



# Glaucoma Awareness and Knowledge Among Ethiopians in a Tertiary Eye Care Center

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## ABSTRACT

**Introduction:** Glaucoma outcomes are closely associated with patients' awareness of the disease. However, little is known about glaucoma awareness and knowledge in Addis Ababa, a densely populated and ethnolinguistically diverse capital city in Ethiopia, the second largest country in Africa.

**Methods:** We performed a cross-sectional survey in the ophthalmology waiting room at St. Paul's Hospital, a tertiary care center in Addis Ababa. Respondents included patients, patient family members, and non-clinical staff. Participants were asked if they had read or heard about glaucoma to gauge basic awareness of the

disease; those with awareness were asked to take a quiz to measure their objective glaucoma knowledge. We performed multivariable regression to identify factors associated with glaucoma awareness, quiz performance, and self-rated ability to use eye drops.

**Results:** Of 298 respondents, 145 (48.7%) were female, and the average age was  $44.9 \pm 17.2$  years. A majority (167; 56.0%) had primary school or less than primary school education. Only 131 (44.0%) had basic glaucoma awareness. Of these, 95 (72.5%) knew that glaucoma causes permanent vision loss, 103 (78.6%) knew glaucoma is often asymptomatic in early stages, 62 (47.3%) identified elevated intraocular pressure as a glaucoma risk factor, and 124 (94.7%) knew glaucoma was treatable. A majority of this subset (126; 96.2%) said they would be willing to use medicated eye drops, and 130 (99.2%) indicated a willingness to undergo surgery if recommended. Education level was independently associated with glaucoma awareness ( $p < 0.001$ ) and glaucoma quiz performance ( $p = 0.03$ ).

**Conclusion:** In a population sample from an ophthalmology waiting room in Addis Ababa, glaucoma awareness was poor and most strongly associated with education level. Educational interventions at public health and provider-patient levels are warranted. Our results suggest high receptiveness to both medical and surgical treatment.

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### Key Summary Points

#### Why carry out this study?

Glaucoma represents a significant cause of preventable blindness in Ethiopia. Increasing public awareness and understanding of glaucoma and its treatments could help alleviate this burden.

This study sought to assess the prevalence of glaucoma awareness and knowledge within an Ethiopian population. Through understanding the factors that influence glaucoma awareness and understanding, efforts to improve these metrics can be directed in an efficient manner.

#### What was learned from the study?

Awareness of glaucoma was found in just 44% of study participants, and just 28.2% of participants reported that their knowledge of glaucoma was good or very good.

A higher level of education was associated with both awareness of glaucoma and a higher score on an objective measure of glaucoma knowledge. A personal history of glaucoma was associated with a higher self-reported knowledge of glaucoma.

Future studies should further investigate reasons for low glaucoma awareness and interventions to increase awareness in this community.

## INTRODUCTION

Glaucoma is the leading cause of irreversible blindness and visual impairment globally, affecting an estimated 80 million people worldwide [1]. Numerous population-based studies have demonstrated that glaucoma disproportionately affects people of African origin [2–4]. Within countries of eastern Sub-Saharan Africa (SSA) like Ethiopia, glaucoma is responsible for an estimated 11.7% of total blindness, a relatively larger proportion of blindness than is seen in other regions of the world [5]. It is generally recognized that patients in limited resource environments, on average, present later in the disease course. For glaucoma, this means that patients typically present with higher intraocular pressure (IOP), more advanced optic nerve cupping, and greater loss of peripheral and central vision. One recent clinic-based survey in Addis Ababa, Ethiopia noted that 26% of patients diagnosed with glaucoma exhibited either low vision (< 6/18 in the better eye) or blindness (< 3/60 in the better eye) [6].

Proven treatments exist to halt or slow the progression of glaucoma by lowering IOP. These modalities include pharmacologic medications, such as topical eyedrops, as well as laser therapy and surgery. However, a treatment is only useful if the individuals suffering from the condition are aware of their need for it and have access to care. For therapies that require self-administration, patients must be willing to apply the treatment and possess the necessary knowledge to do so effectively. As such, any initiative that seeks to improve glaucoma outcomes for a given population must focus on increasing public awareness, which will in turn lead to improved knowledge and understanding with the potential to drive behavioral change. Therefore, it is important to characterize the overall awareness and knowledge of a given population with regard to glaucoma and its available treatments, particularly in regions with a relatively high prevalence of the disease.

## DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features

In 2007, a glaucoma consortium was established in Ethiopia with the intent of raising public awareness about the disease [7]. Through radio campaigns, TV advertisements, and community events, this group saw early results suggesting that awareness of glaucoma was spreading among Ethiopian communities. Despite these efforts, little information exists regarding the actual awareness of glaucoma within Ethiopia. Our study sought to assess the prevalence of glaucoma awareness, the degree of knowledge possessed by those who were aware of glaucoma, and the self-reported ability of those individuals to use eyedrops, the main first-line treatment for glaucoma. It was hypothesized that awareness of glaucoma and its associated treatments within the study population, a low- to middle-class subset of individuals seeking low-cost care at St. Paul's Hospital in Addis Ababa, would be relatively low.

## METHODS

This clinic-based, cross-sectional observational study was approved by both the University of Michigan (HUM00148963) and St. Paul's Hospital Millennium Medical College (SPHMMC) Institutional Review Boards and was conducted in accordance with the tenets of the Declaration of Helsinki. All subjects provided informed consent to participate in the study. Data were collected between March–April 2019 in the ophthalmology clinic waiting room of SPHMMC in Addis Ababa, Ethiopia, a hospital with a catchment population of over 5 million people comprising all of Ethiopia's major ethnolinguistic groups. Participants consisted of patients of the clinic as well as non-patient family members and non-clinical staff. Persons < 18 years of age, those who were not fluent in English, Amharic, or Afan Oromo, and those unable or unwilling to provide verbal informed consent were excluded. Because the research was conducted as a sub-study of a periocular anthropometrics study to be published separately, persons with a history of orbital disease were excluded. The informed consent script and survey questions were translated in real time

from the original English documents by study staff who were fluent in English and Amharic and/or Afan Oromo (as appropriate for the patient's preferred language), and participants' responses were marked on paper data collection documents by study staff in real time.

We collected demographic information including age, sex, primary language, education level, profession, district ("woreda") of residence, and primary ethnicity (Amhara, Oromo, Gurage, Tigray, Silt'e, Gamo, or other). Participants with fewer than three grandparents of one ethnicity were recorded as mixed ethnicity. We asked participants if they had heard of or read anything about glaucoma to assess their basic awareness of the disease; those who answered negatively were not asked to answer additional questions about glaucoma. Of those participants who indicated an awareness of the disease, we asked where they had learned about glaucoma and if they knew they had glaucoma. Additionally, we asked these respondents to self-rate their knowledge of glaucoma and ability to successfully use medicated eye drops on a 5-point Likert scale, where 1 represented very poor knowledge/ability and 5 represented very good knowledge/ability. Participants answered quiz questions in true-or-false and multiple-choice formats to assess their objective knowledge of glaucoma. They were then asked whether they would undergo surgery for glaucoma or use eye drops for as long as necessary to treat glaucoma if these interventions were recommended by a doctor. The complete screening checklist, informed consent checklist, and glaucoma survey are available in Online Appendix 1.

Analyses were performed with SAS University Edition (SAS Institute, Cary, NC); all inferential analyses used a two-tailed significance cutoff of 0.05. We converted participants' quiz responses to a 20-point objective knowledge score based on the number of items answered correctly and calculated the percent correct. We performed multiple linear regression modeling for objective knowledge using age, sex, education level, primary ethnicity, and personal history of glaucoma as covariates. We performed logistic regression modeling for basic glaucoma awareness, good or better self-rated glaucoma

knowledge, and good or better self-rated ability to use eye drops utilizing the same covariates.

## RESULTS

Of 298 participants, 145 (48.7%) were female, and the average age was  $44.9 \pm 17.2$  years. One hundred three (103, 34.6%) were primarily of Amhara ethnicity, 89 (29.9%) were of Oromo ethnicity, and 52 (17.4%) were of Gurage ethnicity. The remaining 54 (18.1%) were of mixed ethnicity. A majority of participants (167; 56.0%) had primary school or less than primary school education. The demographic data are summarized in Table 1.

