Title:

Ethnicity and deprivation are associated with blindness among adults with primary glaucoma in Nigeria.

Results from the Nigeria National Blindness and Visual Impairment Survey.

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Abstract

Purpose: We explored the risk factors for glaucoma blindness among adults aged ≥40 years with primary glaucoma in Nigeria.
Participants and methods: 13,591 participants aged ≥40 years were examined in the Nigeria National Blindness and Visual Impairment Survey; 682 (5.02%, 95CI 4.60-5.47%) had glaucoma by ISGEO's criteria. This was a case-control study (n=890 eyes of 629 persons): glaucoma blind were cases and glaucoma not-blind were controls. Education level and occupation were used to determine socioeconomic status scores, which were divided into three tertiles (affluent, medium and deprived). We assessed socio-demographic, biophysical and ocular factors by logistic regression analysis for association with glaucoma blindness. Multinomial regression analysis was also performed with non-glaucoma as the reference category.
Results: 119/629 (18.9%; 95%CI 15.9-22.4%) persons were blind in both eyes, leaving 510 as controls. There was inter-ethnic variation in odds of blindness; age, male sex, socio-economic status, prior diagnosis of glaucoma, hypertension, intra-ocular pressure and lens opacity were associated with glaucoma blindness. Axial length, mean ocular perfusion pressure and angle-closure glaucoma were associated with blind glaucoma eyes. In multivariate analysis, Igbo ethnicity (OR2.79, 95%CI 1.03-7.57) had higher risk as was being male (OR4.56, 95%CI 1.72-12.09), and unmarried (OR2.46, 95%CI 1.03-5.93). Deprivation (OR3.72, 95%CI 1.55-8.93), prior glaucoma diagnosis (OR5.45, 95%CI 1.67-17.74) and higher intraocular pressure (OR1.07, 95%CI 1.02-1.13) were also independent risk factors for glaucoma blindness.
Conclusion: Approximately 1-in-5 people with primary glaucoma were blind, with ethnic variation in risk. Male sex and deprivation were strongly associated with blindness. Services for glaucoma need to improve in Nigeria, focussing on poor communities and men.
Key words: glaucoma blindness; ethnicity; deprivation; risk factors; population-based; Nigeria.

Introduction

Glaucoma is the leading cause of irreversible blindness worldwide.[1] Although there are very few population-based blindness prevalence surveys in Africa,[2] data suggest that the prevalence of glaucoma blindness in Africa is the highest in the world.[3, 4] In sub-Saharan Africa, the proportion of people with glaucoma identified in population-based surveys who are blind is alarming. In Ghana (2001) 10% of participants aged 30 years and above with glaucoma were blind.[5] Among participants aged 40 years and above, the proportion of people with glaucoma who were blind was 14% in Kongwa, Tanzania (1996),[6] 15% in Mamre, South Africa (1992),[7] and 33% in Temba, South Africa (1998).[8] Glaucoma occurs all over the world,[9] but risks for glaucoma blindness vary.[10, 11] Early diagnosis and treatment delay vision loss and prevent blindness from glaucoma[12] as the rate of progression of optic nerve damage is slowed by treatment.[13, 14] Recent advances in technology for diagnosing glaucoma, greater therapeutic options, and treatment monitoring have decreased the probability of glaucoma blindness in patients in the care system in industrialized countries.[15] Conversely, without treatment there is a very high rate of progression of visual field loss.[16] Who goes blind from glaucoma is influenced by biomedical factors such as age at onset, duration of disease and rate of progression of glaucoma.[17, 18] In many low income settings aggravating factors relating to the health care system include low provision of glaucoma services and access to services,[17-20] poor quality of care,[21] and inadequate compliance with treatment and follow-up,[18, 20] the latter being compounded by low levels of education.[22] Few studies of risk factors for glaucoma blindness have been undertaken in Africa where glaucoma has an earlier age of onset and a more aggressive course. Services for glaucoma are also inadequate and acceptance and compliance with treatment are low.

The increase in susceptibility of retinal ganglion cells to premature death may be mediated by genetic factors which may also interact with environmental factors.[23] Family studies and genome-wide association studies (GWAS) for open-angle glaucoma (OAG) have demonstrated genotype-phenotype correlations of heritable ocular features such as central corneal thickness (CCT),[24] optic disc size, vertical cup:disc ratio (VCDR)[25] and intraocular pressure (IOP).[26] However, only one molecular genetics study of glaucoma has been undertaken to date in Africa and the investigators did not observe significant association with any of the previously reported genes and loci in OAG cases in the Ghana study population.[27] Determining variation in the susceptibility to and severity of glaucoma among different ethnic groups who share common ancestry, is a first step in assessing the role of genetic factors in the pathogenesis of OAG in Africa. In an earlier study arising from the Nigeria National Blindness and Visual Impairment Survey (hereafter referred to as the Nigeria Blindness Survey) 94% of glaucoma was undiagnosed and untreated, and the crude prevalence was significantly higher in the Igbo ethnic group (7.77%; 95%CI 6.57-9.16).[28] In this paper we present findings on risk factors for blindness, including ethnic groups, among those identified with glaucoma during the Nigeria Blindness Survey.

The Nigeria Blindness Survey was the largest population-based blindness survey ever undertaken in Africa, providing data on the major blinding diseases,[29] including glaucoma which was the second commonest cause (16.7%).[30] The prevalence of blindness in adults aged $\geq$40 years was 4.2% (95%CI 3.8-4.6)[31] and the glaucoma-specific blindness prevalence was 0.7% (95%CI 0.6-0.9).[30] Systematic sample of 1-in-7 participants provided normative values[32] for defining glaucoma using the International Society of Geographic and Epidemiology Ophthalmology (ISGEO) levels of evidence.[33] The prevalence of glaucoma of all types was 5.02% (95%CI 4.60-5.47), one-fifth of whom were blind in both eyes.[28]

Materials and Methods

Details of the methods used in the Nigeria Blindness Survey,[29] normative values for diagnosing glaucoma[32] and the prevalence and types of glaucoma in Nigeria[28] have been published; and data on risk factors for OAG have been accepted for publication. A summary of the clinical assessments, with particular reference to classification of glaucoma and how potential risk factors for glaucoma blindness were measured and categorised, are described here.

Ethics

Ethical approval was obtained from the Ethics Committee of the London School of Hygiene & Tropical Medicine and the Federal Ministry of Health, Nigeria. Informed consent was obtained from community leaders, heads of households and all participants. The study adhered to the tenets of the declaration of Helsinki. Persons with medical or eye conditions including glaucoma needing further assessment and treatment were referred to the nearest healthcare facility.

