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GLAUCOMA

Prevalence of glaucoma in Germany: results from the Gutenberg Health Study

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Abstract

Purpose To determine the prevalence of glaucoma according to the International Society for Geographical and Epidemiological Ophthalmology (ISGEO) classification in an adult German cohort.

Methods The Gutenberg Health Study is a population-based, prospective cohort study in the Rhine-Main Region in mid-western Germany with a total of 15,010 participants. In this study, the first 5000 subjects with an age range between 35 and 74 years were included. Optic disk pictures were obtained by a non-mydriatic fundus camera (Visucam™) and analyzed using the Visupac™ software. Glaucoma prevalence was determined in two steps. First, the ISGEO classification was applied using "hypernormal subjects" (normal visual field) as reference. In the second analysis, we additionally considered the disk area (DA) in relation to the vertical cup-to-disk ratio by quantile regression. All results are given as weighted numbers for the population of Mainz/Bingen.

Results The prevalence of definite glaucoma in our sample was 1.44% ($n = 72$). The prevalence adjusted for disk area was 1.34% ($n = 67$). The prevalence gradually increased in both models with each decade of age (from 0.9 to 2.4%, respectively). In both models, none of the glaucoma cases had a small optic disk (< 1.6 mm^2). Glaucoma prevalence in medium optic disks was 1.0% (without DA adjustment) vs. 1.6% (with DA adjustment) and in large optic disks 5.6 vs. 2.5%.

Conclusions The prevalence of definite glaucoma was similar to other European population-based cohorts, with slightly higher prevalence in younger subjects. Our analysis highlighted the influence of optic disk size in determining the diagnosis of glaucoma based on cup-to-disk ratio in epidemiological studies.

Keywords Glaucoma · Prevalence · Population-based cohort · Gutenberg Health Study · ISGEO

Introduction

Glaucoma, the leading cause of irreversible blindness, has an estimated prevalence of 3.54% or 64 million affected people in 2013 worldwide [1], which will increase up to estimated 112 million patients in 2040. Primary open-angle glaucoma (POAG) is the most common type of glaucoma with a worldwide prevalence of 3.05% or 44 million POAG patients in 2013. However, the prevalence of POAG is known to vary significantly in different populations or continents. The lowest prevalence is found in Asia and Europe with about 1.8–2.3 and 2.0–2.5%, respectively [1, 2]. Higher prevalence is found

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in African and Latin America/Caribbean countries with 4.2–4.5 and 3.4–3.65%, respectively [1, 2]. The prevalence increases with age in all populations, but especially in Latin American/Caribbean populations (50-fold rise between 40 and 90 years) as well as in Caucasians (25-fold rise between 40 and 90 years) [2]. However, all these data are derived from population-based studies using different definitions for POAG with a significant impact on prevalence figures [3]. In 2002, the International Society for Geographical and Epidemiological Ophthalmology (ISGEO) published a definition and classification of glaucoma in prevalence surveys based on structural (vertical cup-to-disk ratio, VCDR) and functional (visual field) damage related to glaucoma with the goal to standardize results and make them comparable among different studies and populations [4]. Another aim was to develop a classification system that does not depend on complete data of every single subject. This classification still represents the gold standard to provide prevalence data in population-based studies. While several Asian and African studies published ISGEO-based prevalence of POAG and primary angle closure glaucoma (PACG), only one US study considered the ISGEO classification in Caucasians [5].

The first goal of our study was to provide the first ISGEO prevalence data of glaucoma in a European population (and the first German prevalence data). An issue of the ISGEO classification is the use of VCDR without considering the correlation between optic disk size and VCDR [6, 7]. As a consequence, larger disks will be overrepresented in the glaucoma cases based on the ISGEO classification. Thus, the second goal of our study was to investigate the influence of optic disk size on glaucoma classification based on the ISGEO system and the related prevalence in small, medium, and large optic disks.

