	2.07 (0.48–8.95)	0.33	3.37 (0.92–12.32)	0.066
Birth weight 2500–4000 g*	Reference		Reference		Reference	
Birth weight >4000 g*	1.35 (0.39–4.65)	0.64	1.09 (0.30–3.97)	0.89	1.23 (0.24–6.19)	0.80

* Low birth weight $n = 358$; normal birth weight $n = 5328$; high birth weight group $n = 806$.

† Poisson regression analysis was performed assessing the association of the different birth weight groups with the binary variables AMD prevalence (any type), early AMD, and late AMD.

‡ Model 1: crude model without adjustment.

§ Model 2: adjusted for sex, age.

|| Model 3: adjusted for sex (female), age (years), SES, smoking (yes), arterial hypertension (yes), body mass index (kg/m^2), refraction (spherical equivalent in diopter), low-density lipoprotein (mg/dL), high-density lipoprotein (mg/dL), triglycerides (mg/dL).

Discussion

This study presents new data of a relationship between low birth weight and AMD prevalence in adulthood. The low birth weight group showed a 70% higher prevalence of AMD compared to the normal birth weight group.

Adverse fetal growth was identified as risk factor for different chronic diseases in adulthood such as coronary heart disease.[6] Low birth weight as an indicator of adverse fetal growth is acknowledged as a decisive risk factor for these diseases. The theory presented by Barker[6,23] first described low birth weight as an indicator of fetal origins for adult cardiovascular disease. Low birth weight leads to multiple morphologic changes of the eye during infancy and childhood,[8,24–26] which may conceivably predispose these individuals to AMD. Our study observed a higher prevalence of AMD in low birth weight compared to normal birth weight individuals. However, as we could not control our analyses for gestational age, it is likely that low birth weight and prematurity contributed together to a potentially increased risk for AMD. We may speculate in accordance with Barker's theory that there may be "fetal origins of adult eye diseases" and former low birth weight and/or premature individuals may show an increased risk for eye diseases in adulthood.

Our unadjusted results are in line with two previous studies showing a higher prevalence of AMD in high birth weight subjects. A UK hospital-based cohort study (Hall et al.[9]) reported that higher birth weight was associated with increased odds of AMD (odds ratio 1.5 [95% CI: 1.1–2.0 for each SD (1 lb, 5 oz) increase in birth weight]) after adjustment for age, sex, and known risk factors for macular degeneration in a cohort of 392 white subjects born between 1922 and 1930. The authors invited twice as many high birth weight subjects as low birth weight subjects. Liew et al.[10] reported in a collective of 4744 participants (aged 45–64 years) that birth weight is not linearly associated with AMD. They further found in a subgroup of white study participants that high birth weight was associated with AMD. These findings are in line with our results indicating that there is more of a U-shape association than a linear relationship. In contrast to our study, all former newborns with a history of prematurity were excluded in the study of Liew et al.,[10] which might have diminished the effect of low birth weight as preterm-born subjects have lower birth weight. In contrast, Sayer et al.[11] reported in an investigation of 717 individuals born between 1920 and 1930 that low birth weight was not related to AMD in later life. An explanation for these varying results might be the different age of study participants and the lower number of study participants compared to our study.

Preterm birth and low birth weight were found to be important parameters for altered development of the macula in childhood.[7,8] Macula formation begins between the 11th to 13th week of gestational age with differentiated cone and retinal pigment epithelial cells.[27] Impaired growth in this

Table 3. Associations of Cumulative 5-Year AMD Incidence for Birth Weight Groups in the Gutenberg Health Study*

	Model 1		Model 2		Model 3	
Incident AMD	RR (95% CI)†	*P*	RR (95% CI)‡	*P*	RR (95% CI)§	*P*
Birth weight <2500 g	2.43 (1.17–5.05)	0.017	1.98 (0.98–3.97)	0.056	1.83 (0.89–3.79)	0.100
Birth weight 2500–4000 g	Reference		Reference		Reference	
Birth weight >4000 g	1.17 (0.58–2.35)	0.67	0.98 (0.49–1.95)	0.95	0.96 (0.48–1.94)	0.92

* Poisson regression analysis was performed assessing the association of the different birth weight groups with the binary variable cumulative 5-year incidence of AMD.

† Model 1: crude model without adjustment.

‡ Model 2: adjusted for sex, age.

§ Model 3: adjusted for sex (female), age (years), SES, smoking (yes), arterial hypertension (yes), body mass index (kg/m^2), refraction (spherical equivalent in diopter), low-density lipoprotein (mg/dL), high-density lipoprotein (mg/dL), triglycerides (mg/dL).

