

## Prevalence of Retinal Vascular Anomalies in the German Population: Results from the Gutenberg Health Study

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### ABSTRACT

**Purpose:** To determine the prevalence of retinal vascular anomalies in the general population in Germany and to analyse potential associations with ocular and systemic factors.

**Methods:** The Gutenberg Health Study is a population-based cohort study, including 15,010 participants aged 35–74 years. We performed fundus photographs of the macula and the optic disc. Vascular anomalies of the retina were graded. The prevalence was computed. We conducted multivariable logistic regression analysis including generalized estimating equations to assess associated factors.

**Results:** We included 12,956 participants (mean age  $55.0 \pm 11.1$  years; 49.8% female). Retinal arterial tortuosity (RAT) was present in 5.9% in at least one eye and in 3.7% in both eyes. Systolic (OR = 1.01,  $p = 0.0039$ ) and diastolic (OR = 0.98,  $p = 0.0039$ ) arterial blood pressure, low-density lipoproteins (LDL) levels (OR = 1.0,  $p = 0.036$ ), and spherical equivalent (OR = 1.06,  $p < 0.0001$ ) were associated with RAT. Birth weight (OR = 0.97,  $p < 0.0001$ ) and age (OR = 0.85,  $p = 0.0004$ ) were inversely associated, while high-density lipoproteins (HDL), body mass index, and smoking were not associated with RAT. Temporal cilioretinal arteries (CRA) were prevalent in at least one eye in 40.2% and in 9.2% in both eyes. Spherical equivalent was associated with the prevalence of CRA (OR = 1.03 per dpt,  $p = 0.0006$ ). Branch-building CRA had a prevalence of 0.5% in at least one eye.

**Conclusion:** This study describes prevalence of retinal vascular anomalies for the first time in a German population. CRA were positively associated with spherical equivalent and thus might be protective for myopia. RAT was associated with cardiovascular risk factors and with lower birth weight.

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## Introduction


Knowledge about the prevalence and associated factors of retinal vascular anomalies is essential to profoundly evaluate the vascular status of the eye. While some anomalies are inherited and mostly not clinically relevant others are associated with systemic diseases, including common cardiovascular risk factors. Certain anomalies can even be beneficial or disadvantageous when present alongside ophthalmologic pathologies.<sup>1,2</sup>

Reported prevalence on more common features, like retinal arterial or venous tortuosity or cilioretinal arteries

(CRA), vary greatly, whereas rare anomalies like arterio-arterial or veno-venous vascular junctions and prepapillary arterial or venous vascular loops are rarely reported at all.

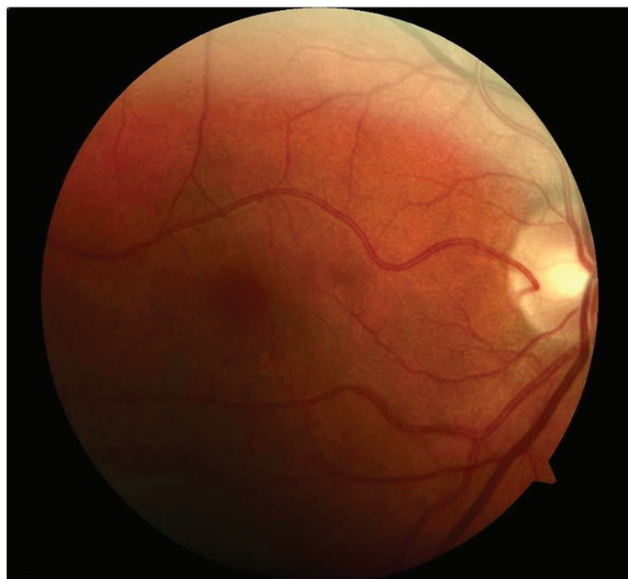
CRA arise either from the short posterior ciliary arteries or directly from choroidal vessels and often contribute significantly to the macular circulation in an individual extent (Figure 1).<sup>3</sup> Their presence can significantly influence the clinical outcome of severe ocular pathologies such as central retinal artery occlusion.<sup>1</sup> The reported prevalence of CRA in at least