Study design and study population

The study design for the analysis of risk factors for glaucoma blindness was a case-control study: people with glaucoma that were blind in both eyes (visual acuity [VA] worse than 3/60 in the better eye) were classified as cases; and people with glaucoma but not blind were classified as controls. For analysis of risk of blindness in eyes with glaucoma, the cases were glaucoma eyes that were blind (VA worse than 3/60) and the controls were glaucoma eyes that were not blind. The analysed sample consisted of persons classified as glaucoma and with no identified features suggesting secondary glaucoma (Figure 1). A person was classified as having glaucoma if the condition was present in one or both eyes. The sample size calculated for the Nigeria Blindness Survey was 15,375 persons aged ≥40 years in 310 clusters.[29]

Data collection and clinical assessment

Participants were invited to a temporary examination site set up within the community. All were interviewed to obtain relevant personal and socio-demographic data. Evidence of glaucoma surgery, presence of cataract and evidence of cataract surgery were noted. Some investigations were not possible in participants who could not come to the examination center and who were examined in their home.

Glaucoma classification

Glaucoma was classified according to the ISGEO criteria, using percentile distributions of VCDR, VCDR asymmetry and IOP in *normal* Nigerians, derived from the normative subset (n=1759) of this study population.[32] The diagnosis of glaucoma started with VCDR findings. Level 1 classification required structural and functional evidence i.e. 97.5th percentile of the VCDR (≥0.7) or VCDR asymmetry (≥0.1) in our normal population and visual field loss typical of glaucoma. Level 2 required advanced structural damage i.e. 99.5th percentile VCDR (≥0.75) or VCDR asymmetry (≥0.2) in the absence of visual field evidence. Level 3 applied when the optic disc was not seen and visual field testing was not possible, and used: a) blindness (VA<20/400) with the 99.5th percentile IOP (≥28mmHg), or b) diagnosed with/being treated for glaucoma. An additional level of evidence (level 2b) was added where the optic disc was visualized but the VCDR was <99.5th percentile and there were no visual fields available, but there was other compelling evidence such as RAPD, high IOP and/or corneal edema. These cases were adjudicated by glaucoma specialists (RW and WN). A person was said to have glaucoma if there was glaucoma in one or both eyes.

Visual acuity measurement and definition of blindness

Presenting VA was assessed by a trained ophthalmic nurse using a reduced logMAR tumbling-E chart[34, 35] at 4 meters. If the participant could not see any letters at 4 meters, testing was repeated at

1 meter. Participants unable to see any letters at 1 meter were assessed for counting fingers, hand movement or perception of light (PL) or no PL (NPL). Visual acuities were categorized using World Health Organization (WHO) definitions of blindness and visual impairment (VI)[36] where blindness at the person level is defined as VA worse than 3/60 in the better eye. An eye was classified as blind if the VA was worse than 3/60 in the affected eye.

Determining the cause of blindness

All participants with a VA worse than 6/12 in one or both eyes were examined by the experienced ophthalmologist. All disorders that may have contributed to visual loss in each eye were determined from a list of disorders. The principal/main cause was then selected for each eye and then for the person in the order of most preventable cause first (e.g. corneal opacity) then most treatable (e.g. refractive errors, cataract) and then other avoidable causes (e.g. glaucoma). Causes of blindness were determined using the World Health Organization's algorithm for use in surveys, which emphasizes treatable and preventable causes. In the Nigeria survey, glaucoma was only assigned as the cause if, in the view of the examiner, other more readily treatable causes, such as clinically significant cataract were not present. For example, in a blind person with clinically significant cataract and glaucoma, the main cause of blindness would be cataract.

In this paper, *glaucoma blindness* refers to a person with glaucoma in one or both eyes and with a VA of worse than 3/60 in the better eye. A *blind glaucoma eye* has glaucoma with VA worse than 3/60 in the affected eye.

Risk factors assessment and classification

Variables were analysed as continuous (age, axial length, IOP and mean ocular perfusion pressure [MOPP]) or binary (sex, marital status, literacy, place of residence, history of glaucoma, presence of hypertension, random blood glucose level [RBG], lens opacity, type of glaucoma and history of glaucoma surgery); or categorised into groups (ethnicity, socio-economic status [SES], geo-political zone [GPZ], severity of hypertension and body mass index [BMI]).

Participants were asked about their ethnicity, marital status, ability to read and/or write, education level and occupation. Ethnic groups represented by $\geq$200 participants were analysed separately (Fulani, Hausa, Ibibio, Ibo, Ijaw, Kanuri, Nupe, Tiv, Urhobo and Yoruba). Marital status was classified as married and unmarried (single, divorced or widowed). Being literate was any ability to read and/or write, otherwise the participant was classified as illiterate. Proxies were used to determine household SES. Occupations were ranked from zero (not employed) to seven (professional) and the highest level of school attended were from zero (no schooling) to four (tertiary education). The sum of these scores were calculated for each individual and the mean of sum of these ranks within the household was assigned as the SES score for each individual in order to take into account of heterogeneity and household size. The SES scores were further divided into 3 equal tertiles as deprived, medium and affluent. Rural place of residence was defined as a settlement with a population of $\leq$20,000 residents, and GPZ are the 6 administrative zones in Nigeria – North Central, North East, North West, South East, South South and South West.

Blood pressure (BP) was measured with the Omron wrist instrument (Omron Healthcare Ltd, Milton Keynes, England). The average of three readings was used in analysis. Hypertension was defined as BP$\geq$140/90mmHg and severity was categorised using WHO categories: stage 1 for systolic/diastolic BP$\geq$140/90 mmHg, stage 2 $\geq$160/100 mmHg and stage 3 $\geq$180/110 mmHg.[37] BMI was calculated by dividing body weight (kg) by height (m) squared and categorised according to the international classification i.e. underweight (<18.5 kg/m^2), normal (18.5–24.9 kg/m^2), overweight (25.0–29.9kg/m^2) and obese ($\geq$30.0 kg/m^2).[38] Every 1-in-7 participants and all participants suspected to have diabetic retinopathy on examination had RBG tested with Omron one-touch ultra blood glucose meter (Omron

Healthcare Ltd, Milton Keynes, England), and grouped as normal (<11.1 mmol/L) or raised (≥11.1mmol/L).[39]

Ocular axial length was measured by ultrasound A-scan biometry (Bioline Biometer OPTIKON 2000 S.p.A Roma, Italy) and IOP was measured by Goldmann applanation tonometry using standard methods. To explore the association of vascular perfusion and glaucoma blindness, MOPP was calculated from diastolic BP (DBP), systolic BP (SBP) and IOP as $^{2}/_{3}$[DBP+$^{1}/_{3}$ (SBP-DBP)-IOP].[40] Lens grading was performed using the Mehra-Minassian[41] and the WHO grading systems.[42] Lens opacity was classified as positive if it was visually disabling and VA<6/12 in the affected eye.

