Intraocular Pressure and Its Relation to Ocular Geometry: Results From the Gutenberg Health Study

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Purpose. The purpose of this study was to investigate the association between intraocular pressure (IOP) and ocular geometry.

Methods. The Gutenberg Health Study is a population-based cohort study in Mainz, Germany. Study participants underwent a comprehensive ophthalmologic examination including noncontact tonometry, objective refraction, optical biometry, and Scheimpflug imaging of the anterior segment at the first 5-year follow-up examination (in 2012–2017). Multivariable linear regression analysis was carried out to determine associations of IOP and geometric parameter of the human phakic eye, namely central corneal thickness (CCT), corneal curvature, anterior chamber depth (ACD), lens thickness, and axial length. In addition, the relationship of IOP and the anterior chamber angle (ACA) width was analyzed.

Results. There were 6640 participants with phakia (age 57.3 ± 10.2 years, 49.1% women) that were included in this cross-sectional analysis. Mean IOP was 14.8 ± 2.9 mm Hg in the right eyes and 14.9 ± 2.9 mm Hg in the left eyes. IOP increased with higher CCT, greater posterior segment length, higher age (all $P < 0.001$), thicker lens ($P = 0.003$), and female sex ($P = 0.05$), whereas the ACD was not associated with higher IOP. The IOP increased with a narrower ACA in univariable analysis ($P < 0.001$), but not in adjusted analysis in subjects with an open angle.

Conclusions. IOP values are related to ocular geometry, as shown in this population-based study on Caucasian subjects. Thus, knowledge of the architecture of the eye is an important factor when measuring IOP. Longitudinal evaluation will analyze whether some of these parameters are also risk factors for the development of glaucoma.

Keywords: epidemiology, intraocular pressure, axial length, central corneal thickness, anterior chamber angle, population-based study

Intraocular pressure (IOP) is the only modifiable risk factor for glaucoma, that can be lowered to reduce the risk of onset and progression of glaucoma. First, Goldmann and Schmidt reported that central corneal thickness (CCT) and the corneal elasticity might have an effect on IOP measurements, but they assumed that this would not lead to substantial error.[1] Strong associations between IOP and CCT were reported in several later studies.[2] Although some of them included only patients with glaucoma or patients with other ocular diseases,[3,4] others were population-based surveys in different ethnic groups.[5–16] Only a few studies were carried out in large Caucasian populations.[17–22]

These results show a considerable scattering of the association of IOP and CCT, and it was previously assumed that this scatter was due to individual variations in the stiffness properties of the cornea,[23] the difference of corneal properties between ethnicities,[6,9,24] and potentially between patients with glaucoma and healthy controls.[25–27] Doughty et al. concluded that the impact of CCT on IOP measurements performed by applanation tonometry in healthy eyes was unlikely to achieve clinical significance.[28]

The available data on the relation between other ocular geometric parameters, such as corneal curvature, axial length, lens thickness, and IOP are controversial.[18,29–31] According to Tabuchi et al., not only CCT but mean corneal curvature showed an association with IOP[31] in patients undergoing cataract surgery. Contrary to these results, Sánchez-Tocino et al. did not find such an association,[32] whereas Zakrzewska et al. reported a positive correlation only in patients with thick corneas.[33]

Ocular geometric parameters might influence IOP measurements. Therefore, this study aims to investigate these relationships in a German population-based cohort using noncontact tonometry and hypothesizes that a large amount of the variability of IOP measurement can be explained by ocular geometric parameters.

Methods

The Gutenberg Health Study (GHS) is a prospective, population-based, observational, single-center cohort study that is carried out in the Rhine-Main region of Germany (Rhineland-Palatinate). The sample was drawn randomly from local governmental registry offices. The sample was equally stratified for sex, residence (urban or rural), and for each decade of age between the age of 35 and 74 years at study inclusion. 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). According to the tenets of the Declaration of Helsinki, written informed consent was obtained from all participants prior to entering the study. The baseline examination was carried out between 2007 and 2012, including 15,010 subjects with a consecutive 5-year follow-up examination between 2012 and 2017.

