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Title:

Glaucoma features in an East African population: a six-year cohort study of older adults in Nakuru, Kenya

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Abstract (250 words)

Purpose

Glaucoma is a leading cause of blindness in people of African descent. Minimal data is available from African population-based cohort studies. The primary aims of this study were to describe the normative distribution of glaucoma features to enable glaucoma classification and to assess risk factors for those with glaucoma at follow-up among people aged ≥ 50 years in Kenya.

Materials and Methods

Random cluster sampling with probability proportionate to size was used to select a representative cross-sectional sample of adults aged ≥ 50 years in 2007-8 in Nakuru District, Kenya. A six-year follow-up was undertaken in 2013-14. Comprehensive ophthalmic examination included visual acuity, digital retinal photography, visual fields, intra-ocular pressure, OCT and independent grading of optic nerve images. We report glaucoma features, prevalence and predictors for glaucoma based on the ISGEO criteria. Measures were estimated using a Poisson regression model and including inverse-probability weighting for loss to follow up.

Results

At baseline, 4,414 participants aged ≥ 50 years underwent examination. Anterior chamber OCT findings: mean anterior chamber angle of 36.6° , mean central corneal thickness of $508.1\mu\text{m}$ and a mean anterior chamber depth of 2.67mm . 2,171

participants were examined at follow-up. The VCDR distribution was 0.7 and 0.8 at the 97.5th and 99.5th percentiles, respectively. A total of 88 (4.3%, 95% CI, 3.5-5.9%) of participants at follow-up had glaucoma consistent with ISGEO criteria. A RAPD and raised IOP were associated with the diagnosis.

Conclusions

Glaucoma is a public health challenge in low-resource settings. Research into testing and treatment modalities in Africa is needed.

Keywords: Africa, glaucoma, optic nerve, Cohort, Population-based.

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Introduction

Glaucoma is a leading cause of blindness globally.¹ The proportion of the worldwide magnitude of blindness attributable to glaucoma increased by 50% between 1990 and 2010 from 4.4% to 6.6%.² This trend is expected to continue over coming decades, with the estimated numbers with glaucoma predicted to rise from 60.5 million people in 2010 to 79.6 million by the year 2020³ and then to 111.8 million by 2040.⁴ Glaucoma is the second most common cause of blindness in sub-Saharan Africa (SSA),⁵ with estimates suggesting that there were 6.5 million people with glaucoma in SSA in 2010 projected to increase to 8.4 million by 2020, though data are sparse.⁶

Whilst blindness from glaucoma may be preventable, this is dependent upon early diagnosis and delivery of long-term effective treatment. Glaucoma poses a particular problem in sub-Saharan Africa due to both higher age-specific prevalence, higher risk for open-angle glaucoma,⁷⁻¹⁰, late presentation¹¹ and low levels of coverage and adherence with treatment.^{12, 13} Adherence to topical treatment is sufficiently poor that the primary treatment of choice in SSA is often surgery⁵ in the hope that a single intervention achieves long term control of intra-ocular pressure (IOP) as the main modifiable risk factor.¹¹⁻¹³ Furthermore, clinical features of glaucoma may be different in a sub-Saharan African setting compared to elsewhere, necessitating different therapeutic approaches.

The objectives of this study were, within the context of a population-based cohort study in Nakuru, Kenya: i) to describe normative features of glaucoma in this cohort, ii), to describe the prevalence of glaucoma or specific glaucoma features at baseline and at follow up, iii) to assess baseline risk factors for having glaucoma at follow up and iv) to describe clinical signs predictive of glaucoma at follow up.¹⁴ The distribution

of key features of glaucoma (optic nerve morphology, intraocular pressure, visual acuity, angle morphology) and the risk factors associated with changing optic disc morphology that occurred over the six year follow up period will also be described.

Materials and Methods

Ethics Statement

The London School of Hygiene & Tropical Medicine (LSHTM) Ethics committee and the African Medical Research Foundation (AMREF) granted ethical approval for the study. Approval was also granted by the Provincial Medical Officer for Nakuru County. Written approval was sought from the administrative heads in each cluster, usually the village chief. All participants gave written or thumbprint consent to participate. People requiring medical treatments were referred to the appropriate health care service.

Sampling Strategy and Recruitment

The study baseline fieldwork was carried out between January 2007 and November 2008. The follow-up study took place between October 2012 and March 2014. At baseline, 100 clusters were selected across Nakuru County with a probability proportional to the size of the population using the electoral roll as the sampling frame. A cluster was defined as the area served by a polling station. Households were selected within clusters using a modified compact segment sampling method¹⁵. Each cluster was divided into segments so that each segment included approximately 50 people aged ≥ 50 years. One segment was selected at random, and all eligible people were included sequentially until 50 had been examined.

The sample size of 5000 people was sufficient to estimate a prevalence of disease at 3.0% among those aged ≥ 50 years, with a required precision of 0.5%, 95% confidence, a design effect to account for clustering of 1.5, and a response rate of 90% (Epi Info 6.04, Centers for Disease Control and Prevention, Atlanta, GA). In total, 4,381

participants were recruited at baseline (response rate 81%). All participants were invited to attend an examination clinic at a central location within the cluster (see below).