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**Figure 1.** Cilioretinal artery.

one eye ranges from 6.9%<sup>4</sup> to 49.5%.<sup>5</sup> CRA can contribute only to a small segment of the retina or as a major trunk such as a vascular arch.<sup>6</sup>

Retinal arterial or venous tortuosity (Figures 2 and 3) can be present in segments, generalized, in one or both eyes and might be congenital or acquired under pathological circumstances. Awareness for their existence increases due to their association with various ocular and systemic disease like diabetic retinopathy, elevated arterial blood pressure, cerebrovascular and coronary artery disease.<sup>7–9</sup> It is important to note that those associations were not shown consistently in epidemiologic studies and before using the appearance of retinal



**Figure 2.** Retinal arterial tortuosity.



**Figure 3.** Retinal venous tortuosity.

vessels as a screening tool profound knowledge of their prevalence is crucial.

We aim to determine the prevalence of different retinal anomalies and associated ocular and systemic factors in the German population for the first time.

## Material and methods

### Study population

The Gutenberg Health Study (GHS) is an observational, population-based, prospective, single-center cohort study at the University Medical Center of the Johannes Gutenberg University, Mainz. The participants were randomly selected from local residents' registration offices Mainz and District of Mainz-Bingen. Residents aged 35–74 years were eligible ( $n = 210,867$ ) and stratified by gender, decade of age, and residence (rural vs urban). A total of 35,008 residents were randomly selected and contacted. The recruitment efficacy proportion was 61.2% ( $n = 15,010$ ). The baseline examination took place from 2007 to 2012 and consisted of an ophthalmological examination, several cardiovascular and general examinations, as well as interviews and questionnaires. All persons gave their written informed consent prior to inclusion in the study. The research adhered to the tenets of the Declaration of Helsinki.

### Ophthalmic examination

The ophthalmic evaluation performed on all 15,010 GHS participants included measurements of distant corrected visual acuity and objective refractive error, measured without cycloplegia (Humphrey Automated Refractor/

Keratometer (HARK) 599; Carl Zeiss Meditec, Jena, Germany). Spherical equivalent of the refractive correction of each eye was computed. Intraocular pressure was measured by non-contact tonometry (Nidek NT-2000, Nidek, Japan). A slit-lamp examination was carried out, and fundus images were taken with a non-mydratric fundus camera (Visucam PRO NM, Carl Zeiss) from both eyes with physiological pupils in a darkened room after an adaption phase of 15 min. Three photographs per eye were taken: 30° centered on the macula and 30° and 45° centered on the optic nerve head.

The ophthalmic study design was described in detail elsewhere.<sup>10</sup>

### **Investigated factors and comorbidities**

Multiple parameters like age, sex, height (in cm), body-weight (in kg), and body mass index (BMI) were evaluated. Obesity was defined as a BMI  $\geq 30$  kg/m<sup>2</sup>.<sup>11</sup> Systolic and diastolic blood pressures after 3, 8, and 11 min of rest were measured using Omron HEM 705-CP II (OMRON, Mannheim, Germany). Arterial hypertension was diagnosed if antihypertensive drugs were taken, in cases with a mean systolic blood pressure of  $\geq 140$  mmHg in the 2nd and 3rd standardized measurement or a mean diastolic blood pressure of  $\geq 90$  mmHg in the 2nd and 3rd standardized measurement. A venous blood sample was taken after at least 8 h of fasting and blood sugar levels (mg/dl), HbA1c (%), LDL (mg/dl), HDL (mg/dl), and triglycerides (mg/dl). A diagnosis of diabetes was defined in individuals with a definite diagnosis who were receiving treatment for diabetes by a physician, or who had a fasting blood glucose level of  $\geq 126$  mg/dl at the baseline examination or a blood glucose level of  $\geq 200$  mg/dl at the baseline examination. Dyslipidemia was defined as a definite diagnosis of dyslipidemia by a physician or an LDL/HDL ratio of  $\geq 3.5$ . More parameters were evaluated in a computer-assisted interview: smoking status was dichotomized into non-smoker (never smoker and ex-smoker) and smoker (occasional smoker and smoker). Birth weight was classified into low ( $>1500$  g) and high ( $>5000$  g), and history of myocardial insult or stroke were asked. The socioeconomic status was evaluated with a multidimensional aggregated index used in the German Health Update 2009.<sup>12</sup>

### **Grading of fundus photography**

All fundus images were graded at the Mainz Ophthalmic Reading Center, which provides standard operating procedures for its standardized working

stations. The image quality was graded for every photograph in “good”, “fair”, “poor”, and “not available”.