The type of glaucoma was determined by gonioscopy without corneal compression performed with Volk's 1-mirror non-flanged lens and Van Herick's (VH) method for the estimation of the anterior chamber (AC) angle.[43] Grades 3 and 4 VH AC angle estimation had a 99.1% sensitivity and 93% positive predictive value in identifying open angles by gonioscopy (risk factors for OAG, paper submitted for publication). Thus glaucoma eyes in which Schwalbe's line could be seen, or had grades 3 or 4 by VH estimation if gonioscopy was not done, were classified as OAG. Glaucoma eyes in which Schwalbe's line could not be seen, or had grades 0, 1 or 2 by VH estimation if gonioscopy was not done, were classified as angle-closure glaucoma (ACG). The eyes were unclassified if there was no gonioscopy or VH estimation of the AC angle. Participants were asked about history of ocular surgery and examined for evidence of glaucoma surgery such as bleb and peripheral iridectomy.

Statistical analysis

Socio-demographic, biophysical and ocular factors were analyzed for associations with glaucoma blindness after identifying participants with primary glaucoma who were blind or not blind (Figure 1). Statistical analysis was performed using Stata/IC 13.0 (Stata Corp, College Station, TX).

We examined the association between glaucoma blindness and each risk factor separately and report odds ratios (OR) with 95% confidence intervals. We also assessed associations between blind glaucoma eyes and each of the six ocular factors. We used logistic regression to assess the independent effect of each risk factor on glaucoma blindness and blind glaucoma eyes and report adjusted odds ratios and 95% confidence intervals. Likelihood ratio tests and joint Wald tests were performed to check the fit of the model and the effect of levels of categorical variables and those with missing data. We assessed the variance inflation factor (VIF) for the covariates. Collinear variables were not included in the same multiple logistic regression model. The following covariates were included and adjusted for in the main multivariable model for glaucoma blindness: age, sex, ethnicity, marital status, literacy, SES, rural/urban residence, history of glaucoma, BP, BMI, axial length, IOP, lens opacity and history of glaucoma surgery. The association of MOPP was explored in a model without BP and IOP. Associations for GPZ and type of glaucoma were explored in separate models. All eyes were analyzed to take into account bilateral cases and ocular variables for within-person correlation clustered for pairs of eyes, with robust standard errors.

To determine associations for a glaucoma eye being blind, all ocular variables were included in the multivariate model.

To explore the magnitude and direction of the relative risk ratios (RRR) of the two glaucoma outcomes (not-blind and blind) compared to the non-glaucoma group, we performed multinomial logistic regression analysis with the non-glaucoma subset as the reference category. The variables age-group, sex, ethnic group, marital status, literacy, SES and place of residence were included in the model. We tested the overall effect of each of the covariates and levels of ethnic group and SES on predicting the two glaucoma outcomes. The marginal predicted probability plot of glaucoma blindness by age-group with sex and with SES were produced. P-values <0.05 were considered as statistically significant. Missing values were excluded.

Results

In the study sample, 12,909 participants did not have glaucoma: 11,651 (90.3%) had both optic discs assessed and classified as non-glaucoma (Figure 1). For eyes that VCDR could not be assessed (n=1751 eyes, 6.8%), there was no level 3 evidence for glaucoma. In this analysis of risk factors for glaucoma blindness 890 eyes of 629 participants were included (Figure 1): 119 had glaucoma (18.9%;95%CI 15.9-22.4) and blind in both eyes (cases); and 510 controls. A further 139 participants with glaucoma had monocular blindness. Nearly half of those with glaucoma (258; 41%) were therefore blind in at least one eye. Glaucoma was the main cause of blindness in both eyes of 60/119 persons (50.4%) and in one eye of 31 persons. Thus glaucoma was the main cause of blindness in at least one eye of 91/119 (76.5%). Other main causes of blindness were cataract, optic atrophy and macular degeneration. The main cause of blindness at the person level in the 119 participants was glaucoma in 83 (70%) and cataract in 16 (13%)(Table 1). Of the 890 eyes with glaucoma included in the analysis there were a total of 323 (36.3%) blind eyes with glaucoma in 358 participants.

Glaucoma blind persons were older (mean age 68.5 years/SD 13.3) than the non-blind (mean age 63.4years/SD 13.0; p=0.0001)(Table 2). The number blind increased with increasing age up to the age-group 70-79 years.

There was a higher proportion of unmarried glaucoma blind participants than married. Stratified by sex, among the 43 unmarried glaucoma blind, 33 (76.7%) were women (p<0.001).

A history of prior glaucoma diagnosis was positive in 38/629 (6.0%) participants; 15.1% known to have glaucoma were blind compared with 3.9% of undiagnosed cases (Table 2).

The likelihood ratio tests on categorical covariates: ethnic group across all levels (p=0.001), blood pressure groups (p=0.005) and socioeconomic status (p<0.001) indicate that these variables create a statistically significant improvement in the fit of the main multivariable model; whereas for BMI categories p=0.53 and type of glaucoma p=0.27. For the joint Wald test (ethnic, BPgp, BMI) p=0.001.

Risk factors associated with glaucoma blindness

Ethnicity and GPZ were not predictors of SES. In univariate analysis, people with glaucoma blindness were more likely to be older, male and in deprived households. They were also more likely to be known glaucoma and have hypertension, and the odds of blindness increased with increasing severity of hypertension. The Igbo, Hausa, Fulani and Ijaw ethnic groups had significantly higher odds of glaucoma blindness than the reference ethnic group (Yoruba). Higher IOP (OR1.06;95%CI 1.04-1.08; p<0.001) and presence of visually disabling lens opacity (vdLO) (OR2.72;95%CI 1.89-3.91; p<0.001) also increased the odds of glaucoma blindness (Table 3).

