

# Hypertensive Retinopathy is Not Associated with Low or High Birth Weight – Results from the Population-Based German Gutenberg Health Study

Achim Fieß<sup>1,\*</sup>, Sandra Gißler<sup>1,\*</sup>, Philipp S Wild<sup>2-4</sup>, Karl J Lackner<sup>5</sup>, Thomas Münzel<sup>6</sup>, Matthias Michal<sup>7</sup>, Michael S Urschitz<sup>8</sup>, Norbert Pfeiffer<sup>1</sup>, Alexander K Schuster<sup>1</sup>

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

\*These authors contributed equally to this work

Correspondence: Achim Fieß, Department of Ophthalmology, University Medical Center of the Johannes Gutenberg University Mainz, Langenbeckstr. 1, Mainz, 55131, Germany, Tel +49-6131-17-5150, Fax +49-6131-17-8495, Email Achim.fuess@gmail.com

**Abstract:** This study investigates the association between self-reported birth weight (BW) and the prevalence of hypertensive retinopathy (HR) in a large population-based cohort in Germany, as part of the Gutenberg Health Study (GHS). The study involved analyzing fundus photographs of 6855 participants, aged 35 to 74, to assess signs of HR, classified according to the Mitchell-Wong Classification. The research aimed to explore the correlation between fetal growth restriction indicated by BW and the frequency of HR. The results showed that the frequency of HR did not significantly differ among groups with different BW ranges. In the univariable analysis, HR was initially associated with high BW, but this association disappeared after adjusting for age, sex, and cardiovascular risk factors. No association was found between low BW and HR. The study reveals novel insights as there are no prior population-based studies specifically exploring this association.

**Keywords:** birth weight, hypertensive retinopathy, epidemiology, population-based study

## Introduction

Individuals with low birth weight (BW) are more likely to develop high blood pressure later in life. Although the exact mechanisms underlying these findings remain unclear, many studies have shown that high blood pressure in adulthood is a major risk factor for developing hypertensive retinopathy (HR).<sup>1</sup> As previous findings in this cohort were able to show that extreme BW in both directions is linked to a higher prevalence of diabetic retinopathy,<sup>2</sup> this study aims to assess the frequency of HR and its correlation with fetal growth restriction indicated by self-reported birth weight in a large population-based cohort in Germany.

## Materials and Methods

The Gutenberg Health Study (GHS) is an observational cohort study that aims to gather prospective data from a population-based sample. The study involves analyzing fundus photographs of individuals between the ages of 35 and 74. Various signs of HR were graded according to the Mitchell-Wong-Classification.<sup>3</sup> The measurements were conducted by two examiners, showing a high inter-rater reliability of 0.90. For statistical analysis, HR was dichotomized into “HR present in at least one eye” and HR “not present in any eye”. Birth weight information was obtained via self-reported responses in a questionnaire.

The distribution of low, normal, and high birth weights in our cohort was compared to reported birth weight data in the medical literature and to data of the German Federal Statistical Office. Furthermore, birth weight data reported by a subset of participants born at the University Medical Center Mainz (UMCM) was validated against data recorded in medical charts and birth registries at the UMCM. This comparison showed a strong intraclass correlation coefficient of 0.89 (confidence interval 0.83; 0.92), indicating that the self-reported birth weights are highly accurate.

## Results

A GHS subsample of 6855 participants (3714 females, aged  $51.23 \pm 10.5$  years) with self-reported BW and available grading for HR were assessed. Both univariable and multivariable logistic regression analyses were conducted for linear and categorical birth weight data. The multivariable analysis took into account potential confounding factors such as age, sex, and cardiovascular risk factors that have been previously associated with HR. Adjustments were made to account for these variables and evaluate their impact on the association between BW and HR.

Descriptively, HR-frequency did not differ between the low BW group (<2500g) (10.3%; 39/379) and the normal BW group (2500–4000g) (9.6%; 540/5609) and the high birth weight group (12%; 104/867). In univariable analysis, HR showed a significant association with high BW (>4000g) (model #1: OR = 1.28 [1.02, 1.6];  $p = 0.03$ ). However, when adjusted for age and sex [female], BW was not associated with hypertensive retinopathy (model #2: OR = 1.08 [0.85; 1.36];  $p = 0.53$ ) and also remained non-associated when we additionally adjusted for cardiovascular risk factors (diabetes [yes], BMI, family history of stroke [yes] or myocardial infarction [yes], dyslipidemia [yes], smoking [yes]) (model #3: OR = 1.08 [0.86; 1.37];  $p = 0.51$ ) (Table 1). No association was observed between low BW and HR neither in univariable nor in multivariable analyses. No association was observed for linear relationships.