At the 5-year follow-up examination, all participants underwent a standardized ophthalmological examination, including distant-corrected visual acuity and measurement of objective refraction (Humphrey Automated refractor/Keratometer [HARK] 599, IOP measurement (with a noncontact tonometer; NT 2000, Nidek Co./Japan, average of 3 measurements) and biometry (Lenstar LS900; Haag-Streit, Bern, Switzerland). Anterior segment Scheimpflug imaging (Pentacam; Oculus, Wetzlar, Germany) took place under mesopic light conditions. Posterior segment length was defined as posterior segment length = axial length – (CCT + anterior chamber depth [ACD] + lens thickness). The spherical equivalent was calculated by adding the spherical correction value to half the cylinder value. Phakic eyes were defined according to an algorithm of Scheimpflug images as described earlier.[34] The anterior chamber angle (ACA) width was automatically measured using the integrated software of the Scheimpflug imaging device (Pentacam, version 1.20r41; Oculus), as reported before.[35] Scheimpflug images only with high quality (Pentacam quality status 0 or 1) were included. Furthermore, a plausibility check was performed for all extreme values and opening of the eye lids and centration of the Scheimpflug imaging on the central cornea were checked. More details of the study design have been described by Höhn et al.[36]

Study Sample

This is a cross-sectional analysis of the 5-year follow-up visit (2012 to 2017). There were 12,423 subjects of the original cohort presented for the 5-year follow-up examination (82.8% of the original cohort $n = 15.010$). Study participants with IOP measurement in at least one eye, optic biometry data, and phakic lens status were included. Pseudophakic or aphakic eyes were excluded, and those eyes with extreme values (CCT > 680 µm or ACD > 4.5 mm, not been verified by another examination). IOP difference between baseline and 5-year follow-up examination was computed.

Diabetes was diagnosed in those individuals with HbA1c ≥ 6.5%, taking diabetic medication or having been diagnosed by a physician. Arterial hypertension was defined by the use of antihypertensive medication, systolic blood pressure > 140 mm Hg, diastolic blood pressure > 90 mm Hg, or diagnosis by a physician. Socioeconomic status was defined according to the index used for the German Health Update 2009 (GEDA) and ranged from 3 to 21.

Statistical Analysis

For statistical analysis, absolute and relative frequencies were computed for categorical variables. Median, interquartile range, minimum, and maximum were calculated for all continuous variables. For variables found to be within normal distribution, mean and standard deviation were computed.

Association analysis of IOP was carried out using univariable and multivariable linear regression with generalized estimating equations to incorporate two eyes of one study participant. As independent variables, age, sex, CCT, mean corneal radius, ACD, lens thickness, and posterior segment length were included in model 1. In model 2, the associations of IOP with age, sex, and ACA width was computed. In addition, model 3 incorporated age, sex, CCT, mean corneal radius, ACD, lens thickness, posterior segment length and ACA width.

As sensitivity analysis, those subjects with IOP lowering medication were excluded. A further analysis was conducted excluding those with previous corneal refractive surgery.

Data were processed by statistical analysis software (R, version 4.0.0; http://www.R-project.org/, provided in the public domain by R Core Team, Vienna, Austria). This is an explorative study; thus P values should be interpreted as a continuous measure of statistical evidence.

Results

A total of 6640 subjects (3380 men and 3260 women) were included in this cross-sectional analysis. The characteristics of the sample are given in Table 1. IOP in phakic right eyes was 14.8 ± 2.9 mm Hg and 14.9 ± 2.9 mm Hg in the left eyes, the distribution is given in Figure 1 (a: right eyes; b: left eyes). Posterior segment length was 15.5 ± 1.2 mm in both eyes.