Generalized arterial or venous tortuosity were evaluated separately and only affirmed when tortuosity was visible in all big arteries or veins.

Furthermore, CAR were detected and then described whether they were temporal, nasal, superior or inferior, and branch building or not. Branch-building CRA were subdivided in arteries supplying one or two quadrants of the fundus.

In addition, less frequent vascular anomalies like arterio-arterial or veno-venous vascular junctions (outside of the optic disc (out of Elschnig-Ring), prepapillary arterial or venous vascular loops, and disc vein edge of Kraupa were detected and counted.

### **Statistical analysis**

Medians, IQRs, minimums, and maximums were calculated for all primary and secondary continuous variables. For variables distributed normally, means and SD were computed. For dichotomous variables, absolute and relative frequencies separately for the right and left and at least one or both eyes were computed.

One-third of all fundus images were graded by three independent observers. Before the actual grading process was started an experienced grader (AK Schuster) who graded a core sample which was then evaluated multiple times by all three observers until all morphologies were graded correctly. Then, the fundus photographs of the first 100 probands were graded and randomly selected 10% were graded again after an interval of at least 24 h to evaluate the intraobserver repeatability. During the following grading process after every 250 probands, another core sample was graded. After the three observers completed their sample, 10% of all graded probands were graded by the two other observers to evaluate the interobserver repeatability. Inter- and intraobserver repeatability were evaluated with Cohen's kappa coefficient.

In an item non-responder analysis, all participants with no or no gradable fundus images were compared in relation to anthropometric, cardiovascular, and ophthalmologic parameters with participants with gradable fundus images.

Prevalence data for retinal arterial or venous tortuosity, temporal or branch-building cilioretinal vessels, arterio-arterial or veno-venous loops and shunt vessels were given as absolute numbers and as relative numbers in percent including the 95% confidence interval. All data were separately analyzed for the right and left or at least one or both eyes. Furthermore, the detected prevalence was stratified for gender, age decade (35–44,

45–54, 55–64 and 65–74 years), grader and image quality (“good”, “fair”, and “poor”). We designed three different multivariable logistic regression models. The first model considered the patients’ anthropometric parameters (age, sex, and birth weight). The second model considered, additionally as independent variables, ophthalmologic parameters like intraocular pressure and spherical equivalent. The last model also considered cardiovascular parameters (smoking, BMI, LDL, HDL, triglyceride and HbA1c levels, systolic and diastolic blood pressure). Generalized estimating equations was used if both eyes of one participant were considered.

Statistical analysis was performed using R V.3.5.2.

## Results

Key findings are summarized in Table 1.

**Table 1.** Key findings.

Prevalence ( <i>n</i> = 12,956)	At least one eye	Both eyes	Associations
Retinal arterial tortuosity	5.9%	3.7%	+ Systolic and diastolic arterial blood pressure + LDL levels + Spherical equivalent – Age – Birth weight
Retinal venous tortuosity	1.6%	0.6%	+ Systolic and diastolic arterial blood pressure + Body mass index + Smoking + Age
Temporal cilioretinal artery	40.2%	9.2%	+ Spherical equivalent
Branch building cilioretinal artery	0.5%	<0.01% ( <i>n</i> = 1)	None

