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Birth weight and diabetic retinopathy: Results from the population-based Gutenberg Health Study (GHS)

Achim Fieß (MD)¹, Julia Lamparter (MD)^{1,2,3}, Philipp Raum^{1,2}, Tunde Peto (MD)^{2,3}, Katharina A. Ponto (MD)¹, Stefan Nickels¹(MD, MSc), Thomas Münzel⁵(MD), Philipp S. Wild^{6,7,8}(MD), Manfred E. Beutel⁹(MD), Michael S. Urschitz¹⁰, (MD), Karl J. Lackner¹¹(MD), Norbert Pfeiffer¹ (MD), Alexander K. Schuster¹ (MD, MSc)

¹ Department of Ophthalmology, University Medical Center of the Johannes Gutenberg University Mainz, Mainz, Germany

² NIHR Biomedical Research Center at Moorfield's Eye Hospital NHS Foundation Trust and UCL Institute of Ophthalmology, London, United Kingdom

³ Augenzentrum Leinfelden-Echterdingen, Leinfelden-Echterdingen, Germany

⁴ Queen's University Belfast, Centre for Public Health, Northern Ireland, United Kingdom

⁵ Center for Cardiology – Cardiology I, University Medical Center of the Johannes Gutenberg University Mainz, Mainz, Germany

⁶ Preventive Cardiology and Preventive Medicine / Center for Cardiology, University Medical Center of the Johannes Gutenberg University Mainz, Mainz, Germany

⁷ Center for Thrombosis and Hemostasis (CTH), University Medical Center of the Johannes Gutenberg University Mainz, Mainz, Germany

⁸ German Center for Cardiovascular Research (DZHK), partner site Rhine-Main, Mainz, Germany

⁹ Department of Psychosomatic Medicine and Psychotherapy, University Medical Center of the Johannes Gutenberg University Mainz, Mainz, Germany

¹⁰ Division of Biostatistics and Bioinformatics, Institute for Medical Biostatistics, Epidemiology and Informatics, University Medical Center of the Johannes Gutenberg University Mainz, Mainz, Germany

¹¹ Institute of Clinical Chemistry and Laboratory Medicine, University Medical Center of the Johannes Gutenberg University Mainz, Mainz, Germany

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Corresponding author:

Achim Fieß, M.D.

Department of Ophthalmology

Medical Center of the Johannes Gutenberg University Mainz

Langenbeckstr. 1

55131 Mainz

Germany

Tel. +49-(0)6131-17-5150

Fax. +49-(0)6131-17-8495

E-Mail: achim.fiess@gmail.com

<https://orcid.org/0000-0002-3867-2350>

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Abstract

Purpose

This study investigates the relationship between diabetic retinopathy (DR) and birth weight (BW) in diabetic subjects sampled from the general population.

Methods

The Gutenberg Health Study (GHS) is a population-based, observational cohort study in participants aged from 35 to 74 years. Criteria for diabetes diagnosis were HbA1c $\geq 6.5\%$ at study entry, a doctor-diagnosis of diabetes, or diabetes medication. The presence of DR was determined by evaluating fundus photographs. BW was assessed by self-reports. GHS participants were divided into three different BW groups (low:<2500g; normal:2500-4000g; high:>4000g). Logistic regression analysis was conducted as uni- and multivariable analysis with adjustment for age and sex. Effect mediators were separately investigated.

Results

A total of 1,124 GHS participants (7.5% of the cohort) had diabetes at study entry. Of these, 402 subjects (35.8%) had gradable fundus photographs, reported BW data and were included into this study. Overall, 91/402 subjects (23%) had DR. With regard to BW groups, DR was descriptively more frequent in subjects with low (28.1% [95%-CI: 14.4% - 47.0%; n=32]) and high BW (30.8% [95%-CI: 19.1% - 45.3%; n=52]) compared to normal BW (20.8% [95%-CI: 16.5% - 25.7%; n=318]). Both, high and low BW were associated with DR in multivariable analysis (high: OR=1.68, p=0.037; low: OR=1.81, p=0.05). The BW effect was mediated by duration of diabetes in both BW groups and by arterial hypertension in the low BW group.