Methods

Subjects

The Gutenberg Health Study (GHS) is a population-based, prospective, observational, single-center cohort study in mid-western Germany that includes consecutive follow-ups every 5 years. The baseline examination included a total of 15,010 participants aged 35 to 74 years and took place from 2007 to 2012 and consisted of an ophthalmological examination, several cardiovascular and general examinations, as well as interviews and questionnaires. The study participants were randomly drawn and equally stratified for sex, residence (urban or rural), and for each decade of age via the local residents' registration offices. Exclusion criteria were the following: insufficient knowledge of German and physical or mental inability to participate in the examinations in the study center at the University Medical Center Mainz/Germany. 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 their entry into the study.

In this analysis, the first 5000 subjects from baseline visit were included, which were chosen to be representative for the source population due to draws in waves of equal stratification for each 5000 subjects.

Measurements

All participants underwent a standardized protocol with a general cardiovascular and ophthalmic examination, which included corrected visual acuity (Humphrey® Automated Refractor/Keratometer (HARK) 599™; Carl Zeiss AG, Jena, Germany), slitlamp biomicroscopy (Haag-Streit BM 900, Koeniz, Switzerland), non-contact tonometry (Nidek NT-2000™, Nidek Co., Japan), fundus photography, central corneal thickness, keratometry measurement (Pachycam, Oculus, Wetzlar, Germany), and visual field testing. The ophthalmic study design was described in detail elsewhere [8].

Cardiovascular risk factors (CVRFs) were defined as follows. Smoking was dichotomized into non-smokers (never smoker and ex-smoker) and smoker (occasional smoker and smoker). Arterial hypertension was diagnosed if antihypertensive drugs were taken, in cases with a mean systolic blood pressure of ≥ 140 mmHg in the 2nd and 3rd standardized measurement (Omron HEM 705-CP II, OMRON, Mannheim, Germany) after 8 and 11 min of rest, respectively, or a mean diastolic blood pressure of ≥ 90 mmHg in the 2nd and 3rd standardized measurement after 8 and 11 min of rest, respectively. 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 blood glucose level ≥ 126 mg/dl at the baseline examination after overnight fasting for at least 8 h or a blood glucose level of ≥ 200 mg/dl at the baseline examination after a fasting period of at least 8 h. Obesity was defined as a body mass index (BMI) ≥ 30 kg/m^2. Dyslipidemia was defined as a definite diagnosis of dyslipidemia by a physician or an LDL/HDL ratio of ≥ 3.5.

Visual field testing and grading

Visual field testing was performed with the frequency doubling technology (FDT) Humphrey® Matrix Perimeter (program N-30-5). Subjects with a refractive error between + 6.0 and − 6.0 diopters spherical equivalent underwent the examination without correction; subjects with a refractive error higher or lower than + 6.0 or − 6.0 diopters spherical equivalent used their corrective devices (glasses or contact lenses). If defects with a threshold of either one abnormal cluster/field with $P < 1\%$ or two adjacent clusters/fields with $P < 5\%$ became apparent, the examination was immediately repeated for the affected eye.

Visual field defect was determined by a 2-2-1 algorithm requiring 2 complete tests per eye, with at least 2 abnormal fields ($P < 1\%$) in each test and 1 common abnormal field [9]. In the case that only one complete test per eye was available, at least 2 abnormal fields ($P < 1\%$) were classified as visual field defect.

Optic disk assessment

Optic disk pictures were obtained by a non-mydriatic fundus camera (Visucam®$^{\text{PRO NM}}$) and analyzed by one ophthalmologist (RH) using the semiautomatic Visupac™ software. Two images were centered on the optic disk (30° and 45° field). VCDR assessment was primarily done in 30° pictures and, if image quality did not allow measurement in 30° images, was done in 45° pictures. These images were available in 4540 right eyes and 4554 left eyes (4513 subjects with assessment in both eyes). Optic disk size calculation was only possible in 30° pictures and patients with available data on refraction and keratometry based on Littmann correction incorporated in the Visupac™ software [10]. Optic disk area data was available in 3010 subjects. A sample of 200 eyes was additionally graded by a trained epidemiologist (SN) to estimate the inter-rater reliability. An optic disk area of < 1.6, 1.6–2.8, or > 2.8 mm^2 was defined as small, medium, or large optic disk, respectively [11].

Definition of glaucoma

Glaucoma cases were classified according to the International Society for Geographic and Epidemiological Ophthalmology (ISGEO) criteria [4]. Definite glaucoma is divided into three categories of different structural and functional evidence levels for glaucomatous optic neuropathy. The definitions of these categories are shown in Table 1, including the definition for glaucoma suspect cases. All parameters except rim width and drainage angle characteristics were available in our study.