Follow-up

Approximately one week before the follow-up examination clinic was carried out for a given cluster, a field officer studied the maps of the village including GPS coordinates recorded at baseline and made phone contact with the village chief or guide to arrange the visit. At the planning visit a list of study participants were given to the chief and a local village guide was recruited to assist locating the study participants. Two days prior to the clinic, the field officer reminded chiefs of the visit by phone and notified them and the guide of the advance team's arrival. On the day prior to the examination clinic, a study team visited homes of baseline participants and confirmed their identity using National Identity cards and invited them to attend the examination clinic the following day. All identified participants were also asked to help locate baseline participants that had not been found.

On the examination day, the advance team confirmed the identity of participants against data from baseline (age, date of birth, name, and identity cards). In cases of uncertain identity, confirmation was made based on retinal examination verified by comparison of retinal photos with baseline photo (n=12).

In both baseline and follow-up, an examination clinic was established at a central location where there were appropriate amenities such as electricity, water and road access. The following examination protocols were implemented at both baseline and follow-up.^{14, 16}

Ophthalmic and General Examination

Visual Acuity

All participants at baseline and follow-up underwent visual acuity testing on each eye separately at four meters using a reduced LogMAR tumbling 'E' chart¹⁷ in an appropriately illuminated area, as described elsewhere.^{18, 19} The presenting visual acuity was defined as the number of letters read correctly without glasses if the participant did not have glasses, or with glasses if they had them.

Anterior Segment Examination

At baseline the anterior segment assessment was made on the slit lamp by a single ophthalmologist (WM). The Van Herick angle assessment was performed.²⁰

Anterior Chamber OCT

Gonioscopic assessment of the angle was not undertaken, however a Heidelberg Slit Lamp-adapted Optical Coherence Tomography (SL-OCT) (Heidelberg Engineering, Heidelberg, Germany) was used at baseline to examine the anterior segment to provide population normative data on the Angle Opening Distance (AOD), Anterior Chamber Angle (ACA), Central Corneal Thickness (CCT) and Anterior Chamber Depth (ACD). These normative data analyses excluded eyes that were pseudophakic. Furthermore, eyes with trachomatous or non-trachomatous corneal opacities and those with disorganized globes (phthisis, staphyloma) were excluded from the corneal

thickness analysis. All measurements were obtained from scans using the interactive distance measurement of the SL-OCT proprietary software (Heidelberg Eye Explorer v1.5.9.0; Heidelberg Engineering, Heidelberg, Germany). Analyses based on naso-temporal (horizontal) meridians. Anterior chamber depth was assessed using peaks of the corneal reflectivity profile to identify the central cornea as well as the anterior and posterior boundaries of the cornea. Calipers were aligned from the posterior border of the central cornea. Two measurements were averaged for each eye. Anterior chamber angle opening distance was taken as posterior cornea and opposite peripheral iris with the apex lying in the angle recess. All anterior segment measurements were taken with the pupil undilated.

Gonioscopy

At follow-up, an assessment of the opening angle of participants' right and left eyes using direct visualisation was made using a four-mirror gonioscopy lens (Zabbys). This lens does not require coupling fluid and was chosen to minimize impact on the quality of retinal photographs. Angles were recorded using standard Shaffer grading and further classified as "open", "occludable" or "closed" based on standard referral criteria.²¹ Angle OCT was not performed at follow-up. Occludable angles were defined at follow up as: pigmented trabecular meshwork not visible in 3/4 or more of angle circumference in primary position without manipulation, in presence of low illumination. If the patient could not cooperate with gonioscopy, the Van Herick (VH) technique²⁰ was used for grading with an anterior chamber depth of less than quarter of the corneal thickness being considered occludable.

Intraocular Pressure (IOP)

At baseline and follow-up participant's eyes were anesthetized using tetracaine 1% eye drops (Kenya Society for the Blind, Eye Drop Production Unit, Nairobi, Kenya) and the tear film stained with fluorescein-impregnated paper. IOP was measured using a Goldmann Applanation Tonometer. One reading was taken from each eye and analysed independently. The tonometer was checked for calibration weekly and disinfected between patients.

Visual Field Assessment

At baseline, all individuals with suspect or abnormal discs on clinical slit-lamp examination underwent automated visual field testing. The Humphrey[®] Field Analyzer II - 720i series (Carl Zeiss Ophthalmic Systems, Oberkochen, Germany) was used. A suspect or abnormal disc was defined as a vertical cup to disc ratio (VCDR) of 0.7 or above; optic disc cupping asymmetry between the eyes of more than 0.2 VCDR; or any other abnormal features including notching, disc haemorrhages or disc pallor. A random sample of five individuals per cluster (10%) also underwent visual field testing to provide normative data.