In multivariate analysis, being male, unmarried, living in a deprived household, severe hypertension and higher IOP remained independent risk factors for glaucoma blindness. Being poor/deprived had three-and-half times higher odds of glaucoma blindness (OR3.57; 95%CI 1.46-8.72; p=0.005) than affluent participants. A prior diagnosis of glaucoma had a significantly higher odds of glaucoma blindness (OR5.89;95%CI 1.79-19.40; p=0.004) (Table 3). Being unmarried was also an independent risk factor with higher odds of being blind (OR2.50;95%CI 1.03-6.07; p=0.04). The Igbo, Fulani, Ijaw and Tiv ethnic groups had higher odds for glaucoma blindness than the Yoruba (reference group) (Table 3).

Risk factors associated with blind glaucoma eyes

About half of the eyes with glaucoma and vdLO were blind (206/415; 49.6%), and almost two-thirds of eyes with ACG were blind (42/66; 63.6%)(Table 4). There was evidence of glaucoma surgery in

19/629 (3.02%) participants of whom eight had surgery in both eyes (total 27/890 eyes); all of which were trabeculectomy. There was no significant difference in blindness status in eyes that had undergone trabeculectomy.

In univariate analysis, longer axial length, higher IOP, lower MOPP, vdLO and ACG were significantly associated with blind glaucoma eyes. However, when adjusted for age, sex, ethnicity, marital status, SES, location and other factors in the multivariable model, only higher IOP (OR1.09;95%CI 1.05-1.13) and vdLO (OR2.13;95%CI 1.36-3.33) remained independent risk factors. There was no statistically significant association between trabeculectomy and glaucoma blindness or blind glaucoma eyes.

Relative risk of the two glaucoma outcomes (not-blind and blind) compared to non-glaucoma (Table 5)

RRR>1 signifies that there is an increase in the outcome (not-blind or blind) when compared to the reference group, non-glaucoma; given that the other variables in the model are held constant. Table 5 shows the frequency distribution and the RRR of the covariates for the two outcomes of glaucoma. The factors that increased the outcome for glaucoma are shown.

Glaucoma not-blind relative to non-glaucoma

Increasing age was the only independent factor that had an increased relative risk for glaucoma not-blind compared to non-glaucoma; from RRR 1.84 (95%CI1.37-2.48) in the 50-59 years age-group to 6.69 (95%CI4.63-9.67) in the 80+ year-olds (Table 5).

Glaucoma blind relative to non-glaucoma

Older age-groups were more likely to have glaucoma blindness, with a RRR increasing from 3.51 (95%CI1.77-6.99) in the 60-69 years age-group to 10.08 (95%CI4.85-20.93) in the 80+ year-olds.

The Igbo ethnic group had a non-statistically significant increase in relative risk for glaucoma not-blind (RRR 1.18, 95%CI0.91-1.54; p=0.21) but were more likely to be glaucoma blind by a factor of 3.71 (95%CI2.01-6.85; p<0.001). Males were more likely than females to be glaucoma blind compared to non-glaucoma with an expected increase by a factor of 3.00 (95%CI1.87-4.83).

Deprivation did not increase the outcome of glaucoma not-blind (RRR0.94, 95%CI0.73-1.21). However, for people with glaucoma, the deprived were more likely than the affluent to be blind with glaucoma by a factor of 4.42 (95%CI2.50-7.80). The overall effect of SES was statistically significant. More specifically, we tested the effect of deprivation in predicting glaucoma not-blind and glaucoma blind and this showed that the effects were statistically different from each other, i.e. the deprived were not at higher risk than the affluent to have glaucoma but were more likely to be blind with it. The Igbo, Hausa and Fulani ethnic groups also showed different effects in outcome of glaucoma. (Table 5).

Figure 2 shows the marginal predicted probabilities of glaucoma blindness by increasing age and by SES. For a 70-79 year-old male, the average marginal probability of being glaucoma blind was about 3.5% compared to 1% for a female of the same age-group.

Compared to the affluent, deprivation increased the average marginal probability of glaucoma blindness by approximately 0.5% in the younger age-group, to 4% in 70-79 year age-group and over 5% in the 80+ ages.

Discussion

To our knowledge, this is the first population-based study of risk factors for blindness among individuals with glaucoma in a black population in Sub-Saharan Africa. In this study the vast majority

of participants with glaucoma had undiagnosed and untreated disease (96%) at the time of the survey, and so the findings largely reflect the natural history of untreated glaucoma.

A set of post-estimation statistical analysis tools that would aid the understanding, interpretation and presentation of the relationship between the assessed risk factors were used. Being of Igbo ethnicity was an independent risk factor for glaucoma blindness. The Fulani, Ijaw and Tiv ethnic groups had odds ratios with very wide confidence intervals hence we cannot draw meaningful conclusions on these. Those with higher IOP and vdLO, being male and those living in deprived households also had increased odds of blindness.

Although there are over 250 languages spoken in Nigeria, each ethnic group has similar ancestry and may be of common genetic stock. As ethnic group did not correlate with socio-economic status, ethnic differences in risk of glaucoma blindness suggest that there may be genetic similarities that lead to more aggressive disease in some ethnic groups, in terms of higher IOP or greater susceptibility of the optic nerve head to glaucoma, or gene-environment interactions. In the Nigeria Blindness Survey, about half (56%) of the eyes with glaucoma had IOP $\leq$22mmHg (mean IOP+2SD),[28] and there was variation in optic disc parameters as well as IOP among some ethnic groups.[32] These data are being explored to assess whether different ethnic groups are at increased risk of normal tension glaucoma, which may reflect genetic susceptibility to structural optic nerve damage (as in the Japanese population, for example),[44] or have differing frequencies of genetic variants such as CDKN2BAS associated with normal tension glaucoma.[45]

Most of earlier studies have been retrospective, facility-based studies of glaucoma patients in the care system, showing that severity of glaucoma at diagnosis and poor control of IOP were key risk factors for progression to blindness.[46-50] They buttress the paradigm that glaucoma visual loss could be prevented by earlier diagnosis and consistent and adequate treatment with IOP lowering as the cornerstone. Hospital reviews in Nigeria and sub-Saharan Africa also highlight factors that limit glaucoma patients' ability to access or maintain treatment, thus worsening their visual prognosis.[51-56] One population-based study reported older age as the only factor associated with progression/severity of glaucoma in untreated individuals who were re-examined after 10 years of the initial survey.[16]

In our study a staggering 1-in-5 people with glaucoma were already blind suggesting that services for glaucoma are either not available or poorly accessible. This is in contrast to data from a glaucoma clinic in Scotland, where glaucoma blindness was uncommon.[57] In Norwich, Ang's review of treated glaucoma patients reported 3.3% blind, none of whom was certified due to glaucoma.[58] However, in Sweden glaucoma patients had a lifetime risk of glaucoma blindness of 15%.[59] These studies did not include those undiagnosed in the population and may have overestimated the risk of glaucoma blindness.