The percentiles were calculated using hypernormals (only subjects without visual field defects: 4141 right eyes, 4151 left eyes) as reference. The 97.5th percentiles for VCDR in right eyes, VCDR in left eyes, VCDR asymmetry, and IOP in both eyes were 0.68, 0.67, 0.2, and 20.0 mmHg, respectively. The 99.5th percentiles for VCDR right and left eyes, VCDR asymmetry, and IOP in right and left eyes were 0.76, 0.73, 0.28, 23.0, and 23.3 mmHg, respectively.

Statistical analyses

Analyses were performed using SPSS version 23 (Statistical Package for the Social Sciences, Chicago, Illinois, USA), SAS software 9.4 (SAS Institute Inc., Cary, NC, USA), and R version 3.1.1 (2014-07-10, R Core Team (2014). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL http://www.R-project.org). Descriptive statistics included means and standard deviations. Prevalence data were given as relative numbers in percent including the 95% confidence interval. All results were weighted for the local population of Mainz/Bingen (indicated as weighted) because the older age decade was overrepresented in the study sample. To estimate repeatability of VCDR measurements (RH versus SN), we calculated the intraclass correlation coefficient (ICC). Quantile regression analysis was carried out in hypernormals (only subjects without visual field defects) to derive 97.5 and 99.5% percentiles of VCDR in dependency on disk area.

We used the following quantile regression formulas to calculate individual cut-off values for VCDR with respect to dikc area:

$$97.5\text{th percentile (VCDR right eye)} = 0.32 + 0.14^{*}\ \text{disc area (right eye)}$$
$$99.5\text{th percentile (VCDR right eye)} = 0.36 + 0.16^{*}\ \text{disc area (right eye)}$$
$$97.5\text{th percentile (VCDR left eye)} = 0.34 + 0.13^{*}\ \text{disc area (left eye)}$$
$$99.5\text{th percentile (VCDR left eye)} = 0.42 + 0.11^{*}\ \text{disc area (left eye)}.$$

With this approach, individual cut-off values for VCDR with respect to disk area were computed and integrated in the analysis.

Results

Of the 5000 subjects, 67 glaucoma cases were identified in the disk area adjusted analysis based on the ISGEO classification. This resulted in an overall prevalence of 1.34%. Glaucoma cases were slightly more often female (60.5%) and older (60.5 versus 52.1 years), suffered more often from arterial hypertension (59.3 vs. 45.2%), and cardiovascular diseases (12.5 versus 8.2%), but smoked less likely (16.4 versus 21.0%) than non-glaucoma subjects. The characteristics of the study sample and the glaucoma cases are shown in Table 2. Without consideration of optic disk size, 72 glaucoma cases were found corresponding to a prevalence of 1.44%. The ICC of the VCDR measurements was 0.74 (95% CI 0.67; 0.79) indicating a sufficient interrater agreement of the measurement method.

Glaucoma cases

The distribution of glaucoma cases according to the ISGEO classification and the age dependency by decades is shown in

Table 1 Diagnostic criteria for glaucoma in prevalence surveys according to the ISGEO

Category 1[a]	VCDR or VCDR asymmetry ≥ 97.5th percentile or neuroretinal rim width[b] ≤ 0.1 CDR
	AND
	definite VF defect
Category 2[a]	VCDR or VCDR asymmetry ≥ 99.5th percentile
	AND
	normal or incomplete VF
Category 3	IOP > 99.5th percentile *AND* < 3/60 visual acuity
	OR
	Visual acuity < 3/60 *AND* glaucoma surgery or documented history of glaucoma
Suspect	VCDR or VCDR asymmetry ≥ 97.5th perc. *AND* normal VF
	OR
	VCDR or VCDR asymmetry < 97.5th perc. *AND* definite VF defect
	OR
	IOP ≥ 97.5th percentile
	OR
	Optic disk hemorrhage
	OR
	Occludable drainage angle[b]

[a] Alternative explanations for VCDR findings or the visual field defect were excluded

[b] Parameter was not available

VF visual field, *CDR* cup to disk ratio, *IOP* intraocular pressure

Table 3. In both models, most of the cases were identified by categories 1 and 2, reflecting the categories with the highest evidence.