Univariable analysis revealed a statistically significant association between IOP and CCT (Fig. 2), mean corneal curvature, lens thickness, and posterior segment length, but not with ACD (Table 2). In multivariable analysis, higher IOP was associated with older age, a thicker central cornea, a thicker lens, and a longer posterior segment length (see Table 2). The strongest association with IOP had CCT (beta per standard deviation [SD] = 0.478), followed by posterior

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Table 1. Characteristics of the Analysis Sample of Phakic Eyes Having IOP Measurement and Optical Biometry

Characteristics	Overall (*n* = 6640)	Male (*n* = 3380)	Female (*n* = 3260)
Age, mean (SD)	57.3 (10.2)	57.6 (10.3)	56.9 (10.0)
Sex: female, (%)	3260 (49.1)	0	3260
SES, median [IQR]	13.0 [10.0, 17.0]	14.0 [11.0, 18.0]	12.0 [9.0, 16.0]
Arterial hypertension (%)	3287 (49.5)	1861 (55.1)	1426 (43.8)
Diabetes mellitus (%)	551 (8.3)	350 (10.4)	201 (6.2)
Body mass index, mean (SD)	26.6 [24.0/30.0])	27.2 [25.0/30.1]	25.7 [22.9/29.7]
Ophthalmological characteristics			
logMAR right eye, median [IQR]	0.10 [0.00, 0.20]	0.10 [0.00, 0.10]	0.10 [0.00, 0.20]
logMAR left eye, median [IQR]	0.00 [0.00, 0.10]	0.00 [0.00, 0.10]	0.10 [0.00, 0.10]
IOP right eye in mm Hg, mean (SD)	14.8 (2.92)	15.0 (3.03)	14.7 (2.80)
IOP left eye in mm Hg, mean (SD)	14.9 (2.93)	15.1 (2.98)	14.8 (2.87)
SE right eye in dpt, mean (SD)	−0.12 [−1.38/0.88]	−0.12 [−1.38/0.88]	−0.12 [−1.25/1.00]
SE left eye in dpt, mean (SD)	−0.12 [−1.38/0.88]	−0.12 [−1.38/0.88]	−0.12 [−1.38/1.00]
CCT right eye in µm, mean (SD)	550 (33)	553 (33)	546 (33)
CCT left eye in µm, mean (SD)	550 (33)	553 (33)	547 (33)
ACD right eye in mm, mean (SD)	3.26 (0.35)	3.31 (0.35)	3.21 (0.34)
ACD left eye in mm, mean (SD)	3.24 (0.34)	3.29 (0.35)	3.20 (0.34)
Lens thickness right eye in mm, mean (SD)	4.35 (0.37)	4.36 (0.38)	4.33 (0.35)
Lens thickness left eye in mm, mean (SD)	4.41 (0.36)	4.44 (0.37)	4.38 (0.34)
Axial length right eye in mm, mean (SD)	23.8 (1.2)	24.1 (1.2)	23.5 (1.1)
Axial length left eye in mm, mean (SD)	23.7 (1.2)	24.0 (1.2)	23.4 (1.1)
Antiglaucomatous medication (%)	124 (1.9)	68 (2.0)	56 (1.7)

Data from the Gutenberg Health Study (2012–2017).
SD, standard deviation; SES, socioeconomic status; IQR, interquartile range; IOP, intraocular pressure; SE, spherical equivalent; CCT, central corneal thickness; ACD, anterior chamber depth.