**Table 2.** Characteristics of the study sample with fundus photography from the Gutenberg Health Study.

Features	Total (12,956)	Men (6501)	Women (6455)
<i>n</i> (%)	49.8% (6455)	0% (0)	100% (6455)
Age (years)	55.0 ± 11.1	55.2 ± 11.1	54.8 ± 11.1
Body mass index (kg/m <sup>2</sup> )	26.6 (23.9/30.0)	27.3 (25.0/30.2)	25.7 (22.8/29.8)
Systolic arterial blood pressure (mmHg)	131.6 ± 17.5	134.2 ± 16.3	128.9 ± 18.2
Diastolic arterial blood pressure (mmHg)	82.5 ± 9.5	83.9 ± 9.5	81.1 ± 9.5
High-density lipoprotein (mg/dl)	57.4 ± 15.7	50.3 ± 12.4	64.4 ± 15.4
Low-density lipoprotein (mg/dl)	139.2 ± 35.6	138.2 ± 35.0	139.6 ± 36.2
Triglycerides (mg/dl)	105.0 (78.0/147.0)	117.0 (86.0/164.0)	95.4 (72.0/130.0)
Glycosylated haemoglobin A1c (%)	5.50 (5.20/5.80)	5.50 (5.20/5.80)	5.50 (5.20/5.80)
Hypertension (yes)	49.7% (6432)	54.4% (3535)	44.9% (2897)
Obesity (BMI ≥ 30) (yes)	25.1% (3257)	26.2% (1703)	24.1% (1554)
Dyslipidaemia (yes)	34.7% (4490)	43.2% (2805)	26.2% (1685)
Diabetes (yes)	9.3% (1195)	11.3% (733)	7.2% (462)
Family history of myocardial or cerebral insult (yes)	22.2% (2872)	20.2% (1312)	24.2% (1560)
Smoker (yes)	19.6% (2529)	21.0% (1365)	18.1% (1164)
Socioeconomic status	12.88 ± 4.48	13.60 ± 4.61	12.15 ± 4.22
Birth weight (g)	3407 ± 653	3555 ± 649	3281 ± 630
Intraocular pressure (mmHg)			
Right eye	14.14 ± 2.87	14.23 ± 2.97	14.06 ± 2.77
Left eye	14.29 ± 2.90	14.44 ± 3.01	14.13 ± 2.79
Spherical equivalent (dpt)			
Right eye	−0.12 (−1.12/0.88)	−0.12 (−1.25/0.88)	0 (−1.12/0.88)
Left eye	0 (−1.25/0.88)	−0.12 (−1.25/0.75)	0 (−1.12/1.00)
Visual acuity (logMAR)			
Right eye	0 (0/0.10)	0 (0/0.10)	0 (0/0.10)
Left eye	0 (0/0.10)	0 (0/0.10)	0 (0/0.10)

## Study participants

From 15,010 GHS participants at baseline examination, 12,956 had an evaluable fundus photograph and were included. The mean age of the study participants was 55.0 ± 11.1 years. The study sample is further characterized in Table 2. Non-responder analysis revealed that the included subjects were more often female with a slightly lower BMI and higher low-density lipoprotein levels. Furthermore, included participants had better visual acuity and lower intraocular pressure, while other factors showed a comparable distribution (Table S1).

Image quality was also evaluated in different categories: overall quality was “good” in 85.1%, “fair” in 12.9%, and “poor” in 2% of all included images. Intraobserver reliability was high for all measures with a Cohen’s kappa coefficient between 0.81 and 1 and interrater reliability between 0.55 and 0.7.

## Prevalence

Retinal arterial tortuosity (RAT) was present in 5.9% (95% CI: 5.5%–6.3%) of study patients in at least one eye and in both eyes in 3.7% (95% CI: 3.4%–4.1%). Retinal venous tortuosity was present in 1.6% of study patients in at least one eye and in 0.6% (95% CI: 1.4%–1.8%) in both eyes.

Temporal CRA were prevalent in 40.2% (95% CI: 39.3%–41.1%) of all studied patients and in 9.2% (95% CI: 8.7%–9.7%) in both eyes. Branch-building CRA were less common with a prevalence of 0.5% (95% CI: 0.4%–0.6%) in at least one eye and only one patient had branch-building CRA in both eyes.

Rare vascular anomalies were discovered as well: arterio-arterial or veno-venous vascular junctions were found in four patients each (prevalence 1:6.000). Prepapillary arterial vascular loops were detected more often than venous vascular loops (8 vs. 4 times respectively 1:6.000 vs 1:3.000). In one patient, a disc vein edge of Kraupa was detected.