The glaucoma prevalence gradually increased in both models (N-DA/DA) with each decade of age from 1.2%/0.9% to 2.5%/2.4%, respectively. While both models showed a small, implied linear increase of prevalence up to the age of 64, the rise increased exponentially above the age of 65 (see Fig. 1).

To investigate the influence of optic disk size when applying the ISGEO classification for detection of glaucoma cases, we looked at the case distribution depending on optic disk size. Optic disk area was available in a subsample of 3010 subjects (weighted $n = 2979$) and no glaucoma case was seen in subjects with a small optic disk. For medium and large optic disks, there was a marked difference in case distribution and prevalence, whether disk area was considered or not. The prevalence in medium optic disks was 1.0% ($n = 27$) vs. 1.6% ($n = 42$) and in large optic disks 5.6% ($n = 18$) vs. 2.5% ($n = 8$) applying the non-adjusted vs. the DA-adjusted classification, respectively. The complete results are shown in Table 4. For glaucoma suspect cases, the same shifting of cases from large to medium disks was observed when considering disk area in the classification.

We further looked into the electronic case report file of the identified glaucoma subjects to search for information indicating angle closure or secondary glaucoma. One case of congenital and two cases secondary to trauma were found. None of the identified cases showed evidence of pseudoexfoliation, pigment dispersion, history of acute angle closure, iridotomy, or iridectomy. To assess the risk for chronic angle closure glaucoma, we looked at the spherical equivalent (SE) as a surrogate for angle closure: 10 subjects with glaucoma had a SE of + 2.0 to + 2.99 dpt., and 2 subjects of + 4.0 to + 4.99 dpt., which might have a chronic angle closure component. However, by far, most cases were open-angle glaucoma.

Glaucoma suspect cases

Suspicion of glaucoma according to the ISGEO classification occurred with a weighted disk size adjusted prevalence of 8.5% ($n = 423$) or 9.0% ($n = 448$) without adjusting for disk size.

In both models (DA/N-DA), a nearly two-fold increase in prevalence was seen from 6.2%/6.9% in the youngest age decade (35–44 years) to 11.9%/12.0% in the oldest age decade (65–74 years) (see Table 3). Optic disk size was also crucial in the diagnosis of glaucoma suspects (see Table 4). Without consideration of disk size, every fifth subject (20.3%) with large disk was classified as a glaucoma suspect. After adjusting for disk size only, every 10th (10.3%) was suspicious for glaucoma.

In subjects with medium disk size, the influence of disk size was not as remarkable with a prevalence of 8.0% (N-DA model) versus 9.2% (DA model).

Table 2 Study sample characteristics, weighted

	Total ($n = 5000$)	Glaucoma cases	
		No ($n = 4933$)	Yes (n = 67)
Age, mean (SD)	52.2 (11.1)	52.1 (11.1)	60.5 (11.0)
Female, *n* (%)	2507 (50.1%)	2466 (50.0%)	41 (60.5%)
Cardiovascular risk factors			
Diabetes, *n* (%)	395 (7.9%)	391 (7.9%)	4 (6.5%)
Dyslipidemia, *n* (%)	2003 (40.1%)	1980 (40.2%)	24 (35.1%)
Hypertension, *n* (%)	2269 (45.4%)	2229 (45.2)	40 (59.3%)
Smoking, *n* (%)	1045 (20.9%)	1034 (21.0%)	11 (16.4%)
Obesity, *n* (%)	1141 (22.8%)	1124 (22.8%)	17 (25.5%)
Body mass index, kg/m^2 (SD)	27.0 (4.8)	27.0 (4.8)	26.7 (5.2)
Systolic blood pressure, mm Hg (SD)	130.8 (17.0)	130.7 (17.0)	134.0 (16.0)
Diastolic blood pressure, mm Hg (SD)	82.9 (9.4)	82.9 (9.4)	83.8 (9.6)
Cardiovascular diseases, *n* (%)	410 (8.2%)	402 (8.2%)	8 (12.5%)
Ocular parameters			
Visual acuity decimal, mean (SD)		0.9 (0.2)	0.8 (0.3)
Spherical equivalent, diopter (SD)		− 0.4 (2.5)	− 0.7 (3.1)
Intraocular pressure, mm Hg (SD)		14.0 (2.8)	15.2 (3.8)
Central corneal thickness, µm (SD)		554 (36)	547 (37)
Self-reported glaucoma, *n* (%)	91 (1.9%)	80 (1.7%)	12 (17.4%)
Self-reported family history of glaucoma, *n* (%)	241 (4.8%)	235 (4.8%)	7 (10.4%)