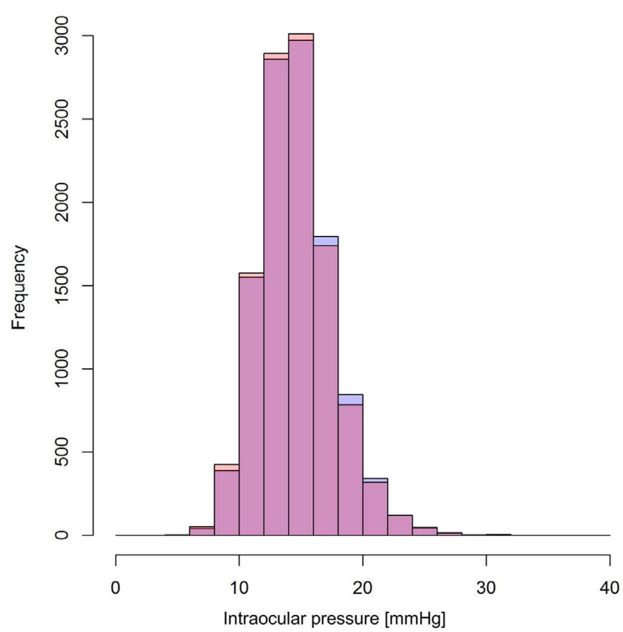

Figure 1. Distribution of IOP in phakic eyes. Data from the population-based Gutenberg Health Study (2012–2017) in subjects aged 40 to 80 years (in *red*: right eyes, in *blue*: left eyes; in *purple*: overlap of both eyes). Intraocular pressure [mm Hg].

segment length (beta per SD = 0.077) and age (beta per SD = 0.068 per 10 years). This multivariable model explained 25% of the variance. Sensitivity analysis revealed similar associations when excluding those with IOP lowering medication (Supplementary Table S1) and those with previous corneal refractive surgery.

With respect to ACA, a narrower ACA was associated with a higher IOP (−0.02 mm Hg per 1 degree increase; 95% confidence interval [CI] = −0.03 to −0.01). After adjustment for other ocular parameters, including age and sex, ACA was no longer associated with IOP ($P = 0.13$; Table 3). Mediation analysis revealed that association of IOP and ACA was fully mediated by CCT (CCT is associated with ACA = −0.334, 95% -I = −0.429 to −0.240, $P < 0.0001$). When taking both CCT and ACA into the model, ACA is no longer significant.

IOP increased over time at all ages, as shown in Figure 3.

Discussion

This population-based study evaluates IOP and its association with ocular geometric parameters, including ACA width. Our study highlights the high correlation of IOP measures with older age, thicker central cornea, a thicker lens, and a longer posterior segment length. Anterior chamber angle was associated with higher IOP in univariable analysis, although not when adjusting for age, sex, and other ocular parameters.

CCT is one of the best studied parameters regarding its effect on IOP measurement. The physiological interest of CCT was revived in the 1950s by David Maurice and its clinical significance is well recognized in the context of glaucoma diagnosis and management.[37–39] Several studies have shown an association between IOP measurements and CCT. Both clinical trials and population-based studies have demonstrated that CCT is higher in ocular hypertensives and thinner in patients with glaucoma. Furthermore, subjects from African American descent have thinner corneas than Caucasian subjects.[17,22,40,41]

The analysis of association between IOP and biometric factors is influenced by a variety of factors. That is, measurement variability due to the examination techniques used in this population cohort. It is known that noncontact tonometry overestimates IOP compared to Goldmann