## Association analysis

RAT was associated with younger age (p-value 0.04; OR: 0.92 per 10 years, 95% CI: 0.86–1.0) and lower birth weight (p-value < 0.0001; OR 0.97 per 100 g, 95% CI: 0.96–0.98). In the second and third model RAT was associated with systolic (p-value 0.0039; OR = 1.01 per mmHg, 95% CI: 1.00–1.02) and diastolic (p-value 0.0039; OR = 0.98 per mmHg, 95% CI: 0.97–0.99) arterial pressure, LDL levels (p-value 0.036; OR = 0.998 per mg/dl, 95% CI: 0.995–1.00) and spherical equivalent (p-value < 0.0001; OR = 1.06 per diopter, 95% CI: 1.03–1.09).

Retinal venous tortuosity was associated with systolic (p-value < 0.0001; OR = 1.03 per mmHg, 95% CI: 1.02–1.05) and diastolic (p-value < 0.0001; OR = 0.94 per mmHg, 95% CI: 0.92–0.97) arterial blood pressure as well. Additionally, BMI (p-value < 0.0001; OR = 1.07 per kg/m<sup>2</sup>), 95% CI: 1.04–1.11) and smoking (p-value 0.0073; OR = 1.75, 95% CI: 1.16–2.64) were associated. In contrast to arterial tortuosity, not younger but increased age was associated (p-value 0.0023; OR = 1.31 per 10 years, 95% C I: 1.11–1.54).

Temporal CRA were associated with the spherical equivalent (p-value 0.00057; OR = 1.03 per dpt., 95% CI: 1.01–1.04) and with a more hyperopic refractive error; therefore, myopia seems to be inversely associated. However, subgroup analysis of participants with a temporal cilioretinal artery in only one eye (*n* = 3701) did not show a difference of spherical equivalent between both eyes. Branch-building CRA did not show any association to the spherical equivalent.

## Discussion

This population-based study reports on the prevalence and associated systemic and ocular factors of retinal vascular abnormalities in a very large German cohort. Previously reported prevalence on more frequent features such as retinal arterial or venous tortuosity or cilioretinal arteries vary greatly and associated ocular and systemic factors are rarely evaluated elaborately.<sup>3,13,14</sup> Uncommon anomalies like arterio-arterial or veno-venous vascular junctions and prepapillary arterial or venous vascular loops are rarely reported.<sup>13</sup> Often presented data are generated in very specific study populations, namely patient groups, and therefore assignability to the general population is limited. Findings of the prevalence and associated ocular and systemic factors from the Gutenberg Health study as a large population-based cohort study are more likely to be transferable.

Based on this population-based study, RAT was present in 5.9% of study patients in at least one eye and in 3.7% in both eyes. Retinal venous tortuosity was present in 1.6% study patients in at least one eye and in 0.6% in both eyes. Reported prevalence for arterial retinal tortuosity ranges from 0.5%<sup>13</sup> to 14%,<sup>14</sup> whereas venous retinal tortuosity is mostly reported as less common between 1.9%<sup>13</sup> and 2.7%.<sup>15</sup>

To our best knowledge, we are the first to report the prevalence in a large European population-based study. Apart from the examined study, population results are dependent on the used definition of tortuosity. In our study, tortuosity was only affirmed when tortuosity was visible in all major retinal arteries or veins. In the literature, automated vascular analysis tools have been described which can additionally quantify retinal tortuosity.<sup>16,17</sup> Those tools were not used in this study due to the various entities examined. However, a quantification of, for example, retinal tortuosity might even enhance the described associations.