Cardiovascular diseases = pooled data of myocardial infarction, coronary heart disease, stroke, peripheral artery occlusive disease

Discussion

The overall optic disk size adjusted and weighted prevalence of glaucoma in our population-based European cohort 35 to 74 years of age based on the ISGEO classification was 1.34%. This is the first report on glaucoma prevalence in Europeans using the ISGEO classification and first population-based results for Germany, the most populous country in Europe.

The diagnosis of glaucoma in cohort studies has been under discussion for at least 20 years. Wolfs et al. [3] showed the enormous prevalence variation depending on the glaucoma definition used in different cohort studies. In 2002, the ISGEO classification[4] was introduced and remained the international standard in prevalence surveys to date. The main aim was to standardize the enclosed parameters to make study results worldwide comparable. Surprisingly, only one US study has published open-angle glaucoma prevalence in Caucasians based on the ISGEO classification so far[5]: Glaucoma prevalence in the National Health and Nutrition Examination Survey (NHANES) was about 2.0% in Whites older than 40 years [5, 12], which was a higher frequency than in our cohort. These results were based on an ISGEO-based [5] and an expert-based [12] approach. This discrepancy to our data is attributable to the inclusion of participants older than 75 years in the NHANES study, due to the exponential increase in the prevalence with increasing age compared to a linear rise before the age of 60 (2.3% for 60–69 years old, 4.3% for 70–79 years old, and 7.5% for 80 years of age and older). Among subjects in their forties (0.5%) or fifties (0.7%), there was a lower prevalence than found in our sample (0.9 and 1%, respectively). The prevalence estimates for Whites/Caucasians reported by Kapetanakis et al. [2] showed also lower prevalences from age 35 to 54 (0.3 to 0.7% versus 0.8 to 1.1%) and similar prevalences from age 55 to 74 (1.0 to 2.7% versus 1.3 to 2.4%) than our sample, respectively.

The ISGEO-based prevalence approach is inconsistent with the self-reported glaucoma prevalence, which in our study was 2.3% [8]. This was 0.9% or about two-thirds higher than the ISGEO prevalence. Other studies showed an even larger difference in self-reported versus graded cases: e.g., in the NHANES, self-reported glaucoma (6.9%) [13] was reported three times more often than the graded glaucoma cases (2.0%) [12]. The ISGEO classification itself is designed for identifying moderate and advanced glaucoma cases and, thus, underestimates the overall glaucoma prevalence. Subjects who are clinically classified as glaucoma patients, such as those with early glaucoma or ocular hypertension, are missed by the classification. The NHANES study [12] reported that 4.1% of those without graded glaucoma reported the diagnosis of glaucoma, which was twice as much as in our study (2.1%). On the other hand, only 18.1% of our graded glaucoma cases

Table 3 Weighted glaucoma and glaucoma suspect case distribution according to ISGEO categories and depending on age decades without and with consideration of optic disk size (N-DA and DA, respectively)

Age decade in years	Category 1		Category 2		Category 3		Suspect	
	N-DA	DA	N-DA	DA	N-DA	DA	N-DA	DA
35–44, *n* [95% CI]	2 [0;6]	2 [0;6]	15 [5;26]	10 [2;18]	1.7 [0;5]	1.7 [0;5]	109 [83;136]	98 [73;123]
45–54, *n* [95% CI]	3 [0;7]	4 [0;9]	11 [4;17]	13 [5;20]	0	0	119 [97;140]	106 [86;127]
55–64, *n* [95% CI]	2 [0;4]	1 [0;3]	13 [6.7;18]	12 [6;18]	0	0	105 [88;122]	106 [89;123]
65–74, *n* [95% CI]	7 [2;11]	6 [2;10]	16 [9;23]	17 [10;24]	0.6 [0;2]	0.6 [0;2]	115 [98;132]	114 [97;131]
Total, *n* [95% CI]	14 [7;22]	13 [5;21]	55 [40;71]	52 [37;66]	2 [0;5.7]	2 [0;5.7]	448 [407;490]	423 [383;464]

CI confidence interval

reported a diagnosis of glaucoma compared to 43.7% by Gupta et al. [12] or about 50% by Topouzis et al. [14].