## Discussion

Our findings could not show an association of either low or high BW with HR. To our knowledge, up to this point there are no population-based studies, which have conducted research regarding this particular association. While Liew et al found an association of low BW and narrower retinal arteriolar caliber in adults,<sup>4</sup> a previous study investigating the retinal vessel calibres in our adult GHS-cohort did not find an association between BW and retinal vessel equivalents.<sup>5</sup> Our observations regarding the lack of association between HR and BW within the same cohort align with these considerations. The absence of a noticeable correlation could be attributed to the relatively younger age of the cohort and advancements in hypertension management strategies. Moreover, it is important to highlight that older participants, who typically have a greater susceptibility to arterial hypertension, may also face a higher likelihood of inaccuracies in self-reported birth weight. This could stem from less precise record-keeping practices in the past, potentially leading to misclassification in our data. In a subcohort of participants, self-reported birth weight showed high validity when compared to individual chart reports (ICC = 0.89; 95%-CI: 0.83–0.92).

**Table 1** Associations of Hypertensive Retinopathy with Birth Weight in the Gutenberg Health Study (2007–2012)

	Crude (m1)		Age and Sex-Adjusted (m2)		CRVF-Adjusted (m3)	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
<b>Hypertensive retinopathy in at least one eye</b>						
Low Birth weight (<2500g)	1.08 (0.67; 1.52)	0.67	0.95 (0.67; 1.35)	0.78	0.93 (0.65; 1.33)	0.69
Normal Birth Weight (2500–4000g)	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
High Birth weight (>4000g)	1.28 (1.02, 1.6)	0.03	1.08 (0.85; 1.36)	0.53	1.08 (0.86; 1.37)	0.51

**Notes:** Logistic regression models were performed assessing the association of hypertensive retinopathy with birth weight (categorical). Model 1: univariate; model 2: adjusted for age (years), sex (female); model 3 adjusted for age (years), sex (female), arterial hypertension [yes], BMI, Smoking [yes], Diabetes [yes], Dyslipidemia [yes], Family History of Stroke or Myocardial Infarction [yes].

**Abbreviations:** g, gram; CI, confidence interval; BMI, Body Mass Index; Ref., Reference Group for categorical birth weight data.

Our results are limited because in only 56% of all participants birth weight data were available and gradable fundus images were not available in about 15%. Furthermore, the reliance on self-reported birth weight data, while a common practice in epidemiological studies due to the logistical challenges of collecting information from a large number of participants may introduce recall bias.

## Conclusion

In conclusion, based on the outcomes of this large population-based study, there is no substantial evidence to support a significant association between birth weight and hypertensive retinopathy.

## Data Sharing Statement

The analysis presents clinical data of a large-scale population-based cohort with ongoing follow-up examinations. This project constitutes a major scientific effort with high methodological standards and detailed guidelines for analysis and publication to ensure scientific analyses on highest level. Therefore, data are not made available for the scientific community outside the established and controlled workflows and algorithms. To meet the general idea of verification and reproducibility of 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 coordinating PI of the Gutenberg Health Study (PSW), convenes once a month. The steering committee decides on internal and external access of researchers and use of the data and biomaterials based on a research proposal to be supplied by the researcher. Interested researchers make their requests to the coordinating PI of the Gutenberg Health Study (Philipp S. Wild; philipp.wild@unimedizin-mainz.de). More detailed contact information is available at the homepage of the GHS ([www.gutenberghealthstudy.org](http://www.gutenberghealthstudy.org)).

## Informed Consent

The study protocol and study documents were approved by the local ethics committee of the Medical Chamber of Rhineland-Palatinate, Germany (reference no. 837.394.17; original vote: 22.3.2007, latest update: 28.06.2022). According to the tenets of the Declaration of Helsinki, written informed consent was obtained from all participants prior to entering the study.

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

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