Participants performed the Swedish Interactive Thresholding Algorithm (SITA) STANDARD 24-2. SITA Fast was used to determine the threshold level in all participants having visual field analysis. Appropriate corrective lenses for refractive errors were used when needed. An automated fixation monitor was used throughout. If the SITA fast test was reliable the SITA standard test was performed. If the SITA fast was unreliable (false-positives, $\geq 20\%$; false-negatives, $\geq 33\%$; fixation losses, $\geq 33\%$),

then this was repeated once. If it remained unreliable then no further testing was done.

At follow-up, a different strategy for visual field testing was used due to challenges at baseline: All subject's eyes with VA equivalent to $\geq 6/60$ Snellen underwent automated visual field testing by a trained visual field technician using the Henson 8000 Visual Field Analyser (TopCon, Tokyo, Japan) The multiple stimulus suprathreshold test was used following manufacturers guidelines (Screening test - 26 test locations). When one or more spots were missed, the 26-point test was repeated for that eye. If any missed spots re-occurred on the second time of testing the test for that eye was extended to 68 test locations. This machine and strategy were used in preference to the baseline methods due to feedback from both patient's and tester at baseline as well as unreliable visual field data from baseline. Patient's found the baseline testing protocol difficult to understand and the time required to complete the test meant only a sub-sample of the population could be investigated.

Visual fields were considered consistent with glaucoma at baseline and follow-up if:

- (1) The test was reliable according to performance indices
- (2) The glaucoma hemifield test was outside normal limits, and
- (3) The test showed three or more abnormal contiguous points clustering in the same hemi field.

Visual Fields were graded at the Moorfields Eye Hospital Reading Centre.

Fundus photography and grading

The participants had two non-stereoscopic digital 45° fundus photographs taken per eye by an ophthalmic clinical officer using a TRC-NW6S Non-Mydriatic Retinal Camera with 10 megapixel Nikon D80 (TopCon, Tokyo, Japan) at baseline and a DRS CentreVue+ (Haag-Streit, Köniz, Switzerland) Retinal Camera at follow-up. One image was centered on the optic disc while the other was centered on the macula.

The digital images were forwarded to the Retinal Grading Centre at Moorfields Eye Hospital Reading Centre (MEHRC) London for grading and confirming the clinical diagnosis of posterior segment disease.

The senior grader graded all discs considered abnormal on clinical examination at the slitlamp at baseline and all optic nerve images at follow-up. Images were first categorized for quality as excellent, good, fair, borderline or ungradeable. They were then graded for vertical cup disc ratio (VCDR). The scleral ring was identified to determine the margins of the disc and delineating the rim identified the cup. The rim was defined as the area between the border of the optic disc and the position of blood vessel bending and the area within the rim as the cup. A vertical measure of both the cup and disc were taken to calculate the VCDR. Discs images were also examined for any abnormality and were graded as normal, suspicious or abnormal. A disc was deemed abnormal if any of neuro-retinal rim (NRR) thinning, notching or disc hemorrhage(s) were present, if VCDR was ≥ 0.7 . A suspicious disc was one where adjudication was necessary to determine if its appearance was abnormal.

In case of difficulties, the adjudicator (TP) decided on the grading of the images. The adjudicator also graded 5% of randomly selected images to ensure quality control.

At baseline and follow-up, all participants' discs were estimated based on image grading.

Data Handling & Statistical Analyses Methods

Data entry

Image data were double entered into a specially developed dataset (EpiData Entry v 2.1) at both baseline and follow up. Consistency checks were performed each evening and inconsistencies corrected the same day.

Data analysis

The International Society for Geographical & Epidemiological Ophthalmology (ISGEO) categorises glaucoma as Primary Open Angle Glaucoma (POAG) and Primary Angle Closure (PAC) based on direct viewing of the angle. POAG is defined in three categories based on the optic nerve VCDR, visual fields, IOP, VA and the presence or absence of previous glaucoma surgery (clinically or from medical records).²² The mean, 97.5th and 99.5th percentiles were calculated for optic disc VCDR and IOP for the participants at follow-up. Based on baseline normative data, the cut-off points required for ISGEO POAG classifications were used to classify accordingly:²²

- **Category 1 with structural and functional evidence:** Eyes with a VCDR or VCDR asymmetry $\geq 97.5\%$ for the normal population that showed a definite visual field defect consistent with glaucoma.
- **Category 2 (advanced structural damage with unproven field loss):** Eyes of those without any or with no valid visual field testing but with a VCDR or asymmetry $\geq 99.5^{\text{th}}$ percentile for the normal population.

- **Category 3 (no view of optic disc and field testing impossible):** Eyes of those with VA<3/60 and the IOP>99.5th percentile, or VA<3/60 and evidence of glaucoma filtering surgery, or previous diagnosis of glaucoma confirmed from medical records.