We found that RAT is associated with lower birth weight. This confirms smaller scaled studies in children and adults in the United Kingdom and Finland.<sup>18,19</sup> Furthermore, we found younger age to be associated the retinal arteriolar tortuosity. This is similar to data from the Singapore Malay Eye Study (SiMES), a smaller comparable structured population-based study. Other studies did not find a correlation what might be due to a small age range or population size.<sup>20,21</sup> In contrast to arterial tortuosity not younger but older participants showed retinal venous tortuosity more frequently. However, in our third analysis model also considering cardiovascular parameters, no association with age was found. We found systolic and diastolic blood pressure as

common cardiovascular risk factors to be associated with arterial and venous retinal tortuosity. Interestingly, systolic blood pressure was positively as was the pulse amplitude being the difference between systolic and diastolic blood pressure. In the SiMES study<sup>22</sup> systolic and diastolic blood pressure were inversely associated whereas the CHASE study<sup>20</sup> found a positive correlation in 10 year old children. Other typical cardiovascular risk factors like HbA1c, triglycerides, BMI or smoking were not significantly associated with RAT. Other studies found partly concordant partly contrary results.<sup>20–22</sup> Therefore, whether our data nor the literature review does conclusively suggest any clinical consequences to evaluate cardiovascular risk factors in particular for patients with RAT. However, it has been shown that atrial and venous retinal tortuosity is more frequent in patients with obstructive sleep apnoea, long-standing diabetes or as a part of hypertensive retinopathy with cerebrovascular diseases.<sup>9,23,24</sup> Interestingly we found an association with body-mass-index and smoking with retinal venous tortuosity. Veluchamy et al.<sup>8</sup> even detected a genetic link between retinal vascular tortuosity and coronary artery disease. Hence, a more detailed anamnesis or general examination might be indicated.

Another retinal vascular anomaly evaluated in our study were cilioretinal arteries which we subdivided into temporal and branch building arteries. Temporal CRA were prevalent in 40.2% of all studied patients and in 9.2% in both eyes. Branch-building CRA were less common with a prevalence of 0.5% in at least one eye and just one patient had branch-building CRA in both eyes. The reported prevalence of CRA in at least one eye ranges from 6.9%<sup>4</sup> to 49.5%.<sup>5</sup> A systematic literature review from Schneider et al.<sup>3</sup> revealed that the reported prevalence is influenced by the used imaging technique. Studies with fluorescein angiography reported the highest prevalence followed by fundus photography and ophthalmoscopy with the lowest reported prevalence. Unilateral presence and temporal location of the cilioretinal arteries were most frequently in all included studies which is consistent with our findings.

Interestingly, we found CRA to be positively associated with spherical equivalent. Therefore, myopia seems to be inversely associated. On the other hand, we did not find a difference in spherical equivalent between both eyes in participants with a temporal cilioretinal artery in only one eye. Branch-building CRA did not show any association to the spherical equivalent. Zhu et al.<sup>25</sup> and Watanabe et al.<sup>26</sup> both investigated CRA in highly myopic eyes and found CRA to be rather less common (reported prevalence of 7.3% and 17.1%) what matches our findings.

Watanabe et al.<sup>26</sup> described additionally a divergent predominant location. CRA in highly myopic eyes were predominantly found in the superior optic disc sector (46%) followed by the temporal disc sector (37%) whereas in non-highly myopic eyes temporal CRA are much more common. Zhu et al.<sup>25</sup> focused on the vascular musculature using optical coherence tomography (OCT) angiography and were able to show that highly myopic eyes with a cilioretinal artery had a significantly higher vessel density and fractal dimension in superficial and deep capillary plexuses combined with a smaller foveal avascular zone than those without. They even reported a better visual acuity in patients with a cilioretinal artery that reached the fovea than without. However, it needs to be addressed that the group with CRA had a small nonetheless significant shorter axial length than the group without ( $28.55 \pm 1.7$  mm vs.  $29.02 \pm 2.13$  mm). Therefore, it remains to be evaluated if CRA benefit the vascular musculature and the clinical outcome of myopic eyes or if the presence of CRA might even be protective of myopia itself which was indicated by the inverse correlation in our epidemiologic study. However, the potential protective effect of CRA on myopia was not detectable on an individual level in participants with a cilioretinal artery in only one eye.

In summary, RAT was more common than retinal venous tortuosity. Both characteristics were associated with systolic blood pressure as a common cardiovascular risk factor. Venous tortuosity was additionally associated with BMI and smoking.

Temporal CRA were prevalent in at least one eye in 40.2% and were positively associated with spherical equivalent and thus might be protective for myopia.

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No potential conflict of interest was reported by the author(s).

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