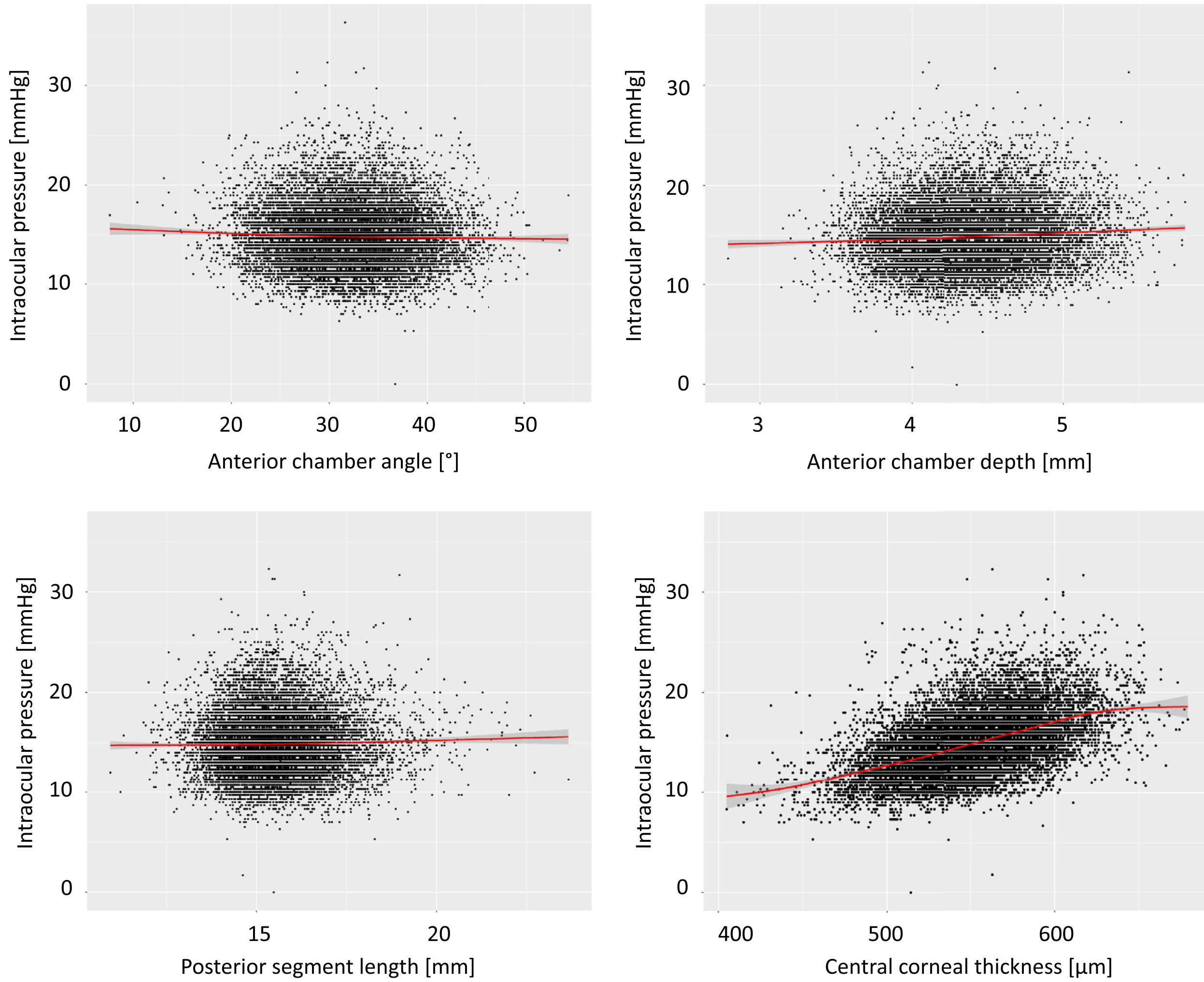

Figure 2. Relation of intraocular pressure and ocular parameters in phakic eyes. Data from the population-based Gutenberg Health Study (2012–2017) in subjects aged 40 to 80 years. The *red line* displays the LOESS (locally weighted scatterplot smoothing) curve and its 95% CI.

Table 2. Association Analysis of IOP With Ocular Geometric Parameters in Phakic Eyes

N **= 13,280 Eyes**	**Univariable**				**Multivariable (R2 = 0.25)**			
Parameter	**B**	**95% CI**	***P*** **Value**	**R2**	**B**	**95% CI**	***P*** **Value**	**B Per SD**
Sex, female					0.122	0.001; 0.244	0.050	0.042
Age, 10 years					0.196	0.133; 0.259	<0.0001	0.068
CCT, mm	0.0418	0.0400; 0.0436	<0.001	0.24	0.042	0.0401; 0.0437	<0.0001	0.478
Anterior chamber depth, mm	0.008	−0.175; 0.190	0.93	0.000	−0.015	−0.234; 0.205	0.90	−0.002
Mean corneal curvature, mm	0.742	0.495; 0.989	<0.001	0.006	−0.192	−0.431; 0.048	0.12	−0.017
Lens thickness, mm	0.388	0.244; 0.531	<0.001	0.007	0.252	0.084; 0.421	0.0033	0.010
Posterior segment length, mm	0.138	0.087; 0.188	<0.001	0.001	0.199	0.144; 0.254	<0.0001	0.077

Data from the Gutenberg Health Study (2012–2017).