Glaucoma suspects were defined as:

- *field suspects:* those with abnormal visual fields consistent with glaucomatous changes but no raised IOP, disc damage or features consistent with trabecular obstruction,
- *disc suspects:* those with VCDR \geq 97.5th percentile for the population but less than the 99.5th percentile and no other feature of glaucoma and no documented field defect. It also included those with optic disc hemorrhages accompanied by no other feature of glaucoma
- *Ocular Hypertensives:* IOP \geq 97.5th percentile with normal optic disc and normal visual field

A normative sample was used to calculate the 97.5th and 99.5th percentiles of VCDR and IOP from those participants examined at follow-up with normal visual fields.

Baseline to follow-up changes

It was not possible to produce an annual glaucoma incidence due to the lack of reliable visual field data and therefore it was not possible to define an “at-risk” baseline group. Individuals at follow-up were classified as suspect or definite glaucoma -based on ISGEO criteria using graded images of the optic disc and visual fields. Participants at follow-up were then classified in a binary manner as normal or glaucoma (glaucoma if

ISGEO categories 1, 2 or 3 were fulfilled for that participant). Multivariable logistic regression analyses were conducted to compare those with and without features of glaucoma at follow-up in terms of baseline demographic, anthropometric and ocular features as potential risk factors of glaucoma.

Results

Follow up rates

At baseline (2007-2008), 4,414 participants had a complete assessment and of these, 2,171 (50%) were seen at follow-up six years later. Characteristics of participants and non-participants at follow-up are described in detail elsewhere.^{23, 24} In summary, compared with those followed-up, participants who had died during follow-up were older, more likely to be male, to have lower education levels and higher systolic blood pressure and have diabetes, but had lower BMI. Compared with participants seen, those lost to follow-up (not known to be deceased) were less likely to be Kikuyu or Kalenjin speakers, had lower levels of education, and were more likely to be from urban areas and be from either the highest or lowest socioeconomic quartile.

Anterior Chamber OCT

Anterior segment findings at baseline using OCT are described in Table 1, the mean angle opening distance (n=6,259) was 631 μ m (SD:167), the mean anterior chamber angle (n=3,484) was 36.6° (SD:7.6), the mean central corneal thickness (n=6,365) was 508.1 μ m (SD:36.9), and the mean anterior chamber depth (n=6,358) was 2.67mm (SD:0.32)

Gonioscopy

Anterior Segment OCT was not available at follow-up, however 2,111 right eyes and 2,107 left eyes had a direct visualisation of the angle using a 4-mirror gonioscope, with only five right and five left eyes (0.2%) considered to have occludable angles (based on visualisation of Schwalbe's line and the anterior meshwork or less); see Table 2.

Intraocular Pressure

The mean IOP at baseline based on 3,745 observations (right eye only) was 15.3mmHg (SD 3.4, Range 2-46mmHg). Of these, there were 1,775 observations (right eyes only) for whom IOP was measured at both baseline and follow-up. Among these, at baseline mean IOP was 15.4 (SD 3.4) for the right eye, and at follow-up (right eyes) was 15.0mmHg (SD 3.2, Range = 1-34mmHg), providing evidence of a lower IOP at follow up compared to baseline among right eyes ($p<0.001$). IOP was significantly higher in the right eye than the left eye at both baseline ($p<0.001$) and follow-up ($p=0.02$). See Table 3.

Optic discs

At baseline, due to camera failure preventing image acquisition in one third of clusters, a slit lamp based clinical assessment of the optic disc vertical cup to disc ratio (VCDR) was made in two ways:

1. Through undilated pupils with +90D lenses using slit lamp biomicroscopy (n=5,917 eyes)
2. After dilating pupils with +90D lenses using slit lamp biomicroscopy (n=7,821 eyes)

Baseline optic disc assessment is summarised in Table 4.1,063 (25.7%) Right Eye discs and 1,078 (25.8%) Left Eye Discs could not be visualised with undilated pupils. There was a statistically significant difference between the mean VCDR for eyes with pupils dilated and non-dilated pupils where the disc was visible in both instances, with the dilated eyes having higher VCDR ratios (0.23, SD 0.15) than non-dilated eyes (0.21, SD 0.13) (paired t test<0.001). Using undilated CDR 1.5% of eyes had CDR \geq 0.7 while using dilated CDR, 2.8% of eyes had VCDR \geq 0.7 ($\chi^2=13.8$ p=0.002).

At follow up, the VCDR for right and left eyes from image grading were available in all clusters from 3,658 of a possible 4,342 eyes (2,171 people). The median VCDR was 0.3 and at the 97.5th and 99.5th percentile it was 0.7 and 0.8 respectively. See Figure 1.

The VCDR percentiles at follow-up in those with a normal visual field (n=1062) remained at 0.7 and 0.8 at the 97.5th and 99.5th percentiles respectively.

At baseline, 3,251 participants had a clinical assessment (i.e. no image grading) of the optic discs, of which 40 (1.2%) were considered abnormal, 536 (16.5%) suspicious and 2,675 (82.3%) normal. At follow-up, 2,003 participants had an image-based assessment of the optic discs, of which 64 (3.2%) were graded as abnormal, 234 (11.7%) suspicious and 1,705 (85.1%) were normal. 89 of 1,255 (7.1%) participants who had a baseline (clinical) and follow-up (image) assessment went from “normal” to either “suspicious” or “abnormal”. Of the 1,499 participants who had optic discs graded at both baseline (clinical) and follow-up (image) 171 (1.1%) were considered abnormal, 236 (15.7%) suspicious and 1246 (83.1%) as normal at baseline. At follow up there were 53 (3.5%) considered abnormal, 174 (11.6%) suspicious and 1272 (84.9%) normal.