The glaucoma cases in our study were younger compared to other ISGEO-based results (mean age 60 years versus around 70 years) [12, 15, 16]. This may be due to the age structure of our study population, which included participants up to 74 years of age, while other studies included older participants (> 75 years). Previous studies reported a prevalence of 0.3 to 0.5% in the age range of 40 to 49 years [12, 17, 18], while in our study, the prevalence was as twice as high (about 1% in the age range of 35 to 54 years). Another interesting finding of our study was the more frequent occurrence of glaucoma in women while most other studies reported a higher prevalence and risk for glaucoma in men [12, 14, 15, 17–21]. One possible explanation might be the larger VCDR in men due to a larger optic disk [5, 22] and the VCDR-based classifications. The mean disk area in our sample was slightly higher in men than in women (2.37 vs. 2.28 mm^2, respectively), but the VCDR was almost identical (0.45 in men vs. 0.44 in women). Thus, women had a larger relative excavation of the optic disk, which would support the higher prevalence of glaucoma compared to men.

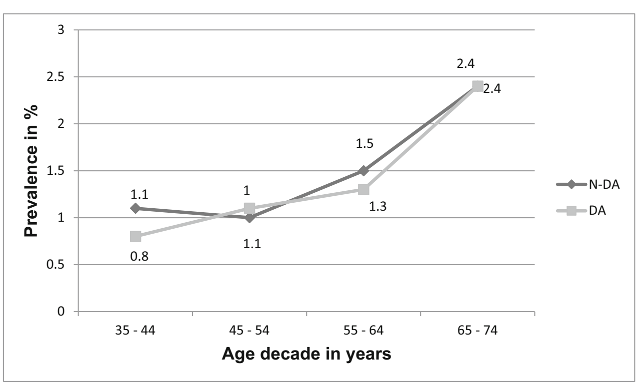

Fig. 1 Age decade-dependent open-angle glaucoma prevalence in the Gutenberg Health Study. N-DA: not adjusted for disk area; DA: adjusted for disk area

Optic disk size

Optic disk size is an important determinant of VCDR [6]. However, thus far, no population-based study has incorporated disk size in the classification of glaucoma cases, although in the Rotterdam Study [3] and Blue Mountains Eye Study [7], the effect of optic disk size on VCDR and its percentiles in population-based samples was demonstrated. Due to the time-consuming and difficult measurement, including correction for magnification, a reliable application of disk size within complex classifications such as the ISGEO classification for glaucoma is a real challenge. Our results clearly emphasize the crucial role of optic disk size to select the appropriate glaucoma cases. Otherwise, it results in an overestimation of glaucoma cases in large disks and the underestimation in small disks, which perfectly matches with clinical daily life experience and pitfalls in the diagnosis of glaucoma [22]. We showed that identifying glaucoma cases without consideration of optic disk size leads to a different selection of cases than incorporating the optic disk area. This aspect is of special importance in cohort studies, as the identified cases serve as source data for many other research projects (e.g., association study, genetic study). To adjust the current classification for optic disk, area should be one important aim in glaucoma epidemiological research.

Type of glaucoma

The most expected type of glaucoma in an adult Caucasian population is by far primary open-angle glaucoma (POAG) [1]. The evaluation of other types of glaucoma in our study was based on ophthalmological history and slit-lamp examination in miosis. Only one congenital and two secondary glaucoma cases due to trauma could be identified. We made an attempt to identify angle closure cases. None of the glaucoma cases had a history of surgical intervention related to angle-closure glaucoma. Thus, we used hyperopia as a surrogate [23] to identify suspicious angle-closure cases.

