

# South African Eye Study (SAES): ethnic differences in central corneal thickness and intraocular pressure

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## Abstract

**Purpose** Glaucoma is the leading cause of irreversible blindness worldwide. South Africa has a diverse population but there is a lack of published ethnic specific normative data. The purpose of the study is to determine the distribution of intraocular pressure (IOP) and central corneal thickness (CCT) values in a multi-ethnic South African population and to determine additional systemic and ocular factors that influence IOP and CCT.

**Patients and methods** This cross-sectional study included a total of 402 participants with 706 eyes aged 18–94 years. Participants underwent a standardized interviewer-administered questionnaire for risk factor assessment followed by a full ophthalmic examination. The averages of six IOP readings were measured with an Icare PRO tonometer and CCT was measured with a Pentacam.

**Results** The mean CCT readings in the African, Mixed ethnicity, and Caucasian participants were  $514.77 \pm 31.86$ ,  $531.77 \pm 35.17$ , and  $549.97 \pm 30.51 \mu\text{m}$  ( $P < 0.001$ ). The mean IOP in the African, Mixed ethnicity, and Caucasian participants were  $15.51 \pm 2.49$ ,  $15.09 \pm 2.12$ , and  $15.13 \pm 2.53 \text{ mm Hg}$  ( $P = 0.07$ ). Africans had significantly higher IOP than Mixed ethnicity ( $P = 0.034$ ) and Caucasians ( $P = 0.011$ ). Hypertensives had a higher IOP ( $P = 0.03$ ). Age and pseudophakia were associated with a lower IOP ( $P < 0.001$ ) and higher CCT ( $P < 0.001$ ). There was a strongly positive correlation between CCT and IOP ( $\beta = 0.021$ ;  $P < 0.001$ ).

**Conclusions** In the South African Eye Study (SAES), Africans had the thinnest corneas and highest IOP followed by Mixed ethnicity and Caucasians. Including systemic and ocular factors that influence IOP specific to each population and ethnic group, will lead to

**a more accurate clinical risk stratification in glaucoma management.**

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## Introduction

Glaucoma is the leading cause of irreversible blindness globally. The highest prevalence of open-angle glaucoma occurs in blacks of African descent. Internationally, there are an estimated 60 million people with glaucomatous optic neuropathy and an estimated 8.4 million people who are blind as a result of glaucoma. These numbers are set to increase to 80 million and 11.2 million, respectively, by 2020.<sup>1</sup> In Africa, glaucoma accounts for 15% of blindness and it is the region with the highest incidence and prevalence of blindness relative to other regions worldwide.<sup>2</sup>

By the year 2020, it is predicted that the number of people with open-angle glaucoma and angle closure glaucoma in Africa will be 8 359 451 and Africa will have the highest ratio (4.39%) of glaucoma to adult population.<sup>3</sup> There is some evidence that glaucoma has an earlier age of onset in blacks<sup>4,5</sup> and has a more aggressive clinical course.<sup>6–8</sup> In Africa, there are the additional factors of poor awareness,<sup>9–16</sup> poor access to care, and less than optimal diagnosis and management.<sup>17–24</sup> Socio-economic deprivation exacerbates the situation, leading to very late presentation.<sup>25–30</sup> Thus, in Africa, glaucoma has been referred to as the 'silent thief of sight'.<sup>31</sup>

Central corneal thickness (CCT) affects intraocular pressure measurements as a thicker cornea will cause a higher-than-actual reading to be obtained and vice versa with a thinner cornea.<sup>32,33</sup> There are various formulas and tables (Ehlers, Dresden, Doughty, Kohlhaas) to adjust intraocular pressure according to CCT to

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obtain the corrected intraocular pressure (cIOP).<sup>5</sup> CCT therefore has a profound effect on true IOP and the risk of developing glaucoma. Knowledge of the distribution of IOP and CCT in different ethnic populations is critical and useful in both clinical and research settings. Studies of ethnic variation in IOP and CCT show that African Americans have lower CCT measurements and lower IOP than Caucasians.<sup>34-39</sup> This lower IOP could be an underestimation of the actual IOP as a result of lower CCT readings potentially resulting in an under-diagnosis of ocular hypertension and glaucoma and an increase in the related morbidity. In the Los Angeles Latino Eye Study, the prevalence of glaucoma was higher among individuals with lower CCTs than in individuals with normal or higher CCTs across all levels of intraocular pressure.<sup>40</sup> South Africa has a diverse population including a group of people with mixed ancestry in whom the relationship between CCT and IOP has not previously been studied. Accurate glaucoma risk stratification is compromised in this important group due to the lack of published normative data.