Conclusion

Low and high BW in persons with diabetes is related to higher risk of diabetic retinopathy. Longer duration of diabetes and higher prevalence of arterial hypertension are factors in these subjects explaining the elevated risk.

Key words:

birth weight, diabetes, diabetic retinopathy, epidemiology, population-based study

Introduction

The high prevalence of diabetes in adulthood is a global burden and has socioeconomic impact particularly because diabetic eye disease is a major cause of blindness in working individuals ¹. Examining the retina mirroring the vasculature system, allows to detect end-organ damage of the underlying diabetic disease at an early stage. To avoid other systemic damage (i.e. nephropathy) and vision loss, screening on population-level is conducted to detect sight-threatening DR in asymptomatic patients.. Screening intervals are based on stage of DR and its risk factors. DR risk factors include age, duration of diabetes, systolic blood pressure, HbA1c-level, creatinine-level in serum and albumin-level in urine ² as well as a genetic predisposition ³. However, the underlying mechanisms are not fully understood, yet.

One factor for an increased risk for DR might be abnormal birth weight. Former low and high birth weight newborns are at increased risk for cardiac disease, metabolic syndrome and diabetes in later life ⁴⁻⁷. Furthermore, it is assumed that intrauterine malnutrition is linked to altered ocular organ development until adulthood ⁸. A fetal origin of adult eye diseases is therefore reasonable. However, up to date it is unclear whether low or high birth weight is an independent risk factor for DR.

Two studies exist assessing the relationship between birth weight and advanced stage of DR ^{9,10}, none of these previous reports observed a clear association. While Agardh et al. ¹⁰ analysed a smaller sample of young individuals with type 1 diabetes, Fagerudd et al. ⁹ examined a large sample of type 1 diabetic patients with respect to a history of retinal laser photocoagulation.

Liew et al. evaluated a sample of subjects with type 2 diabetes in the Atherosclerosis Risk in Community Study from the U.S. and reported no association between birth weight and DR after adjustment for potential confounders ¹¹. Interestingly, in this study in the early 1990s the prevalence of persons with type 2 diabetes was 15%, which is two-times higher than the prevalence reported by the German Gutenberg Health Study for diabetes ¹² indicating its regional variability. In addition, this analysis excluded individuals reporting premature birth.

Overall, due to the numerous long-lasting biological changes caused by low and high birth weight and alterations of retinal vasculature in former low birth weight adults ¹³, we investigated the association between birth weight and DR in a population-based sample of diabetic persons. We hypothesized that abnormal birth weight - low and high – may affect the likelihood of DR in diabetic persons.

Materials and methods

Study population

The Gutenberg Health Study (GHS) is a single-center, population-based, prospective cohort study in midwestern Germany. For the GHS, 15,010 participants aged between 35 and 74 years were examined at baseline between 2007 and 2012. The study sample was stratified for gender and decades of age. The recruitment efficacy proportion was 60.8%. All participants underwent a comprehensive ophthalmological and complete general examination focusing on cardiovascular and psychosomatic parameters as well as laboratory and genetic analyses. A detailed study protocol was reported earlier^{12,14}.

Inclusion criteria and self-reported birth weight data

For the present cross-sectional analysis, all study participants with diabetes were included. Diabetes mellitus was defined if one of the following criteria were met: history of diagnosis of diabetes mellitus by a physician, history of dietary, oral or insulin therapy for diabetes mellitus, or HbA1c $\geq 6.5\%$ at study entry. All individuals were requested at study invitation to look up personal records or family albums for documented birth weight data. Subjects were categorized in accordance to self-reported birth weight information in group #1 with birth weight below 2,500 g (low), in group #2 with birth weight between 2,500 g and 4,000 g (normal), and in group #3 with birth weight above 4,000 g (high) as reported earlier^{8,15-18}. We excluded participants with birth weight $< 1,000$ g and > 6000 g, as these data were suspected to be invalid.