In our study, not all blindness was due to glaucoma and at least 13% could have been prevented by cataract surgery. Highlighting this and other causes underscores the need for providing non-glaucoma interventions. The low cataract surgical coverage in this population[60] compounds the problem. Hence there is a need for integrated comprehensive eye care services and high quality cataract surgery in patients with glaucoma.

A surprising finding was that men were at a considerably higher risk of glaucoma blindness. This is likely to reflect the significantly higher prevalence of glaucoma in men (5.67%; 95%CI 5.05-5.47) than women (4.47%; 95%CI 3.98-5.00; p=0.002)[28] and also an indication of general lack of availability or access to glaucoma services. Being unmarried was also an independent risk factor for glaucoma blindness, particularly among women. This finding probably reflects disempowerment of unmarried women whose health needs are not prioritized by other family members or the community. In our study, those living in deprived households were also at a considerably higher risk of glaucoma

blindness and poor old people were most affected. As in most studies and reviews of poverty and blindness, socio-economic status tends to influence health-seeking behavior, awareness and healthcare access.[61-66] Rural/urban and GPZ location were not independent risk factors in this study, suggesting that services for glaucoma are equally poor across the country. As in the St Lucia study,[16] increasing age was associated with glaucoma blindness, but the association was not significant in multivariate analysis. This may signify that glaucoma occurs at an earlier age in Nigeria with blindness occurring across all age groups, as duration of disease is an important risk factor for blindness.[49, 67] Blindness occurring at an earlier age has also been reported in the black population of Baltimore.[68]

A prior diagnosis of glaucoma was independently associated with blindness. Many facility-based studies in Africa show that a high proportion of newly diagnosed glaucoma patients present with very advanced disease;[19, 51-54, 69] and diagnosed cases were more severely affected than non-diagnosed cases in the population.[13] This underscores the need for an integrated approach for earlier case-finding in the community, and the need for services that are acceptable and affordable.

There are some limitations in this study. The definition of blindness by VA alone would underestimate the total numbers blind from glaucoma. Including visual fields in the definition of blindness might have increased the estimates of blindness by up to 25%.[70] SES was determined by proxy factors i.e. education and occupation rather than using asset scores or other measures as this was not feasible within the constraints of the survey. Data on the duration of glaucoma or of blindness were not collected, as these data would be subjective and unreliable.

The combination of high prevalence of glaucoma, socioeconomic deprivation and lack of access to services means that in Nigeria glaucoma is often a blinding condition. The finding that some ethnic groups are at increased risk of glaucoma and of glaucoma blindness warrants further investigation from a molecular genetics perspective which may further our understanding of the pathogenesis of glaucoma in African populations and among those of African ancestry who live elsewhere.

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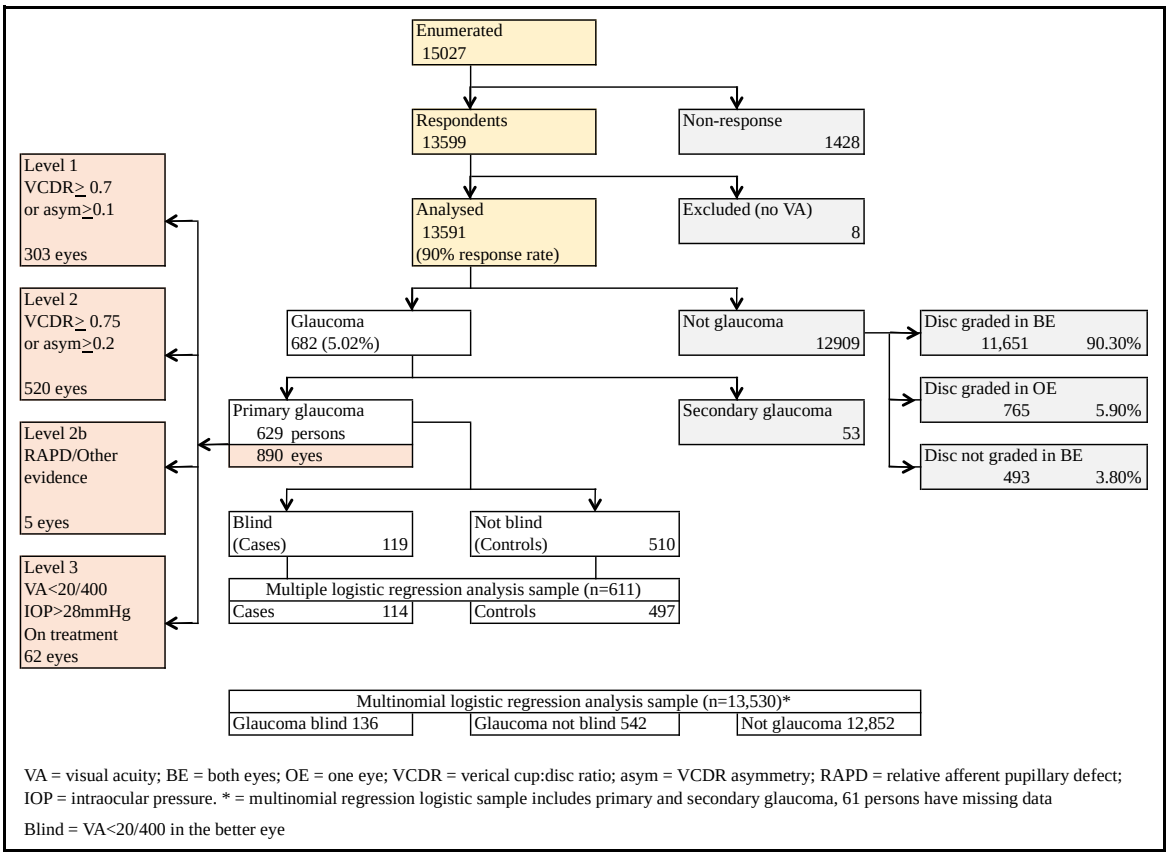
Tables and Figures

Figures

Tables

Figure 1. Selection of Cases and Controls for Analysis of Risk Factors for Glaucoma Blindness and Classification of Glaucoma Eyes by Levels of Evidence