Overall the prevalence of glaucoma in South Africa is 4.5%.<sup>41</sup> The prevalence of glaucoma is between 4.5 and 5.3% in black South Africans.<sup>42,43</sup> In comparison, the prevalence of glaucoma in Mixed ethnicity is 4.8%.<sup>44</sup> In the literature, there is only a historical epidemiology study in South Africa from 1973 which reported that the prevalence of glaucoma in Caucasians was 0.002%.<sup>45</sup> This would appear to be outdated as our scientific methodology and population profile have evolved but it does highlight the need for further epidemiological glaucoma studies to include all the major ethnic groups of South Africa.

### Objectives

This study aimed to examine the ethnic variations in the distributions of CCT and IOP among the three major South African Ethnic groups: Africans, Mixed ethnicity, and Caucasians. Additionally, we aimed to assess other systemic and ocular factors, which affected CCT and IOP.

### Subjects and methods

#### Design

Cross-sectional study in which a one-way analysis of variance (ANOVA) study done pre-recruitment described sample sizes of 105 Africans, 70 Mixed ethnicity, and 35 Caucasians with a total of 210 subjects achieving a power of 80%. In South Africa, it is considered unethical to recruit much more than the sample size deemed to have an adequately powered study.

#### Setting

The study was conducted prospectively on volunteers at Tygerberg Academic Hospital from March to September 2016 after informed consent was obtained. It is a tertiary hospital that is the second largest in South Africa and covers a drainage area serving millions of people. In addition, participants recruited from Stellenbosch University and the staff of Tygerberg Hospital includes people from across South Africa. Both the Biostatistics Department and study supervisor (DPS) agreed that the methodology and context was adequate to conduct this epidemiological study.

#### Participants

Volunteer convenience sampling was used. Participants underwent interviewer-administered questionnaires to collect demographic data and assess risk factors including family history of glaucoma, medical conditions such as diabetes mellitus, current and previous medication use including steroid use and ocular history including known myopia. Ethnicity was self-reported. Exclusion criteria included: history of glaucoma or previous ocular trauma; corneal edema, scarring, ectasia, or dystrophy; intraocular surgery during the preceding 3 months or any previous refractive surgery; contact lens use; a history/clinical evidence of uveitis and suspicious glaucomatous discs. Each participant underwent a complete slit lamp examination and prior to pupil dilation, the averages of six intraocular pressure readings measured with an Icare PRO tonometer (Icare, Vantaa, Finland) were calculated and CCT was measured with an OCULUS Pentacam (OCULUS Wetzlar, Germany). The Pentacam measurement was repeated until the software determined the quality of the images to be acceptable. The study was approved by the Health Research Ethics Committee of Stellenbosch University and the conduct of the study adhered to the Declaration of Helsinki.

#### Statistical analysis

For the person-level analysis, one-way analysis of variance (ANOVA) was performed to compare continuous variables among ethnic groups, and  $\chi^2$ -tests were used for categorical variables.

For the eye-level analysis, to account for some participants having both eyes analysed and some only one eye, analytical weighting was used to adjust for the within-person clustering. Analytical weights are inversely proportional to the variance of an observation. This method was used for one-way ANOVA testing and Bonferroni *post hoc* tests. Simple and multiple linear regression analysis were used to estimate crude and

adjusted coefficients for the various outcomes. Clustering by patient identity was dealt with using cluster robust standard errors. Statistical significance was set at a *P*-value of <0.05. The data were analysed with Stata Version 14.1 (College Station, TX, USA).

## Results

A total of 402 participants with 706 eyes (158 Africans, 177 Mixed ethnicity, and 67 Caucasians) aged 18–94 years were included in the analysis. About 63 participants were excluded due to the presence of exclusion criteria (61) or participant refusal (2).

The mean age  $\pm$  SD was  $35 \pm 12$  years for Africans,  $48 \pm 17$  years for the Mixed ethnicity, and  $47 \pm 20$  years for Caucasians ( $P < 0.001$ ). The average age of all participants was  $43 \pm 17$  years. About 61% of the participants were female. The presence of hypertension was also significantly different between the ethnic groups ( $P < 0.001$ ), but the presence of diabetes was not (Table 1a).