Assessment of fundus photographs and imaging

Fundus photographs were assessed after an adaptation in a darkened room by a non-mydratic fundus camera (Visucam PRO NM, Carl Zeiss AG, Jena, Germany) without pharmacological dilation of the pupils. Retinal examination included one photograph of the macula (30 degree) and two photographs centred on the optic nerve (30 and 45 degree). Grading of these retinal images was performed by two investigators, who were masked to birth weight and clinical data (JL and PR). Depending on these fundus photographs, grading of DR and of its sub-stages was conducted in accordance with the Early Diabetic Retinopathy Study¹⁹ as mild (presence of hard/soft exudate, microaneurysm, retinal haemorrhage, venous beading), moderate (when a combination of two characteristics of mild non-proliferative DR was present), severe non-proliferative (when at least microaneurysm/retinal haemorrhage in 4 quadrants, venous beading in 2 quadrants, intraretinal microvascular anomaly in 1 quadrant was observed), or as proliferative DR (when laser scars, neovascularisation at disc or elsewhere, subhyaloidale haemorrhage or vitreous haemorrhage where visible) as reported earlier²⁰. In the case of fellow eyes with different stages of DR, the eye with the most progressed DR stage was selected for the identification of persons' stage of disease for descriptive purposes. In the analytical

statistics, both eyes of a study participant were included. Participants without fundus photographs or with fundus photographs of inadequate quality were excluded.

Additional measurements and cardiovascular risk factors

Within the GHS, several cardiovascular risk factors were assessed that were potentially associated with DR, namely: (1) mean arterial blood pressure (mmHg); (2) arterial hypertension, defined as median blood pressure of >140/90mmHg of several measurements after rest or a physician's diagnosis or intake of blood-pressure medications; (3) mean assessment of body mass index (kg/m²); (4) HbA1C levels; (5) duration since diabetes onset (years); (6) treatment for diabetes (yes); (7) level of low and high density lipoproteins (mg/dl); (8) triglyceride level (mg/dl); (9) smoking (yes); (10) spherical equivalent (diopter).

Statistical analysis

Data were quality-controlled by a central data management unit, which checked the database for completeness and correctness. Primary outcome was any type of DR in A) all diabetic participants, B) screening-detected diabetic participants and C) already diagnosed diabetic participants. For each parameter descriptive statistics were calculated including absolute and relative frequencies for dichotomous parameters, mean and standard deviations for approximately normal distributed variables, and otherwise, median and interquartile ranges. We performed an item non-responder analysis assessing the difference between participants with available birth weight information and DR-grading and subjects with missing data. Self-reported birth weight data were compared to the medical literature and to data of the German Federal Statistical Office as reported earlier ^{16,21}. Logistic regression analysis using generalized estimating equations to incorporate two eyes of one subject was performed assessing the association of the three birth weight groups (birth weight < 2500 g, birth weight between 2500 and 4000 g, birth weight > 4000 g) with the primary outcome diabetic retinopathy (no/yes). An additional logistic regression analysis was performed incorporating birth weight as a continuous variable using a linear and a quadratic term. A priori, potential confounders were identified by literature search. In model #1, the relationship with DR was investigated with birth weight as independent variable; in model #2 the same relationship was adjusted for age (years) and gender (male/female); in model #3 the relationship was adjusted for age (years), sex (female), arterial hypertension (yes), BMI (kg/mm²), HbA1c, diabetes duration (years), diabetes treatment (yes), smoking (yes), spherical equivalent of the more myopic eye (diopter). A mediation analysis was performed after development of a directed acyclic graph ²² (supplemental figure 1). For this purpose, diabetes duration, arterial hypertension (yes/no), HbA1c-level and spherical equivalent were

separately included into model #2 and the change of the birth weight association was observed. In addition, we conducted mediation analysis as proposed by Rijnhart et al. 2019²³ and calculated mediated proportion based on multiple regression analysis.

Odds ratios (ORs) and their 95 % confidence intervals (CIs) were computed. A sub-group analysis was performed with the inclusion of only screening-detected diabetic study participants and of those with an already known diagnosis. Data were analyzed with R version 3.5.2 (R Core Team (2018). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL <https://www.R-project.org/>).