VA = visual acuity; BE = both eyes; OE = one eye; VCDR = verical cup:disc ratio; asym = VCDR asymmetry; RAPD = relative afferent pupillary defect; IOP = intraocular pressure. * = multinomial regression logistic sample includes primary and secondary glaucoma, 61 persons have missing data

Blind = VA<20/400 in the better eye

Figure 2. Marginal Predicted Probabilities of Glaucoma Blindness by Age-Group With Sex and With Socioeconomic Status

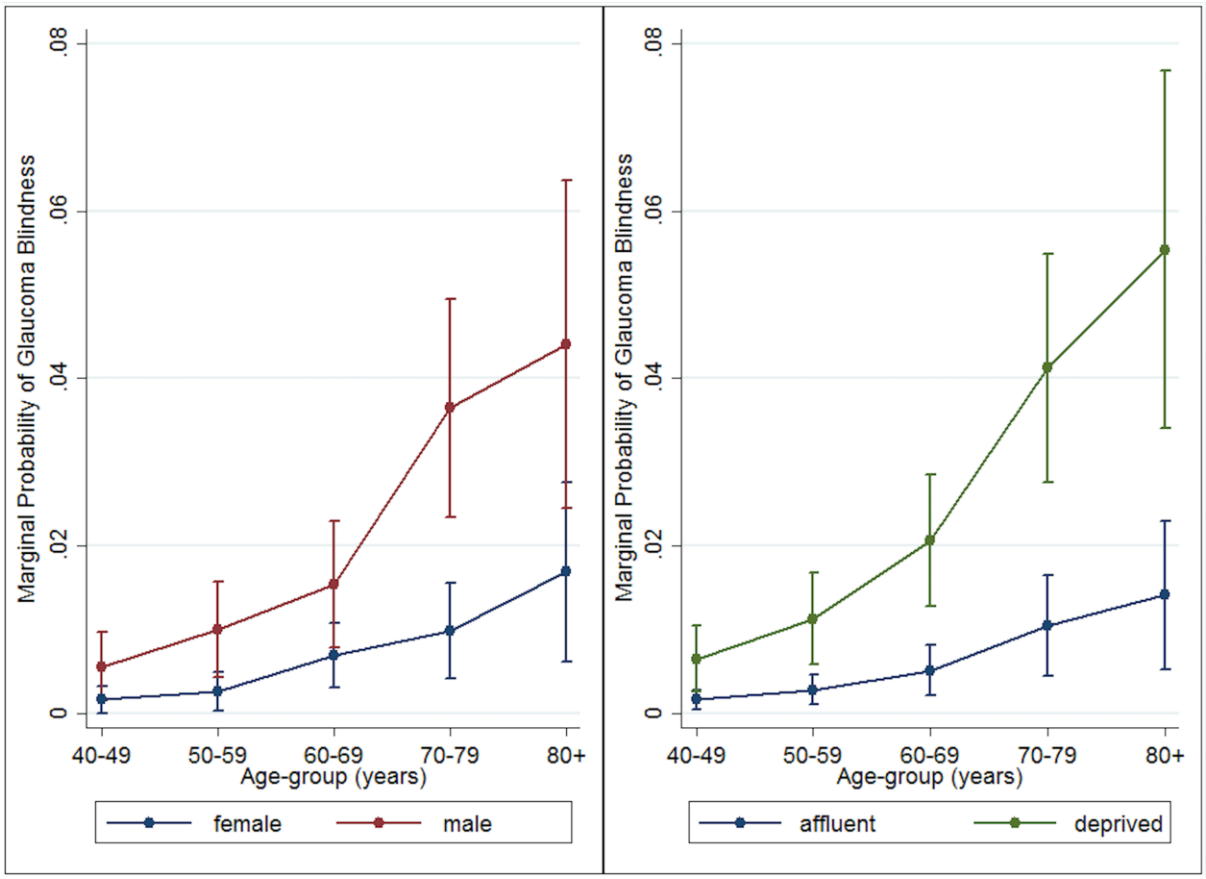


Table 1. Main Causes of Blindness in Participants With Primary Glaucoma

Main cause of blindness	Number	%
Glaucoma	83	69.8
Cataract	16	13.5
Optic atrophy	6	5.1
Macular degeneration	3	2.5
Other posterior segment disease	3	2.5
Corneal opacity	3	2.5
Uncorrected aphakia	2	1.7
Refractive error	1	0.8
Anterior uveitis	1	0.8
Unexplained	1	0.8
Total	119	100.0

Table 2. Distribution Of Glaucoma Participants With and Without Blindness By Socio-Demographic And Biophysical Factors (Total =629)

Variable		**Not blind n (%) 510 (81.1%)**	**Blind n (%) 119 (18.9%)**
Socio-demographic factors			
Age group (years)	40 – 49	78 (15.3)	11 (9.2)
	50 – 59	105 (20.6)	14 (11.8)
	60 – 69	133 (26.1)	29 (24.4)
	70 – 79	125 (24.5)	37 (31.1)
	80+	69 (13.5)	28 (23.5)
	Mean±SD	63.4±13.0	68.5±13.3
Sex	Female	268 (52.5)	43 (36.1)
	Male	242 (47.5)	76 (63.9)
Ethnic group	Yoruba	132 (26.1)	15 (12.6)
	Igbo	112 (22.1)	30 (25.2)
	Hausa	86 (17.0)	24 (20.2)
	Fulani	16 (3.2)	10 (8.4)
	Kanuri	12 (2.4)	4 (3.3)
	Ijaw	10 (1.9)	5 (4.2)
	Ibibio	9 (1.8)	2 (1.7)
	Nupe	8 (1.6)	2 (1.7)
	Tiv	8 (1.6)	3 (2.5)
	Urhobo	7 (1.4)	0 (0.0)
	Others	106 (20.9)	24 (20.2)
Marital status	Married	355 (69.6)	76 (63.9)
	Unmarried	155 (30.4)	43 (36.1)
Literacy	Literate	182 (35.7)	41 (34.5)
	Non-literate	328 (64.3)	78 (65.5)
Socio-economic status	Affluent	138 (27.1)	17 (14.3)
	Medium	192 (37.6)	20 (16.8)
	Deprived	180 (35.3)	82 (68.9)
Place of residence	Urban	116 (22.7)	30 (25.2)
	Rural	394 (77.3)	89 (74.8)
Geo-political zone	South south	85 (16.7)	15 (12.6)
	North east	39 (7.6)	15 (12.6)
	South west	129 (25.3)	18 (15.1)
	North central	70 (13.7)	19 (16.0)
	South east	103 (20.2)	24 (20.2)
	North west	84 (16.5)	28 (23.5)
History of glaucoma[α]	Not known glaucoma	490 (96.1)	101 (84.9)
	Known glaucoma	20 (3.9)	18 (15.1)
Biophysical factors			
Blood pressure (mmHg) <140/90	Normal	374 (73.6)	65 (55.6)
	Hypertension	134 (26.4)	52 (44.4)
≥140/90			