Table 1b shows unadjusted associations between ethnic groups and several ocular characteristics using one-way ANOVA testing. The mean IOP levels were clinically similar in all three ethnic groups ( $P = 0.07$ ). When the IOP was corrected for CCT in each ethnic group using the Dresden formula, the corrected mean IOP in the African, Mixed ethnicity, and Caucasian participants were  $16.90 \pm 2.45$ ,  $15.80 \pm 2.25$ , and  $15.1 \pm 2.35$  mm Hg, respectively ( $P < 0.001$ ). The mean CCT readings in the Africans ( $514.77 \pm 31.86$ ), Mixed ethnicity ( $531.77 \pm 35.17$ ), and Caucasian participants ( $549.97 \pm 30.51$   $\mu$ m) showed significant differences overall and between each ethnicity ( $P < 0.001$  for all comparisons).

The CCT mean values and 95% confidence intervals are contrasted by ethnic group in Figure 1. The presence of

myopia was significantly different between the ethnic groups ( $P = 0.015$ ), but the presence of pseudophakia was not different between the Mixed ethnicity and Caucasians ( $P = 0.864$ ).

Table 2 shows the systemic and ocular factors associated with IOP on simple and multiple linear regressions. The difference in mean IOP between each ethnic group was statistically significant when both ocular and systemic factors were adjusted for in the multivariate analysis. It showed Mixed ethnicity ( $P = 0.034$ ), and Caucasians ( $P = 0.011$ ) had a lower intraocular pressure compared to Africans (0.54 and 0.88 mm Hg, respectively).

In the multivariate analysis, age was a systemic factor associated with lower intraocular pressure ( $P < 0.001$ ). Hypertension was associated with a higher intraocular pressure ( $P = 0.03$ ). The ocular factor associated with a higher intraocular pressure was an increased CCT ( $P < 0.001$ ). Pseudophakia was associated with a lower intraocular pressure ( $P < 0.001$ ).

Table 3 shows that self-reported ethnicity was independently associated with thicker corneas ( $P < 0.001$ ). Compared to the Africans, the Caucasians had on average about 34 microns thicker corneas and the Mixed ethnicity had on average 18 microns thicker corneas. Ocular factors associated with an increased central CCT were IOP and pseudophakia (both  $P < 0.001$ ).

## Discussion

To our knowledge, the South African Eye Study (SAES) is the largest adult epidemiological study in Sub-Saharan Africa (SSA) assessing the ethnic differences in IOP and CCT. In this prospective cross-sectional study of three major adult ethnic groups in South Africa, Africans had

**Table 1a** Demographic and systemic characteristics among the three ethnic groups

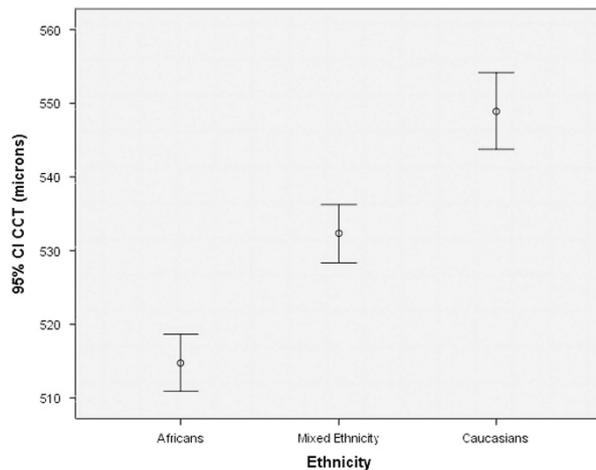
Characteristics	Total n = 402	African n = 158	Mixed ethnicity n = 177	Caucasians n = 67	P-value
Age (years)	43	35	48	47	<0.001
Female	246 (61.2%)	97 (61.4%)	115 (65%)	33 (50.7%)	<0.001
Diabetes	79 (19.7%)	23 (14.6%)	47 (26.6%)	9 (13.4%)	0.08
Hypertension	119 (29.6%)	22 (13.9%)	73 (41.2%)	24 (35.8%)	<0.001