Linear regression analysis with generalized estimating equations (GEE). R2 describe the a pseudo R2 and does not take into account the correlation structure of the GEE model.

CCT, central corneal thickness.

applanation tonometry, in part, due to the shorter deformation of the cornea during measurement. The study protocol of the Gutenberg Health study required noncontact tonometry because study nurses/technical assistants were involved in the measurements who are – per German law – not allowed to perform Goldmann applanation tonometry (GAT). Furthermore, we cannot exclude potential systematic measurement errors in longer eyes or in subjects with CCT and/ or other biometric parameters out of normal range, but we are able to contribute knowledge to the existing literature and reporting associations of intraocular pressure with biometric parameters in the general population analyzing a large cohort and thus been able to identify even small effect sizes.

Table 3. Association Analysis of IOP and Anterior Chamber Angle width in Phakic Eyes Incorporating Parameters of the Anterior Segment

N = 13.280	Multivariable (R2 = 0.26)		
Parameter	**B**	**95% CI**	***P* Value**
Sex, female	0.124	0.003; 0.246	0.047
Age, 10 years	0.201	0.137; 0.264	<0.0001
CCT, mm	0.0422	0.040; 0.044	<0.0001
Anterior chamber depth, mm	0.113	−0.133; 0.359	0.37
Mean corneal curvature, mm	−0.176	−0.417; 0.065	0.15
Lens thickness, mm	0.446	0.275; 0.617	<0.0001
Posterior segment length, mm	0.197	0.142; 0.252	<0.0001
Anterior chamber angle, in degrees	0.007	−0.008; 0.022	0.34

Data from the Gutenberg Health Study (2012–2017).

Linear regression analysis with generalized estimating equations (GEEs).

CCT, central corneal thickness.

R2 describe the a pseudo R2 and does not take into account the correlation structure of the GEE model.

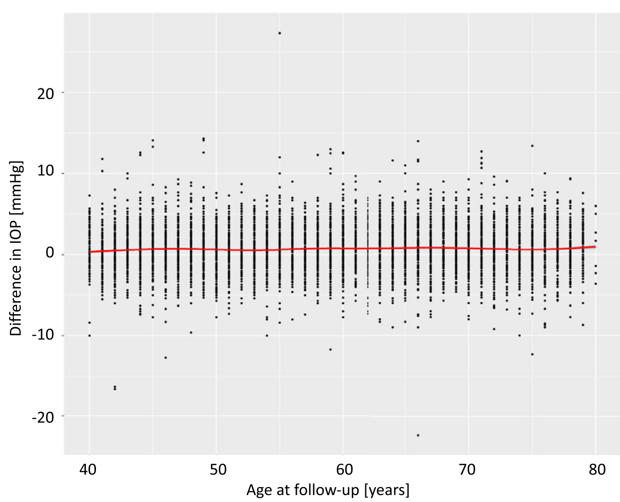

Figure 3. Change in intraocular pressure over 5 years and its relation to age. Data from the Gutenberg Health Study (2007–2017).

The development of adjustment formula has been proven to be insufficient for adjustment of IOP for CCT.[42] It is therefore, suggested to calculate the individual risk for developing glaucoma, including risk factors, such as age, status of glaucoma, refraction, maximal IOP, perimetry data, etc.