Results

Participants

A total of 1,124 study participants had diabetes. Of these, 631 (56.1%) reported birth weight. 402 (35.8%) subjects had both, birth weight data and successful fundus photography grading. Of these, 22.6% (91/402) had DR. Overall, 14.9% (n=60) had mild non-proliferative diabetic retinopathy (NPDR), 2.7% (n=11) had moderate NPDR, 2.0% (n=8) severe NPDR and 3.0% (n=12) proliferative diabetic retinopathy. Mean age of the analysis sample was 60.1 ± 9.4 years and 42.3% were female. 32 (8.0%) participants reported of a birth weight below 2,500 g (group 1), 318 (79.1%) a birth weight between 2,500 g and 4,000 g (group 2), and 52 (12.9%) a birth weight above 4,000 g (group 3). Baseline results across the different birth weight groups are shown in Table 1. Of the 402 diabetic subjects, 114 (28.4%) were newly diagnosed with diabetes at the GHS study examination (screening detected). Baseline characteristics of screening detected diabetic study participants and of those with an already known diagnosis are presented in supplementary Table 1 and 2.

Item non-responder analysis

The comparison of participants with self-reported birth weight and DR grading compared to participants without both data showed small differences regarding age and gender. Those with available birth weight data were younger and more often female compared to item non-responder.

DR and birth weight

With respect to stages of DR, subjects with no DR had a mean birth weight of 3341 ± 715 gram, with mild DR 3259 ± 768 gram, with moderate DR 3491 ± 673 gram, with severe DR 3515 ± 1061 gram and

with proliferative DR 3689 ± 864 gram. Diabetic subjects with high and low birth weight had a descriptively longer diabetes duration (normal birth weight group: median (interquartile range): 3.0 (0.0; 9.0); low birth weight: 8.5 (2.0; 10.0); high birth weight: 5.0 (0.0; 10.0); $p=0.07$) in our analysis sample.

Associations with birth weight as categorical variable

Logistic regression analysis revealed, that study participants with high birth weight were more likely to have DR in a univariate model #1 (BW > 4000 g: OR =1.73; 95%-CI: 1.06 - 2.81; $p=0.027$) and after adjustment for age and gender (model #2: BW > 4000 g: OR =1.68; 95%-CI: 1.03 - 2.73; $p=0.037$) compared to normal birth weight subjects. Low birth weight individuals revealed a tendency to an increased odd for DR in univariate analysis (model #1: BW < 2500 g: OR =1.78; 95%-CI: 0.98 – 3.22; $p=0.058$) and after adjustment for age and gender (model #2: BW < 2500 g: OR =1.81; 95%-CI: 1.00 – 3.30; $p=0.050$) (Table 2). We furthermore conducted association analysis of DR with birth weight groups adjusted for potential effect mediators (Table 3). In both birth weight groups, the effect was partly mediated (crude proportion mediated based on multiple regression) by diabetes duration (change in effect size: 70% for low birth weight and 24% for high birth weight). In the low birth weight group, both, arterial hypertension (29%) and diabetes control (as indicated by HbA1c-level; 49%) partly mediated the effect of birth weight on DR.

Associations with birth weight as continuous variable

The analysis of birth weight as deviation from the sample mean as continuous variable revealed a relationship between its linear and quadratic term (in model #1 (OR =1.19 per kg deviation; 95%-CI: 1.00 – 1.41; $p=0.046$) and model #2 (OR =1.19; 95%-CI: 1.00– 1.42; $p=0.045$)) (Table 4). No association was present when only including the linear term of birth weight (data not shown).

Discussion

This analysis reports new results about an increased DR frequency in low and in high birth weight diabetic persons. ~~Th~~These data indicates that there are fetal origins in these individuals contributing to an increased risk for diabetic retinopathy. is association is mediated by longer diabetes duration and arterial hypertension.