Visual Fields

Interpretation based on visual fields was not possible at baseline. A total of 508 participants (glaucoma suspects and non-glaucoma suspects) were indicated for visual field testing at baseline of whom 342 (67.3%) completed the test on the Humphrey Visual Field Analyser. Of these, 63.2% and 69.1% of normal and glaucoma suspects had abnormal visual field results despite good reliability indices. These baseline results were therefore discarded.

At follow-up, 1,309 (60.3%) participants successfully completed fields on the Henson 8000 Field Analyser with reliable results. 1,074 (82.0%) were normal in both eyes, 122

(9.3%) had one or both eyes with suspicious fields and 113 (8.6%) had an abnormal field in one or both eyes.

Based on gradable optic disc images at follow-up in those with normal visual fields, the 97.5th and 99.5th percentile VCDRs were 0.7 and 0.8 respectively (Figure 1).

Signs of glaucoma

At follow-up, 1,246 individuals had a VF measurement and a disc grading. Of these, 895 (71.8%) had both a normal VF and a normal disc, 141 (11.3%) had a normal VF and suspicious or abnormal disc, 182 (14.6%) had a suspicious or abnormal VF and normal discs and 28 (2.2%) had both suspicious or abnormal VFs and suspicious or abnormal discs.

Using the ISGEO classification 88 participants were considered to have glaucoma based on meeting either the ISGEO 1 (n= 64), 2 (n=22) or 3 (n=2) criteria, 1,973 participants did not meet ISGEO criteria and were deemed non-glaucoma, 110 could not be classified (Figure 2).

Based on follow up optic disc grading from images, visual fields, IOP and visual acuity, participants were defined as glaucoma positive or negative based on the ISGEO criteria. Vision status comparing participants with and without ISGEO glaucoma are described in Table 5 showing participants with glaucoma were more likely to have visual impairment. 85.2% of the non-glaucoma group classified as normal vision, compared to 72.7% in the glaucoma group. Blindness and VI were more prevalent in the glaucoma group, 5.7% and 21.6% respectively compared to those without glaucoma, 1.2% and 13.6% respectively.

Baseline and follow-up risk analyses was conducted and is summarised in Table 6. There was some evidence of an association of glaucoma with gender (male as baseline, Female OR=0.69, 95%CI: 0.45-1.06, p=0.10). No evidence of an association was found between baseline IOP and BMI (p=0.49), height (p=0.58) and weight (p=0.28). Associations of glaucoma with ophthalmic signs at follow-up were seen for both IOP (IOP>21mmHG OR: 4.10 (95%CI, 2.08-8.08), p<0.001) and a relative afferent pupillary defect (RAPD) showing a particularly strong association with being categorised as glaucoma (Confirmed RAPD OR: 7.39 (4.20-13.01), p<0.001).

Discussion

In this study we have described the population distributions and normative ranges from an epidemiological survey of glaucoma in an East African population in Kenya. Structural damage manifest by optic nerve changes was comparable in terms of the population distribution to other studies (described below). In those with glaucoma at follow-up, the strongest predictors were the presence at follow-up of an RAPD and IOP above 21mmHg. No demographic or anthropometric risk factors were associated with glaucoma.

The prevalence of glaucoma on those followed up was 4.3% (CI, 3.5-5.9) which is comparable to other population based studies in Africa which range from 4.2% (3.5-4.9) to 7.3% (5.5-9.1)^{25, 26} with a higher prevalence in west African populations (Nigeria 5.0% (4.6-5.5) and 7.3% (5.5-9.1),²⁶ Ghana 6.5% (5.8-7.1)²⁷) than is East and Southern African populations (Tanzania 4.2% (3.5-4.9),²⁵ South Africa 4.5% (3.2-6.1)²⁸ and 5.3% (3.9-7.1)²⁹).

The basis of the diagnosis of glaucoma in the majority of cases, both in clinical settings and in population based surveys, is correlation of structural optic nerve damage and loss of function demonstrated by visual field testing.³⁰ However, in SSA, where equipment constraints are considerable,³¹ visual field testing is not widely available. A survey in Lagos State, Nigeria identified one visual field analyser for every 2,380,000 population including private and governmental facilities.³² Even where field analysers are available, they are of much less importance in the diagnosis and treatment decision making process than in more resource intense settings; visual field changes were a factor in only 4% of treatment decisions in a review of 344 patients attending a glaucoma clinic in South African.³³ Population based studies have demonstrated that there are substantial difficulties in achieving adequate field testing in SSA populations.³⁴

The lack of a reliable visual field in the baseline of this cohort is consistent with other studies in the region that have faced similar challenges such as the Nigerian National Blindness Survey that used a relatively simple testing modality, the Humphrey Frequency Doubling Technology test, where adequate testing was only available for 60% of 4,538 Nigerian patients.³⁴ Furthermore, the logistical problems obtaining reliable visual field tests mean that they were not included in the flow chart for community diagnosis of glaucoma in a recently published West African algorithm; relative afferent pupillary defect testing was the chosen test of nerve function,³⁵ which the findings of this study concur with.