Ethnicity[6,20,24,43] and the measurement method to determine IOP[44–50] are known factors that influence IOP results: CCT does not seem to interfere with IOP measurements taken by Pascal dynamic contour tonometry.[47] Abah revealed a correlation between CCT and IOP using Perkins applanation tonometry,[5] whereas in the South African Eye Study this association was shown using rebound tonometry.[6] The difference between IOP values obtained by iCare rebound tonometry and Goldman applanation tonometry increased with increasing CCT as well.[48,49] In our cohort, we found a positive relationship between IOP and CCT in multivariable analysis. This association has been found in the baseline cohort of the GHS, reported previously.[19]

Corneal curvature and its association with IOP has been studied in the literature contrarily. Similar to our results, a Caucasian population-based study also revealed no relationship between the corneal curvature and IOP.[17] We found an association between IOP and corneal curvature in univariable analysis only, but not in multivariable analysis. Our study analyzed the association of corneal curvature and IOP in a population-based study design and thus did not investigate the extreme effects of a very flat or steep cornea. Andreanos et al. revealed that flat corneas seem to influence tonometry measurements taken by Goldmann applanation tonometry more compared to Pascal dynamic contour tonometry,[51] whereas Francis et al. showed effects of corneal curvature on IOP measurements with dynamic contour tonometry but not with Goldmann applanation tonometry as part of the Los Angeles Latino Eye Study.[44]

Several studies showed associations between IOP and other ocular parameters. Foster et al. reported a significant positive association between IOP and axial length in the European Prospective Investigation into Cancer (EPIC)-Norfolk cohort,[18] which is in line with our findings with respect to posterior segment length. Whether lens thickness or posterior segment length are also important individual risk factors for glaucoma development or progression, or are surrogates of other risk factors such as myopia, cannot be concluded from the results of our analyses. With respect to clinically relevant effect sizes, the standardized effect size for CCT was six and seven times larger than posterior segment length and age indicating that CCT is the most important factor. CCT also explained 24% of the variability of IOP.

Xu et al. found a strong correlation between IOP and anterior segment optical coherence tomography measurements, including angle opening distance, once these measurement values dropped below some anatomic threshold values, but no correlation in open angle eyes.[52] Chong et al. revealed an association between the extent of angle closure, as assessed on anterior segment optical coherence tomography and gonioscopy, with increasing IOP.[53] Hence, we only found subjects with an open angle in Scheimpflug imaging in this study population, our results are in line to those with an open ACA. We detected a univariable association between IOP and ACA width, that could be explained by age and CCT.

Higher age is a major factor for IOP elevation, as shown in our results independent of other ocular geometric parameters, and previously reported in other studies.[16,54,55] A recent meta-analysis of European cohort studies reported an inverted U-shaped trend between age and IOP with increasing IOP up to 60 years of age and decreasing IOP in older subjects.[56] This effect was not seen in our longitudinal data on IOP showing a constant increase over 5 years over all ages. Other positively related factors were female gender, arterial hypertension, history of diabetes, and darker skin.[16]

There are some limitations of our study. First, the GHS mainly includes subjects from Caucasian origin. Therefore, a generalizability to other population or ethnicities is not possible, especially to the Asian population with a different ocular geometry and a shallower anterior chamber.[57–60] Furthermore, IOP was only measured at one time point and we could not take individual intra- and inter-day variations into account. Using noncontact tonometry to determine IOP is a procedure widely used in clinical practice but not in complete agreement with the reference-standard Goldmann applanation tonometry, which may have biased our results. Further, opening of ACA was not examined using gonioscopy but Scheimpflug images were analyzed. This might lead to risk of misclassification, especially in the upper and lower quadrant where Scheimpflug imaging does not always allow to visualize the ACA due to the lids.

In conclusion, this study shows the relationship among IOP measurements with noncontact tonometry and CCT, posterior segment length, and lens thickness. These ocular parameters should be taken into consideration for a better understanding of the individual risk profile in ocular hypertension and its risk for conversion into glaucoma in future studies.

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