**Table 1b** Ocular characteristics among the three ethnic groups

	Total n = 706	African n = 277	Mixed ethnicity n = 311	Caucasians n = 118	P-value
IOP (mm Hg)	15.26	15.51	15.09	15.13	0.079
cIOP (mm Hg)	16.12	16.90	15.80	15.14	<0.001
CCT ( $\mu$ m)	528.14	514.77	531.77	549.97	<0.001
Myopia (n(%))	37 (9.2%)	9 (5.7%)	16 (9%)	12 (17.9%)	0.015
Pseudophakia (n(%))	22	0 (0%)	16 (5%)	6 (5%)	0.864

the thinnest corneas followed by Mixed ethnicity. Caucasians had the thickest corneas similar to the average CCT reported in the literature.<sup>34,35</sup> The difference in mean IOP between each ethnic group was statistically significant when both ocular and systemic factors were adjusted for in the multivariate analysis. Africans had the highest mean IOP followed by Caucasians and Mixed ethnicity.

Numerous epidemiological studies have been conducted across several Sub-Saharan countries on the normative values of CCT and intraocular pressure in non-glaucomatous participants. A review of the literature collected 1637 non-glaucomatous African patients drawn from five SSA countries (South Africa, Nigeria, Ghana, Cameroon, and Ethiopia). The patients' ages ranged from 5 to 90 years. The outcome of the CCT range was



**Figure 1** Confidence interval distribution in the different ethnic groups.

440–670  $\mu\text{m}$  and its mean value varied from 512 to 550  $\mu\text{m}$  for non-glaucomatous subjects. The thicker and thinner mean values were found in Nigeria and South Africa, respectively.<sup>46</sup> There has only been one previously published CCT IOP study conducted in South Africa on black Africans: 100 participants aged 18–25 had a CCT of  $512.4 \pm 38.9 \mu\text{m}$  with an intraocular pressure between 9–21 mm Hg and a mean of 13.8 mm Hg.<sup>47</sup> The CCT mean and SD in Africans in our study was  $514.77 \pm 31.86$  and included a larger number of black African participants ( $n = 158$ ) and a wider age distribution (18–79 years). The IOP mean of  $15.51 \pm 2.49$  mm Hg in black Africans in our study was higher than the previous South African based study and showed a positive and consistent correlation between CCT and IOP. Interestingly, 21 Africans from 9 other Sub-Saharan African countries were included (Zimbabwe, Congo, Kenya, Somalia, Burundi, Nigeria, Mozambique, Cameroon, and Malawi). Their mean IOP of 16.41 mm Hg was higher than the South Africans' IOP of 15.35 mm Hg ( $P = 0.01$ ). The Sub-Saharan black African group also had thicker corneas of 525  $\mu\text{m}$  compared to 513  $\mu\text{m}$  in South Africans ( $P = 0.01$ ). There are no published normative IOP and CCT values for Africans from Zimbabwe, Congo, Kenya, Burundi, Mozambique, and Malawi. In a small study of Somalian adults, the mean intraocular pressure of Somalians was  $13.76 \pm 3.63$  mm Hg.<sup>48</sup> In Nigeria, the mean CCT was  $548.97 \pm 34.28 \mu\text{m}$  and the mean IOP was  $15.61 \pm 2.69$  mm Hg.<sup>49</sup> In Cameroon, the average CCT was  $529.29 \pm 35.9 \mu\text{m}$  and the average IOP was  $13.01 \pm 2.97$  mm Hg.<sup>50</sup>

Africans are more genetically diverse than other populations. Genetic studies suggest that the Mixed ethnicity group in South Africa has the highest levels of

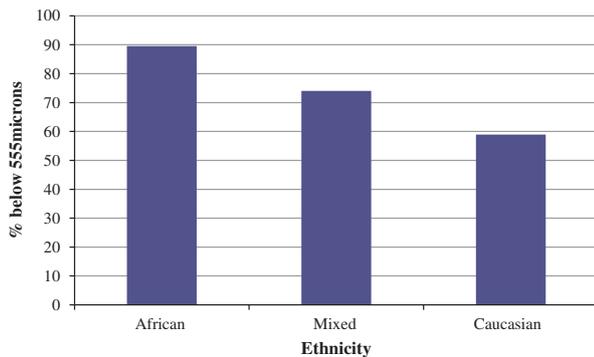
**Table 2** Associations of intraocular pressure with systemic and ocular factors