Diagnosis and management of glaucoma in SSA, therefore, centres very much around IOP and optic nerve assessment, the latter through direct visualisation and pupil assessment. Very little data from longitudinal population-based cohorts exist, with

none to date from SSA, on glaucoma. This cohort study of people aged 50+ undertaken in Nakuru, Kenya, with baseline in 2007-8 and follow-up in 2013-14 was an opportunity to estimate the normative range of various features of glaucoma as well as potential features that are important for clinical decision making in a context where availability of equipment is limited.

The percentile distributions of optic nerve VCDR and IOP in the Nakuru Cohort follow-up subgroup in whom image grading was available was very similar to the Nigeria National Blindness survey, a nationally representative survey of adults 40 years and older, which is to our knowledge the only National survey in SSA to derive percentile values for defining glaucoma in population-based surveys.³⁶ At the 97.5th and 99.5th percentiles the VCDR in Kenya was 0.7 and 0.8 respectively and 0.75 and 0.95 in Nigeria (in all the population with gradable disc images). The median VCDR was lower in Kenya at 0.23 compared to 0.4 in Nigeria.³⁶ Our findings are also consistent with other population-based studies in the region where a VCDR of 0.7 was consistent at the 97.5th percentile however greater variation is found at the 99.5th from 0.7 in Tanzania to 0.9 in South Africa.^{27, 29, 37, 38}

The IOP distribution in Kenya was similar at baseline and follow-up with a higher median than in Nigeria (15 vs. 14mmHg) but lower IOP at the 97.5th and 99.5th percentiles (Kenya: 22, 27mmHg vs. Nigeria: 24, 34mmHg).³⁶

Changes over the period of the cohort were difficult to define conclusively due to the clinical nature of a glaucoma diagnosis, however a strong association between optic discs and visual fields considered to be outside of normal range was demonstrated, in particular with the relative afferent pupil defect (RAPD) test. An IOP over 21mmHg

was also less strongly associated with glaucoma as defined by the ISGEO criteria in this study. The findings suggest a combination of optic nerve assessment by both visualisation including VCDR grading as well as assessing function through the RAPD test are practical means for identifying individuals who have or are at risk of sight loss from glaucoma. Portable tools for assessing vision³⁹ and optic disc imaging⁴⁰ may make this more accessible with IOP being a suitable method to monitor an effect from treatment and various handheld tools now available for accurate IOP assessment independent of a slit lamp.

Management of glaucoma remains a major challenge in SSA with limited availability and poor adherence to medical treatment when available. A primary surgical approach has problems also, in that patients presenting due to visual loss in one eye need to be persuaded to undergo surgery, most frequently with direct financial costs to them, in the other eye which they do not as yet consider to have a problem.^{11,41} The operation of choice, trabeculectomy augmented by anti-metabolites, does not improve the vision in most cases, but in fact can lead to visual acuity reduction. Identification of new treatment options in Africa therefore remains a priority.

Strengths of this study included it being a large, population-based sample, representative of a population on which there is minimal data. A senior ophthalmologist examined all study participants at baseline and follow up. High quality, modern, equipment was used throughout.

Limitations included a high loss to follow up (50%) at six years, this was primarily due to post-election violence affecting the study population with large numbers of people displaced or killed. Major variations in baseline and follow-up data collection protocols

were employed, in part due to challenges at baseline such as unreliable visual field data, retinal camera break down and due to a lack of availability of all baseline equipment at follow-up, e.g. no repeat AC-OCT was undertaken. Key measurement differences and therefore potential measurement bias were i) likely with visual fields at baseline being completed for glaucoma suspects (n=165) and a sub-set of normal participants (n=343) (11.6% of all baseline participants) only and using a Humphrey field analyser with outputs that could not be confidently used to make an assessment of glaucoma, the Henson 8000 was used at follow-up, ii) anterior chamber angle assessment at baseline was based on AC-OCT and on 4-mirror gonioscopy at follow-up, iv) a statistically significant variation between right and left eye IOP at baseline and follow up. IOP was on average higher in the right than the left eye at both baseline and follow-up. This may have arisen because the right eye was tested first and/or because the majority of the population was assumed to be right-handed, and IOP measurement is associated with hand dominance.^{42, 43}

In conclusion, glaucoma remains a public health concern. However, the lack of cost-effective treatments and challenges identifying high-risk individuals means that population-based screening for open-angle glaucoma should not currently be recommended.⁴⁴ Further research in to the risk factors, natural history and aetiology of glaucoma in Africa and the barriers to effective sight loss prevention are required.