Random blood glucose <11.1 (mmol/L) ≥11.1	Normal	84 (96.5)	21 (95.5)
	Diabetes	3 (3.5)	1 (4.5)
Body mass index (kg/m^2) 18.5-24.9	Normal	303 (60.5)	71 (61.2)
<18.5	Underweight	76 (15.2)	21 (18.1)
25.0-29.9	Overweight	81 (16.1)	21 (18.1)
≥30.0	Obese	41 (8.2)	3 (2.6)
Glaucoma surgery	Trabeculectomy	12 (2.4)	7 (5.9)
	No surgery	498 (97.6)	112 (94.1)
Type of glaucoma	OAG	360 (91.8)	102 (91.9)
	ACG	32 (8.2)	9 (8.1)

Table 3a). Univariate and Multivariate Analysis of Risk Factors for Blindness Among Participants With Glaucoma: Socio-Demographic Factors

		n (%) [95%CI]	Univariate analysis			Multivariate analysis			
			Odds Ratio	95%CI	p-value	Odds Ratio	95%CI	p-value	VIF
Blind persons		119 (18.9)[15.9-22.4]							
Age (years)	(Min 40)		1.00			1.00			1.46
	Increasing age		1.03	1.01-1.05	<0.001	0.99	0.96-1.02	0.48	
Sex	Female	43 (13.8)	1.00	Reference		1.00	Reference		1.95
	Male	76 (23.9)	1.96	1.30-2.96	0.001	4.59	1.73-12.16	0.002	
Ethnic group	Yoruba	15 (10.2)	1.00	Reference		1.00	Reference		1.06
	Igbo	30 (21.1)	2.36	1.21-4.60	0.01	2.79	1.03-7.57	0.04	
	Hausa	24 (21.8)	2.46	1.22-4.95	0.01	2.69	0.89-8.14	0.08	
	Fulani	10 (38.5)	5.50	2.12-14.28	<0.001	9.75	2.91-32.67	<0.001	
	Kanuri	4 (25.0)	2.93	0.84-10.26	0.09	2.83	0.62-13.00	0.18	
	Ijaw	5 (33.3)	4.40	1.33-14.61	0.02	15.02	1.17-193.69	0.04	
	Ibibio	2 (18.2)	1.96	0.39-9.92	0.42	2.43	0.29-20.36	0.41	
	Nupe	2 (20.0)	2.20	0.43-11.34	0.35	3.22	0.41-25.02	0.26	
	Tiv	3 (27.3)	3.30	0.79-13.81	0.10	7.92	1.65-37.99	0.01	
	Others	24 (18.5)	1.99	1.00-3.99	0.52	4.01	1.41-11.43	0.01	

Marital status	Married	76 (17.6)	1.00	Reference		1.00	Reference		1.57
	Unmarried	43 (21.7)	1.30	0.85-1.97	0.23	2.50	1.03-6.07	0.04	
Literacy	Literate	41 (18.4)	1.00	Reference		1.00	Reference		1.43
	Non-literate	78 (19.2)	1.06	0.69-1.61	0.80	1.03	0.49-2.19	0.08	
Socioeconomic	Affluent	17 (11.0)	1.00	Reference		1.00	Reference		1.20
Status	Medium	20 (9.4)	0.85	0.43-1.67	0.63	0.50	0.17-1.49	0.21	
	Deprived	82 (31.3)	3.70	2.10-6.53	<0.001	3.57	1.46-8.72	0.005	
Residence	Urban	30 (20.6)	1.00	Reference		1.00	Reference		1.08
	Rural	89 (18.4)	0.87	0.55-1.39	0.57	1.48	0.65-3.37	0.36	
Geopolitical zone	North-east	15 (27.8)	2.18	0.97-4.90	0.06	2.18	0.59-7.97	0.24	
	North-west	28 (25.0)	1.89	0.94-3.79	0.07	1.60	0.53-4.86	0.40	
	North-central	19 (21.4)	1.54	0.73-3.25	0.26	1.07	0.38-3.01	0.90	
	South-south	15 (15.0)		Reference		1.0	Reference		
	South-east	24 (18.9)	1.32	0.65-2.68	0.44	0.87	0.30-2.56	0.80	
	South-west	18 (12.2)	0.79	0.38-1.66	0.53	0.54	0.17-1.67	0.28	
History of glaucoma	Not known	101 (17.1)	1.00	Reference		1.00			1.32
	Known	18 (47.4)	4.37	2.23-	<0.001	5.89	1.79-19.40	0.004	

glaucoma		8.55	

VIF = variance inflation factor for covariates in the main multiple logistic regression model; mean VIF = 1.28

Table 3b). Univariate and multivariate analysis of risk factors for blindness amongst participants with glaucoma: Biophysical factors

		n (%) [95%CI]	Univariate analysis			Multivariate analysis			
			Odds Ratio	95%CI	p-value	Odds Ratio	95%CI	p-value	VIF
Hypertension mmHg									
<140/90	Normal	65 (14.8)	1.00	Reference		NI			
≥140/90	Hypertension	52 (28.0)	2.23	1.47-3.38	<0.001				
Blood pressure mmHg	(severity)								
<140/90	Normal	65 (14.8)	1.00	Reference		1.00			1.03
>140/90 – 160/100	stage 1 mild	24 (25.0	1.92	1.13-3.27	0.02	2.29	1.02-5.14	0.04	
≥160/90 – 180/110	stage 2 moderate	15 (27.8)	2.21	1.15-4.25	0.02	1.59	0.64-3.93	0.32	
≥180/100	stage 3 severe	13 (36.1)	3.25	1.57-6.75	0.002	3.53	1.25-9.98	0.02	
Random blood glucose	mmol/L								
<11.1	Normal	21 (20.0)	1.00	Reference		NI			
≥11.1	Diabetes	1 (25.0)	1.33	0.13-13.62	0.81				
Body mass index kg/m^2	(Categories)								
18.5-24.9	Normal	71 (19.0)	1.00	Reference		1.00			1.08
<18.5	Underweight	21 (21.7)	1.18	0.68-2.04	0.56	0.73	0.34-1.54	0.40	
25.0-29.9	Overweight	21 (20.6)	1.11	0.64-1.91	0.72	0.90	0.40-2.01	0.80	
≥30.0	Obese	3 (6.8)	0.31	0.09-1.04	0.06	0.49	0.09-2.62	0.41	

NI = not included in multivariable models.