Systemic	Univariate model			Multivariate model <sup>a</sup>		
	$\beta$	95% CI	P-value	$\beta$	95% CI	P-value
<i>Ethnicity</i>						
Mixed ethnicity vs Africans	-0.39	-0.871 to 0.091	0.112	-0.54	-1.05 to -0.04	0.034
Caucasians vs Africans	-0.39	-1.08 to 0.29	0.258	-0.88	-1.56 to 0.21	0.011
Age	-0.15	-0.281 to 0.003	0.013	-0.03	-0.05 to -0.01	<0.001
Gender	0.274	-0.191 to 0.170	0.248	0.303	-0.13 to 0.74	0.170
Diabetes	0.589	0.415 to 1.136	0.035	0.535	0.08 to -0.73	0.08
Hypertension	0.202	-0.294 to 0.702	0.81	0.688	0.04 to 1.32	0.03
<i>Ocular</i>						
CCT	0.17	0.10 to 0.23	<0.001	0.02	0.01 to 0.02	<0.001
Myopia	-0.26	0.51	-1.04 to 0.52	-0.16	-0.92 to 0.50	0.67
Pseudophakia	-1.18	-2.24 to -0.13	0.03	-1.40	-2.31 to -0.50	<0.001
Constant				5.35	1.99 to 8.70	0.002

<sup>a</sup>Adjusted for all systemic and ocular factors listed.

**Table 3** Associations of central corneal thickness with systemic and ocular factors

Systemic	Univariate model			Multivariate model		
	$\beta$	95% CI	P-value	$\beta$	95% CI	P-value
<i>Ethnicity</i>						
Mixed ethnicity vs Africans	17.519	10.01 to 25.02	<0.001	15.02	7.49 to 22.54	<0.001
Caucasians vs Africans	34.38	26.33 to 42.42	<0.001	32.22	23.46 to 40.98	<0.001
Age	0.404	0.196 to 0.612	<0.001	0.18	-0.06 to 0.43	0.15
Gender	3.465	-3.75 to 10.68	0.346	0.95	-6.46 to 13.07	0.95
Diabetes	10.09	0.31 to 19.88	0.043	3.30	-6.47 to 13.07	0.51
Hypertension	13.31	5.546 to 21.07	0.001	-0.01	-9.42 to 9.39	0.99
<i>Ocular</i>						
IOP	3.78	2.42 to 5.13	<0.001	4.39	3.24 to 5.53	<0.001
Myopia	4.63	-9.61 to 18.89	0.52	1.80	-12.08 to 15.68	0.80
Pseudophakia	30.32	13.83 to 46.82	<0.001	22.88	8.63 to 37.14	0.002
Constant				439.63	419.02 to 460.24	<0.001



**Figure 2** Percentage of each ethnic group with CCT < 555 microns.

mixed ancestry in the world.<sup>51-53</sup> Our study showed that Mixed ethnicity participants had a mean CCT of  $531.77 \pm 35.17$  microns. This is the first study to describe the ocular characteristics of this unique ethnic group.

In several studies including the Barbados Eye Study Group, black participants had thinner corneas<sup>54</sup> (mean thickness,  $529.8 \mu\text{m}$ ) compared to mixed (black and white) ( $537.8 \mu\text{m}$ ) and white participants ( $545.2 \mu\text{m}$ ), respectively.<sup>55</sup> In our study, the CCT of South African Caucasian participants was  $549.97 \pm 30.5$  microns ( $P < 0.001$ ). It is the first epidemiological study in Sub-Saharan Africa to report on the normative CCT and IOP values of the Caucasian ethnic group.

In the OHTS, a multivariate model showed that a thinner CCT was an important predictive factor for the development of POAG. The OHTS reports a thin CCT of < 555 microns as an independent risk factor for glaucoma.<sup>56</sup> Our study found that the majority of South African participants across ethnic groups have this risk factor. 89.52% of Africans, 74.01% of Mixed ethnicity, and

58.96% of Caucasians had a thin CCT as per OHTS definition illustrated by Figure 2. But this was a completely different population sample based in the United States and highlights the need to clinically integrate CCT in an ethnic and population-specific manner so that a thin cornea is more specifically defined. This will lead to more accurate glaucoma risk stratification in different population groups.

#### Associations between IOP and age

Previous studies have found that IOP increases with age,<sup>57,58</sup> while other studies have found no correlation with age.<sup>59</sup> These differences may be population-specific. African populations and their genomes are highly complex. The bio-geographic variations within South Africa, which includes both indigenous and non-African population groups are further aspects to consider. Cape Town is an urban location and this will also impact on the results. In our study, there was ethnic variation in the multivariate analysis. In Africans, IOP increased with age ( $P = 0.88$ ) while in Mixed ethnicity participants IOP decreased with age ( $P = 0.19$ ). In Caucasians, IOP increased with age under 40 years of age ( $P = 0.33$ ) but decreased over 40 years of age ( $P = 0.01$ ).