Only few studies have investigated the association of birth weight and DR, and these studies focused on severe DR. Agardh et al.¹⁰ retrospectively compared 27 type 1 diabetic patients with progressed retinopathy and photocoagulation treatment for early onset of severe non-proliferative or proliferative retinopathy to 22 type 1 diabetic patients with mild retinopathy. Both groups were matched for age, age at onset of diabetes and duration of diabetes. Analyzing birth weight and birth weight percentiles did not result in a difference between these two groups. Fagerudd and colleagues⁹ analysed 1,543 Finnish patients with type 1 diabetes and compared low (< 10 percentile), normal (10 -90 percentile) and high (>90 percentile) birth weight subjects. They found no difference in laser-treated retinopathy in their study. Nevertheless, these studies are not comparable with our study, as we did not focus only on advance stages of DR in a patients' sample, but on any DR in a population-based sample. Liew et al.¹¹ analysed 609 adult subjects with type 2 diabetes of the population-based Atherosclerosis Risk in Communities Study in the U.S. Despite the fact that the authors found no association in multivariable analysis, the prevalence of DR was highest in the low (21.9%) and high (23.5%) birth weight group compared to the prevalence estimates of the normal birth weight groups (15.9% – 18.8%) which may support our findings. The mean age of the diabetic study participants was comparable to our investigation, nevertheless the diabetes prevalence in the original study cohort was twice as high as in our sample. However, the authors differentiated between the presence of any retinopathy and separately analyzed microaneurysms, hemorrhages, hard exudates and cotton wool spots. Our analyses focused on other aspects, when analyzing different non-proliferative and proliferative stages of DR. Overall, the increased frequency of DR in low and high birth weight persons with diabetes in univariate analysis could be explained by longer diabetes duration. Multivariable analysis did not provide evidence for birth weight as an independently associated risk factor and are therefore in line with these previous reports.

The potential mechanisms underlying our results are still under debate. In recent years the amount of newborn individuals with high birth weight increased in parallel to an increase of obese mothers giving birth²⁴. Maternal insulin resistance are connected with fetal nutritional development²⁵, leading to fetal hypertrophy independently of gestational diabetes. Furthermore, some authors suggest that metabolic stress during intrauterine development leads to epigenetic alterations, decrease of leptin levels and changes in insulin signaling pathways on cellular level^{26,27}. Furthermore, macrosomic

newborns of obese mothers are at increased risk for diabetes [in later life](#) ²⁸. In accordance, previous [studies](#) [showed](#) that high birth weight is associated with an increased risk for diabetes and obesity ⁷. [Kuchelbauer et al.](#) ²⁹ [observed that high birth weight leads to an earlier onset of diabetes in childhood.](#) [It is well known that a longer duration of diabetes leads to an increased risk for diabetic retinopathy](#) ³⁰. [In congruence, the global diabetic retinopathy study highlighted that longer duration of diabetes is a key risk factor for diabetic retinopathy in diabetic patients](#) ³¹. Consequently, we assume that a potential earlier onset of diabetes and the resulting longer diabetes duration in low and high birth weight individuals may have been one factor – amongst others – contributing to the increased risk for diabetic retinopathy. The longer diabetes duration increases the risk for hyperglycemia-induced vascular damage accompanied by inflammatory processes and retinal neurodegeneration leading to an increased risk of diabetic retinopathy ³². [Different metabolic pathways such as the polyol pathway, advanced glycation end products \(AGEs\) accumulation, the protein kinase C \(PKC\) pathway and the hexosamine pathway](#) ³² [have been described leading to diabetic retinopathy.](#) [With respect to arterial hypertension,](#) [Barker et al.](#) ³³ hypothesized that intrauterine malnutrition affects early organ development in specific time frames contributing to organ alterations and dysfunction in later life accompanied by an increased risk for corresponding diseases; they [described an increased risk for arterial hypertension in former low birth weight subjects in later life](#) ³⁴. [It is well known, that arterial hypertension increases the risk for diabetic retinopathy in subjects with diabetes](#) ^{20,35,36}. [van Leiden et al. observed that patients with diabetes and arterial hypertension have a more than two-fold increased risk for developing diabetic retinopathy within 10 years compared to diabetic individuals with normal blood pressure](#) ³⁷. Arterial hypertension [leads to morphological alterations in the retinal vasculature and can contribute to damages in the capillary bed resulting in an increased risk for diabetic retinopathy](#) ³⁸. [But there might be other aspects in preterm-born subjects leading to an altered retinal vasculature.](#) A recent study [using](#) optical coherence tomography angiography (OCT-A) in former preterm infants showed a smaller or absent foveal avascular zone ³⁹. Therefore it is possible, that low birth weight contributes to pathophysiological pathways predisposing former low birth weight persons with diabetes and to an increased risk of DR. However, our results did not show low birth weight as an independent risk factor for DR.