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References

1. Pascolini D, Mariotti SP. Global estimates of visual impairment: 2010. *The British journal of ophthalmology* 2011.
2. Bourne RR, Stevens GA, White RA, et al. Causes of vision loss worldwide, 1990-2010: a systematic analysis. *The Lancet Global health* 2013;1:e339-349.
3. Quigley HA, Broman AT. The number of people with glaucoma worldwide in 2010 and 2020. *The British journal of ophthalmology* 2006;90:262-267.
4. Tham YC, Li X, Wong TY, Quigley HA, Aung T, Cheng CY. Global prevalence of glaucoma and projections of glaucoma burden through 2040: a systematic review and meta-analysis. *Ophthalmology* 2014;121:2081-2090.
5. Cook C. Glaucoma in Africa: size of the problem and possible solutions. *J Glaucoma* 2009;18:124-128.
6. Quigley HA, Broman AT. The number of people with glaucoma worldwide in 2010 and 2020. *Br J Ophthalmol* 2006;90:262-267.
7. Abu-Amero KK, Gonzalez AM, Osman EA, Larruga JM, Cabrera VM, Al-Obeidan SA. Mitochondrial DNA lineages of African origin confer susceptibility to primary open-angle glaucoma in Saudi patients. *Mol Vis* 2011;17:1468-1472.
8. Friedman DS, Wolfs RC, O'Colmain BJ, et al. Prevalence of open-angle glaucoma among adults in the United States. *Archives of ophthalmology (Chicago, Ill : 1960)* 2004;122:532-538.
9. Rudnicka AR, Mt-Isa S, Owen CG, Cook DG, Ashby D. Variations in primary open-angle glaucoma prevalence by age, gender, and race: a Bayesian meta-analysis. *Investigative ophthalmology & visual science* 2006;47:4254-4261.
10. Tielsch JM, Sommer A, Katz J, Royall RM, Quigley HA, Javitt J. Racial variations in the prevalence of primary open-angle glaucoma. The Baltimore Eye Survey. *JAMA* 1991;266:369-374.
11. Abdull MM, Gilbert CC, Evans J. Primary open angle glaucoma in northern Nigeria: stage at presentation and acceptance of treatment. *BMC Ophthalmol* 2015;15:111.
12. Mehari T, Giorgis AT, Shibeshi W. Level of adherence to ocular hypotensive agents and its determinant factors among glaucoma patients in Menelik II Referral Hospital, Ethiopia. *BMC ophthalmology* 2016;16:131.
13. Santos MA, Ayena DK, Kuaovi KR, Vonor K, Djagnikpo A, Balo KP. [Compliance with medical treatment in primary open-angle glaucoma in Lome]. *J Fr Ophtalmol* 2016;39:459-466.
14. Bastawrous A, Mathenge W, Peto T, et al. The Nakuru eye disease cohort study: methodology & rationale. *BMC Ophthalmol* 2014;14:60.
15. Turner AG, Magnani RJ, Shuaib M. A not quite as quick but much cleaner alternative to the Expanded Programme on Immunization (EPI) Cluster Survey design. *Int J Epidemiol* 1996;25:198-203.

16. Mathenge W, Bastawrous A, Foster A, Kuper H. The Nakuru Posterior Segment Eye Disease Study: Methods and Prevalence of Blindness and Visual Impairment in Nakuru, Kenya. *Ophthalmology* 2012;119:2033-2039.
17. Rosser DA, Laidlaw DA, Murdoch IE. The development of a "reduced logMAR" visual acuity chart for use in routine clinical practice. *The British journal of ophthalmology* 2001;85:432-436.
18. Dineen B, Gilbert CE, Rabiou M, et al. The Nigerian national blindness and visual impairment survey: Rationale, objectives and detailed methodology. *BMC Ophthalmol* 2008;8:17.
19. Bastawrous A, Rono HK, Livingstone IA, et al. Development and Validation of a Smartphone-Based Visual Acuity Test (Peek Acuity) for Clinical Practice and Community-Based Fieldwork. *JAMA Ophthalmol* 2015;133:930-937.
20. Van Herick W, Shaffer RN, Schwartz A. Estimation of width of angle of anterior chamber. Incidence and significance of the narrow angle. *American journal of ophthalmology* 1969;68:626-629.
21. Shaffer RN, Schwartz A. Gonioscopy. *Survey of ophthalmology* 1957;2:389-409.
22. Foster PJ, Buhrmann R, Quigley HA, Johnson GJ. The definition and classification of glaucoma in prevalence surveys. *The British journal of ophthalmology* 2002;86:238-242.
23. Bastawrous A, Mathenge W, Wing K, et al. The incidence of diabetes mellitus and diabetic retinopathy in a population-based cohort study of people age 50 years and over in Nakuru, Kenya. *BMC endocrine disorders* 2017;17:19.
24. Bastawrous A, Mathenge W, Wing K, et al. Six-Year Incidence of Blindness and Visual Impairment in Kenya: The Nakuru Eye Disease Cohort Study. *Invest Ophthalmol Vis Sci* 2016;57:5974-5983.
25. Buhrmann RR, Quigley HA, Barron Y, West SK, Oliva MS, Mmbaga BB. Prevalence of glaucoma in a rural East African population. *Invest Ophthalmol Vis Sci* 2000;41:40-48.
26. Ashaye A, Ashaolu O, Komolafe O, et al. Prevalence and types of glaucoma among an indigenous African population in southwestern Nigeria. *Invest Ophthalmol Vis Sci* 2013;54:7410-7416.
27. Budenz DL, Barton K, Whiteside-de Vos J, et al. Prevalence of glaucoma in an urban West African population: the Tema Eye Survey. *JAMA ophthalmology* 2013;131:651-658.
28. Rotchford AP, Johnson GJ. Glaucoma in Zulus: a population-based cross-sectional survey in a rural district in South Africa. *Arch Ophthalmol* 2002;120:471-478.
29. Rotchford AP, Kirwan JF, Muller MA, Johnson GJ, Roux P. Temba glaucoma study: a population-based cross-sectional survey in urban South Africa. *Ophthalmology* 2003;110:376-382.
30. Foster PJ, Buhrmann R, Quigley HA, Johnson GJ. The definition and classification of glaucoma in prevalence surveys. *Br J Ophthalmol* 2002;86:238-242.
31. Razai MS, Jackson DJ, Falama R, et al. The Capacity of Eye Care Services for Patients with Glaucoma in Botswana. *Ophthalmic epidemiology* 2015;22:403-408.