Above 50, there was a strong negative association between age and IOP. IOP decreases with age adjusted for race by an average of 0.8 mm Hg compared to those < 50 years.

#### Diurnal variations with central corneal thickness and intraocular pressure

Our study found no statistically significant fluctuations in IOP and CCT measurements at different times of the day

(0700 or 1800 hours). There was a trend for CCT to be higher in the afternoon ( $P=0.5$ ) in contrast to previous smaller studies where CCT was found to be thickest in the morning and gradually thinned as the day progressed.<sup>60–63</sup> There was also a trend for IOP to be lower ( $P=0.63$ ) in the afternoon, which is similar to the results of previous studies.<sup>64</sup> But overall, none of these trends were statistically significant; thus, the time of day that the measurements were taken was not a confounding factor.

### *Ocular factor associations with central corneal thickness and IOP*

In the multivariate analysis, IOP was 1.40 mm Hg less in pseudophakic eyes ( $P<0.001$ ). This correlates with previous studies that report a drop in IOP of about 1.5 mm Hg in non-glaucomatous patients.<sup>65</sup>

Ocular factors associated with an increased CCT were IOP and pseudophakia ( $P<0.001$ ). For every 4 microns increase in thickness, IOP increased by 1 mm Hg overall.

In addition, corneal hysteresis (CH) may also be related to optic nerve/laminar biomechanics. It has been shown that combining CH and CCT for glaucoma risk assessment improves diagnostic capability compared to using either factor alone.<sup>66</sup>

### *Study strengths and limitations*

In this study, ethnicity was self-reported, which is in keeping with most studies examining ethnic differences of IOP and CCT but this is prone to information bias.<sup>35,37–40,46,47,52–54</sup> Genetic African ancestry (GAA) may be a less 'prejudiced' method to analyze the data. But GAA introduces its own biases to the process since broad coverage of African populations with ethnic diversity are not currently represented.

The strengths of the study include a moderately sized multi-ethnic sample group. Standardized study methodology was used to prospectively collect data for each ethnic group. The average of six IOP readings was taken, which is more accurate than a single measurement. CCT was measured using the Pentacam, which is an accurate means of obtaining this data and measurements were repeated until an acceptable quality was achieved and thus accuracy was ensured. Data were collected from a Mixed ethnicity group not previously reported in the literature. Certain sub-group analysis revealed correlations not previously described in the literature and confirmed trends reported in other studies. This study could serve as a starting point for future genetics-based studies, which could aim to identify the gene(s) responsible for the differences described.

### **Conclusion and relevance**

This study confirms the ethnic variations of CCT and reports on a Mixed ethnicity group with rich genetic ancestry not previously studied. Africans have the thinnest corneas among the three ethnic groups followed by Mixed ethnicity and Caucasians. The majority of all ethnic groups have a CCT of  $<555$  microns, which emphasizes the need for ethnic and population-specific definitions of a thin cornea. Both measured and cIOP adjusted for CCT was highest in Africans. Hypertension correlated with an increased intraocular pressure. Age was associated with a decrease in intraocular pressure. Increased CCT was strongly associated with an increased intraocular pressure. Pseudophakia was associated with an increased CCT and a decreased intraocular pressure. Systemic and ocular factors influence IOP and CCT. There is a need for refining risk factor definitions, which are population and ethnic specific. Including these refined influences will lead to more accurate clinical risk stratification and prognostication for glaucoma screening and management. This has important public health and clinical-care implications.

### **Summary**

#### **What was known before**

- Ethnic differences occur between central corneal thickness and intraocular pressure of different populations and ethnicities, and this influences intraocular pressure readings which impact on glaucoma screening.

#### **What this study adds**

- Establishes normative data of central corneal thickness and intraocular pressure in the South African population's majority ethnic groups.
- Compares the normative data of the South African Eye Study to other international studies with implications for glaucoma screening and prognostication.
- The first epidemiological study of this type that addresses the role of African ancestry in endophenotypes CCT and IOP.

### **Conflict of interest**

The authors declare no conflict of interest.

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## Disclaimer

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