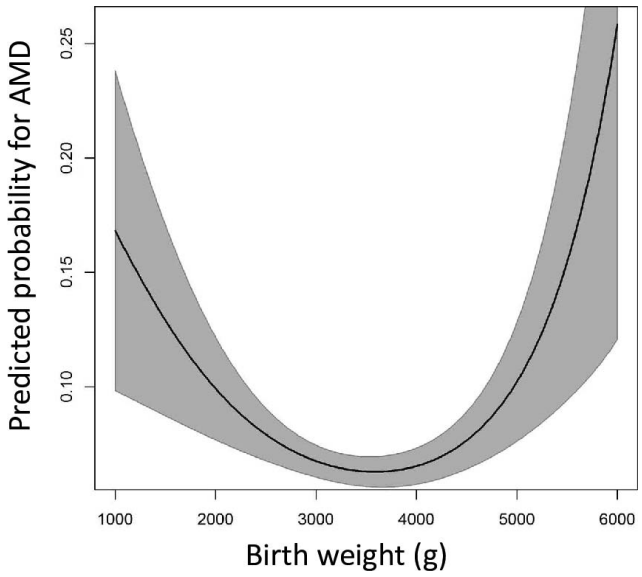

FIGURE. Predicted probability of AMD in correlation to birth weight with 95% confidence intervals. Newborns with low and high birth weight show higher predicted AMD probability compared to normal birth weight newborns in adulthood.

period may affect future organ development and predispose to AMD. Foveal development starts at the 22nd week of gestational age with subsequent opposed retinal migration of inner and outer retinal layers.[28–31] In former preterm low birth weight children, disturbed retinal migration within the fovea was observed.[32] Furthermore, foveal thickening and absence of foveal depression[7,33–36] were reported in former preterm low birth weight individuals in childhood, independently of postnatal occurrence of retinopathy of prematurity (ROP). Even former moderate preterm children showed foveal thickening at an age of 4 to 10 years independent of ROP occurrence.[7] These changes last at least until young adulthood,[37,38] which may indicate that retinal morphologic alterations may persist lifelong.

Functional alterations were reported by Molnar et al.,[39] who observed rod and cone dysfunctions in former preterm children independent of ROP. Because low birth weight newborns are more likely to be preterm, these alterations may also predispose former low birth weight subjects to AMD. However, our analyses reflect the effect of low birth weight in a population rather than the effects of extreme prematurity. Beyond retinal changes, other authors reported choroidal thinning in the macula in former low birth weight children.[8] The choroid provides nutrition and oxygen for the outer segment of the retina and a thinner choroid is observed in subjects with AMD.[40] Therefore, the observed higher risk for AMD in subjects with low birth weight might be associated with choroidal microinsufficiency.

Despite the increased PRs and RRs for AMD in this study, the clinical relevance is still unclear particularly because the association between low birth weight and AMD was predominantly found for early AMD stages. However, late AMD also showed a positive association with low birth weight, although a nonsignificant one, and the fact that AMD incidence is also positively, although weakly, associated with low birth weight may be another indication for the association of low birth weight and AMD. The lack of a statistically significant association of low birth weight with late AMD changes may be due to low case numbers because in total only 0.4% of all examined eyes showed late AMD. Consequently, it is unknown if low birth weight may also be associated with severe AMD with possible need for therapy. However, our data indicate that fetal origins of adverse growth and/or associated factors for which birth weight is a proxy are linked to pathophysiological mechanisms that may lead to AMD in adulthood. Future studies are needed for confirmation of this explorative finding.

Strengths and Limitations

One major restriction of this study is that only 56.1% of all subjects remembered their birth weight, and in a considerable number of participants AMD grading was not possible at baseline or 5-year follow-up examination. Consequently, a potential selection bias due to missing data and loss-to-follow-up data cannot be ruled out and has to be discussed as a potential selection bias. The distribution of birth weight in our cohort was comparable to governmental data documented for the early 1970s[22] as we reported earlier.[14] Assessing birth weight data via self-reported information is the only practical means of getting birth weight data in epidemiological studies.[41] Furthermore, we excluded 40 participants of our analysis with birth weight below 1000 g and above 6000 g because these data were suspected to be unreliable.

A considerable restriction of our analyses is the lack of data for gestational age and the unknown postnatal status of ROP in all subjects. We therefore cannot differentiate the effects of prematurity and low birth weight and, as a consequence, we cannot differentiate between low, appropriate, or large birth weight corresponding to gestational age. In addition, our population-based approach may reflect the effect of low birth weight while the effects of extreme prematurity may differ as only very few of those subjects were included. As low birth weight is associated with cardiovascular risk factors and cardiovascular diseases,[6,42] we adjusted for those parameters, as AMD is more likely in subjects with those risk factors as well. In addition, we cannot rule out the possibility of a chance finding and therefore listed the number of preplanned models. As there were only few incident cases in low and high birth weight groups, we cannot differentiate between true confounding by covariates and loss of statistical power.

This study has several strengths—first, the large sample size and the population-based study design. Second, all examinations were strictly standardized and all study examiners were masked to subjects' low birth weight. Third, each participant was asked at study invitation to review his or her personal records or family album for birth weight documentation. As a consequence, we assume good reliability of birth weight information, as shown in an Australian twin study. The investigators reported an intraclass correlation coefficient of 0.98 (95% CI 0.97–0.98) between self-reported birth weight data and medical records.[43]

Summary

In summary, we report that low birth weight is associated with a higher prevalence of AMD. This may indicate that the risk for AMD has one of its origins in early life, which may be important in the long-term care of low birth weight subjects.

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