32. Adekoya BJ, Shah SP, Adepoju FG. Managing glaucoma in Lagos State, Nigeria - availability of Human resources and equipment. *The Nigerian postgraduate medical journal* 2013;20:111-115.
33. Lenake M, Cook C, Mustak H, Du Toit N. How useful is visual field testing in an African glaucoma clinic? *Clin Ophthalmol* 2014;8:1767-1771.
34. Kyari F, Entekume G, Rabiou M, et al. A Population-based survey of the prevalence and types of glaucoma in Nigeria: results from the Nigeria National Blindness and Visual Impairment Survey. *BMC Ophthalmol* 2015;15:176.
35. Kyari F, Gilbert C, Blanchet K, Wormald R. Improving services for glaucoma care in Nigeria: implications for policy and programmes to achieve universal health coverage. *Br J Ophthalmol* 2017.
36. Kyari F, Abdull MM, Sallo FB, et al. Nigeria normative data for defining glaucoma in prevalence surveys. *Ophthalmic Epidemiol* 2015;22:98-108.
37. Buhmann RR, Quigley HA, Barron Y, West SK, Oliva MS, Mmbaga BB. Prevalence of glaucoma in a rural East African population. *Investigative ophthalmology & visual science* 2000;41:40-48.
38. Rotchford AP, Johnson GJ. Glaucoma in Zulus: a population-based cross-sectional survey in a rural district in South Africa. *Archives of ophthalmology* 2002;120:471-478.
39. Bastawrous A, Rono HK, Livingstone IA, et al. Development and Validation of a Smartphone-Based Visual Acuity Test (Peek Acuity) for Clinical Practice and Community-Based Fieldwork. *JAMA ophthalmology* 2015.
40. Bastawrous A, Giardini ME, Bolster NM, et al. Clinical Validation of a Smartphone-Based Adapter for Optic Disc Imaging in Kenya. *JAMA ophthalmology* 2015:1-8.
41. Abdull MM, Gilbert C, McCambridge J, Evans J. Adapted motivational interviewing to improve the uptake of treatment for glaucoma in Nigeria: study protocol for a randomized controlled trial. *Trials* 2014;15:149.
42. Dane S, Gumustekin K, Yazici AT, Baykal O. Correlation between hand preference and intraocular pressure from right- and left-eyes in right- and left-handers. *Vision research* 2003;43:405-408.
43. Pekmezci M, Chang ST, Wilson BS, Gordon MO, Bhorade AM. Effect of measurement order between right and left eyes on intraocular pressure measurement. *Arch Ophthalmol* 2011;129:276-281.
44. Cook C, Foster P. Epidemiology of glaucoma: what's new? *Can J Ophthalmol* 2012;47:223-226.

Figure and Table Legends

Table 1. OCT Summary of normative findings of the anterior segment at baseline (in those without glaucoma)

Table 2. Gonioscopic grading of the angle in the follow-up of the Nakuru Eye Disease Cohort Study

Table 3. Intraocular Pressure in the Nakuru Eye Disease Cohort

Table 4. Baseline clinical (undilated and dilated) optic disc assessment made at the slit lamp

Table 5 . Visual status of participants at follow-up with and without glaucoma

Table 6. Association of anthropometric risk factors at baseline and ophthalmic risk factors at follow-up with glaucoma at follow-up (*follow-up risk factor)

Figure 1. The distribution of VCDRs at follow up from retinal images

Figure 2. The ISGEO Classification of the Nakuru Eye Disease Cohort follow-up group