Strengths and Limitations

A severe limitation of our analysis is the fact that about 43.9% of GHS study participants did not report their birth weight and that several participants had to be excluded due to missing or upgradable fundus photographs. However, the comparison of participants with versus without birth weight data revealed,

that the included persons with diabetes were slightly younger. At study invitation every participating individual was asked to look-up personal records or family album for documented birth weight notes. Sun et al. reported a high reliability of self-reported birth weight and medical record data supporting our approach of using self-reported birth weight data ⁴⁰. Comparing our sample with governmental data of the German Federal Statistical Office of the early 1970 ²¹, birth weight data had a comparable distribution, as presented earlier ¹⁶. In total, 5.5% of all participants with self-reported low birth weight in our cohort was comparable to 6.3% with low birth weight of the population in former western Germany. Furthermore, self-reported high birth weight in 12.6% of the participants in our cohort was comparable to 9.6% in the governmental data of the early 1970s. Nevertheless, we cannot rule out a selection bias: birth weight might be associated with mortality in persons with diabetes. Another limitation is that we do not have data on gestational age and gestational/maternal diabetes. Thus, we cannot differentiate between the effects of prematurity and intrauterine growth retardation and as a result, we cannot investigate the effects of being small or large at birth with consideration of gestational age. Our sample was population-based and individuals with extreme birth weights were rare. A further restriction of our study is that fundus photographs were taken by non-mydriatic fundus photography which could lead to some missing DR lesions and may lead to an underestimate of the true frequency of DR in our cohort and resulted in some ungradable fundus photographs. On the other hand, one of the particular strengths of this study is the large population-based sample size. Furthermore, all examinations were performed in strict standardized operating procedures and graders of fundus photographs were masked for birth weight and other clinical data.

Summary

In conclusion, we observed that persons with diabetes with low and high birth weight are more likely to have DR [which was at least partly mediated by arterial hypertension and longer diabetes duration](#).

Acknowledgements

Declarations

Ethics approval and consent to participate

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). According to the tenets of the Declaration of Helsinki, written informed consent was obtained from all participants prior to entering the study.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Conceived and designed the study: AF, JL, PR, TP, SN, MEB, TM, PSW, KL, NP and AKS, analyzed and interpreted the data: AF, SN, AKS; wrote the paper: AF, critically revised the manuscript: AF, JL, PR, TP, KP, SN, TM, PSW, MEB, MU, KJL, NP, AKS; all authors read and approved the final manuscript.

Access to data, Responsibility and Analysis:

AKS and PSW had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Statistical analyses were performed by AKS.

The analysis presents clinical data of a large-scale population-based cohort with ongoing follow-up examinations. This project constitutes a major scientific effort in which high methodological standards and detailed guidelines for analysis and publication are applied to ensure that scientific analysis is conducted at the highest level. Therefore, the data are not made available to the scientific community outside the established and controlled workflows and algorithms.

To meet the need for the verification and reproducibility of our scientific findings, we offer access to data at the local database in accordance with the ethics vote upon request at any time. The GHS steering committee, which comprises a member of each involved department and the head of the Gutenberg Health Study (PSW), convenes once each month. The steering committee makes decisions regarding internal and external access by researchers and use of the data and biomaterials based on research proposals supplied by the researchers. Interested researchers should submit their requests to the head of the Gutenberg Health Study (Philipp S. Wild; philipp.wild@unimedizin-mainz.de).

More detailed contact information is available at the homepages of the GHS (www.gutenberghealthstudy.org) and the ophthalmic branch of the GHS (www.unimedizin-mainz.de/augenklinik/forschung/gutenberg-gesundheitsstudie.html).

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Supplemental figure 1: Direct acyclic graph for identification of potential confounders and effect mediators of the relation between birth weight and diabetic retinopathy