Table 4 Weighted glaucoma case distribution and prevalence depending on optic disk size

ISGEO classification (see Table 1)	Small optic disk		Medium optic disk		Large optic disk	
	N-DA	DA	N-DA	DA	N-DA	DA
Category 1, *n* [95% CI] (%)	0	0	5 [0.1;11] (0.2)	8 [1.4;14](0.3)	4 [0;8] (1.2)	3 [0;7](1.0)
Category 2, *n* [95% CI] (%)	0	0	22 [13;30] (0.8)	34 [23;45] (1.3)	14 [6;22](4.4)	5 [0.4;9](1.5)
Category 3, *n* [95% CI] (%)	0	0	0	0	0	0
Suspect, *n* [95% CI] (%)	3 [0.5;6] (7.2)	3 [0.5;6] (7.2)	209 [180;237] (8.0)	239 [209;269] (9.2)	66 [51;81] (20.3)	34 [23;44] (10.3)
Total, *n* [95% CI]	48 [43;53]		2605 [2566;2643]		326 [312;341]	

Small optic disk < 1.6 mm^2, medium optic disk 1.6–2.8 mm^2, large optic disk > 2.8 mm^2

N-DA non-disk area adjusted glaucoma cases, *DA* disk area adjusted glaucoma cases, *CI* confidence interval

Only two cases had an SE of above + 4 diopter making an angle-closure diagnosis likely. However, in the end, over 90% of our glaucoma cases are likely due to be open-angle glaucoma (= 1.2%).

The main limitations of this study were missing information about neuroretinal rim width and gonioscopy of the chamber angle to address all parameters within the ISGEO classification. Although we performed a slitlamp examination, the study protocol did not include anterior chamber depth data such as a classification according to “Van Herrick”. The absence of pseudoexfoliation (PXF) glaucoma cases mainly resulted by the slitlamp examination in non-mydriatic condition. In our sample of 5000 subjects, we identified only 12 PXF cases and 18 suspected PXF. This might lead to a likely underestimation or misclassification of glaucoma cases as well as of angle closure or secondary glaucoma cases. Other limitations are related to the visual field: the ISGEO classification recommends a 24-2 test pattern of the humphrey field analyzer 2 as the gold standard for definition of visual field defects [4]. We used a FDT N-30-5 screening program, which is comparable to standard visual field tests in moderate and advanced stages but slightly inferior in early stages of visual field defects [24]. We have been able to obtain a confirmatory visual field (VF) test for some of the suspicious cases. For the category 1 cases ($n = 16$), a confirmatory second visual field was available in 6 cases. The main reason for the low number of repeated VF tests was the 25-min time limit for all ophthalmological examinations at the study visit and the fact that a pathological VF test with our program lasted at least twice as long as a VF with normal findings. Furthermore, data on optic disk size was only available in about 60% of the sample. Thus, the sample size of subjects with small optic disks was relatively small ($n = 47$).

The strengths of our study were the standardized, population-based study design, the large sample size, the availability of optic disk size, the good repeatability of VCDR measurements (ICC 0.74), and the use of the ISGEO classification.

In conclusion, we found a comparable prevalence of glaucoma in Germany to other European population-based studies, although our sample was a relatively young cohort. In particular, the prevalence was slightly higher in subjects in their forties and fifties compared to estimated prevalence data.

In addition, our results underscore the crucial influence of optic disk area in determining the diagnosis of glaucoma based on cup-to-disk ratio such as in the ISGEO classification.

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Compliance with ethical standards

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 their entry into the study.

Conflict of interest Dr. Pfeiffer received honoraria for lectures or consulting from Thea, Isarna, Novartis, Alcon, Medscape, Boehringer Ingelheim, Ivantis. Dr. Schuster received financial support for other projects by Heidelberg Engineering and Bayer Healthcare. Dr. Wild has received research funding from Boehringer Ingelheim, PHILIPS Medical Systems, Sanofi-Aventis, Bayer Vital, Daiichi Sankyo Europe and receiced honoraria for lectures or consulting from Boehringer Ingelheim, Bayer HealthCare, Bayer Vital, Public Health–Heinrich-Heine-University Düsseldorf, Astra Zeneca and Sanofi-Aventis. All other authors declare that they have no conflict of interest.

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