Table 3c). Univariate and multivariate analysis of risk factors for blindness amongst participants with glaucoma: Ocular factors

	n (%) [95%CI]	Univariate analysis			Multivariate analysis			
		Odds	95%CI	p-	Odds	95%CI	p-	VIF

			Ratio		value	Ratio		value	
Axial length (mm)	(Min 18)	-	1.00			1.00			1.19
	(Max 30)	-	1.15	0.92-1.43	0.22	0.79	0.56-1.11	0.18	
IOP (mmHg) (higher)	(Min 5)	-	1.00			1.00			1.09
	(Max 50)	-	1.06	1.04-1.08	<0.001	1.07	1.04-1.09	<0.001	
MOPP (mmHg)	(Min 6)	-	1.00			1.00			
	(Max 115)	-	0.99	0.97-1.00	0.10	0.99	0.97-1.00	0.14	
Lens opacity	Clear lens	31 (9.9)	1.00			1.00			1.22
	Lens opacity	88 (27.9)	2.72	1.89-3.91	<0.001	1.36	0.78-2.35	0.28	
Type of glaucoma	OAG	102 (22.1)	1.00			1.00			
	ACG	9 (22.0)	1.38	0.69-2.77	0.36	0.63	0.21-1.92	0.42	
Glaucoma surgery	No surgery	112 (18.4)	1.00			1.00			1.23
	Trabeculectomy	7 (36.8)	1.45	0.55-3.96	0.44	0.41	0.09-1.83	0.25	

IOP = intraocular pressure; MOPP = mean ocular perfusion pressure; OAG = open-angle glaucoma; ACG = angle-closure glaucoma.

Table 4. Association of Ocular Factors with Glaucoma Blind Eyes

		For blind eyes						
			Univariate analysis			Multivariate analysis		
			Odds Ratio	95%CI	p-value	Odds Ratio	95%CI	p-value
Eyes with glaucoma	Not blind	**Blind**						
N = 890 eyes (100%)	567 (63.7%)	323 (36.3%)						
Ocular factors*								
Axial length (mm) Mean±SD	22.68±0.87	22.89±1.28						
(Min 19.32)	Min 20.42	Min 19.45	1.00			Reference		
(Max 29.92)	Max 25.14	Max 29.92	1.21	1.05-1.40	0.01	1.03	0.81-1.32	0.80
IOP (mmHg) Mean±SD	20±9	28±13						
(Min 5)			1.00			Reference		
(Max 50)			1.08	1.06-1.09	<0.001	1.09	1.05-1.13	<0.001
MOPP (mmHg) Mean±SD	50±15	44±17						
(Min 6)			1.00			Reference		
(Max 98)			0.98	1.06-1.09	<0.001	1.00	0.98-1.04	0.77
Lens opacity								
Clear lens	358 (75.4)	117 (24.6)	1.00			Reference		

Lens opacity	209 (50.4)	206 (49.6)	3.02	2.27-4.01	<0.001	2.13	1.36-3.33	0.001
Type of glaucoma[@]								
OAG	423 (62.0)	259 (38.0)	1.00			Reference		
ACG	24 (36.4)	42 (63.6)	2.86	1.69-4.83	<0.001	1.25	0.59-2.67	0.56
Glaucoma surgery[@]								
No surgery	553 (64.1)	310 (35.9)	1.00			Reference		
Trabeculectomy	14 (51.9)	13 (48.2)	1.66	0.77-3.57	0.20	0.71	0.20-2.52	0.60

*analysis adjusted for within person correlation; SD = standard deviation; IOP = intraocular pressure; MOPP = mean ocular perfusion pressure; [@] = missing data excluded; OAG = open-angle glaucoma; ACG = angle-closure glaucoma.

Table 5. Relative Risk Ratios of the Glaucoma Outcomes (Glaucoma Not-blind and Glaucoma Blind) Compared to the Non-glaucoma Group

	Frequency distribution (%)			**Relative Risk Ratio (RRR)**						Effect on predicting glaucoma outcome. p<0.05 if the effect is different on the 2 outcomes
	Non-glaucoma N (%)	Glaucoma not blind N (%)	Glaucoma blind N (%)	Glaucoma not-blind RRR	95%CI	p-value	Glaucoma blind RRR	95%CI	p-value	
Total	12909 (94.98)	546 (4.02)	136 (1.00)							
Socio-demographic factor										
Age-group (years)										
50-59	3447 (96.37)	112 (3.13)	18 (0.50)	1.85	1.37-248	<0.001	1.77	0.85-3.70	0.13	
60-69	2595 (93.58)	147 (5.30)	31 (1.12)	3.13	2.34-4.20	<0.001	3.51	1.77-6.99	<0.001	
70-79	1475 (89.23)	134 (8.11)	44 (2.66)	5.10	3.73-6.99	<0.001	7.43	3.75-14.71	<0.001	
80+	596 (85.26)	72 (10.30)	31 (4.43)	6.69	4.63-9.67	<0.001	10.08	4.85-20.93	<0.001	
Male	5892 (94.33)	267 (4.27)	87 (1.39)	1.15	0.92-1.42	0.23	3.00	1.87-4.83	<0.001	
Ethnic groups										
Igbo	1769 (92.23)	116 (6.05)	33 (1.72)	1.18	0.91-1.54	0.21	3.71	2.01-6.85	<0.001	<0.001
Hausa	3245 (96.15)	97 (2.87)	33 (0.98)	0.62	0.48-0.81	0.001	1.94	1.05-3.56	0.03	<0.001
Fulani	810 (96.43)	18 (2.14)	12 (1.43)	0.47	0.29-0.78	0.003	2.39	1.11-5.14	0.03	<0.001
Ibibio	200 (94.34)	10 (4.72)	2 (0.94)	1.14	0.59-2.23	0.70	2.30	0.51-10.47	0.28	0.40
Unmarried	2619 (92.51)	164 (5.79)	48 (1.70)	1.05	0.82-1.33	0.71	1.85	1.14-3.00	0.01	
Deprived	4191 (93.44)	199 (4.44)	95 (2.12)	0.94	0.73-1.21	0.63	4.42	2.50-7.80	<0.001	<0.001