One hundred thirty-one (131; 44.0% of the overall sample) participants reported previously hearing about glaucoma. In the logistic regression model for basic glaucoma awareness (Table 2), secondary school or greater education

level was independently associated with increased awareness of glaucoma (OR = 4.35 [95% CI 2.53–7.48],  $p < 0.001$ ). Older age was also associated with a slightly increased awareness of glaucoma (OR = 1.02 [95% CI 1.01–1.04],  $p = 0.01$ ). Sex, primary ethnicity, and residence did not demonstrate a significant association with increased glaucoma awareness, though there was a slight trend of increased glaucoma awareness among participants from Addis Ababa.

Of the 131 (44.0% of the overall sample) participants who had a basic awareness of glaucoma, 30 (23%; 10% of the overall sample) said they had glaucoma; 57 (43.5%; 19% of the overall sample) stated they had learned about glaucoma from television, the radio, or media other than the internet; 28 (21.4%; 9.4% of the overall sample) indicated that they had learned about glaucoma via direct education by a

**Table 1** Demographic characteristics for 298 participants, 131 with and 167 without basic awareness of glaucoma

Characteristic	All participants ( <i>n</i> = 298)	Aware ( <i>n</i> = 131)	Not aware ( <i>n</i> = 167)	<i>p</i>
Age (years $\pm$ SD)	44.9 $\pm$ 17.2	46.2 $\pm$ 15.3	43.9 $\pm$ 18.5	0.25 <sup>a</sup>
Sex				0.38 <sup>b</sup>
Female	145 (48.7%)	60 (45.8%)	85 (50.9%)	
Male	153 (51.3%)	71 (54.2%)	82 (49.1%)	
Primary ethnicity				0.53 <sup>b</sup>
Amhara	103 (34.6%)	49 (37.4%)	54 (32.3%)	
Oromo	89 (29.9%)	34 (26.0%)	55 (32.9%)	
Gurage	52 (17.4%)	22 (16.8%)	30 (18.0%)	
Mixed or other	54 (18.1%)	26 (19.8%)	28 (16.8%)	
Education level				< 0.001 <sup>b</sup>
$\leq$ Primary	167 (56.0%)	52 (39.7%)	115 (68.9%)	
$\geq$ Secondary	131 (44.0%)	79 (60.3%)	52 (31.1%)	
Residence				0.28 <sup>b</sup>
Addis Ababa	197 (66.1%)	91 (69.5%)	106 (63.5%)	
Other	101 (33.9%)	40 (30.5%)	61 (36.5%)	

<sup>a</sup> By independent-samples *t*-test assuming unequal variances

<sup>b</sup> By chi-square test of independence

**Table 2** Multivariable logistic regression analysis of basic glaucoma awareness among 298 participants

Variable	Awareness of glaucoma		OR (95% CI)	<i>p</i>
	No./total	% (95% CI)		
Age (per 1 year increase)	–	–	1.02 (1.01–1.04)	0.01
Sex				0.45
Female	60/145	41.4 (33.4–49.4)	1 [reference]	
Male	71/153	46.4 (38.5–54.3)	1.22 (0.73–2.04)	
Primary ethnicity				
Amhara	49/103	47.6 (38.0–57.2)	1 [reference]	
Oromo	34/89	38.2 (28.1–48.3)	0.72 (0.37–1.40)	0.33
Gurage	22/52	42.3 (28.9–55.7)	1.23 (0.59–2.57)	0.58
Mixed or other	26/54	48.1 (34.8–61.4)	1.46 (0.71–2.99)	0.30
Education level				< 0.001
≤ Primary	52/167	31.1 (24.1–38.1)	1 [reference]	
> Primary	79/131	60.3 (51.9–68.8)	4.35 (2.53–7.48)	
Residence				0.74
Addis Ababa	91/197	46.2 (39.2–53.2)	1 [reference]	
Other	40/101	39.6 (30.1–49.1)	0.91 (0.51–1.62)	

healthcare provider. Only 37/131 (28.2%) self-rated their knowledge of glaucoma as good or very good, but 100/131 (76.3%) self-rated their ability to use eye drops as good or very good. Receptiveness to glaucoma treatment was high, with 126/131 (96.2%) stating a willingness to use eye drops to treat glaucoma and 130/131 (99.2%) indicating a willingness to undergo surgery for glaucoma if it was recommended by an ophthalmologist.

In the logistic regression for self-rated knowledge of glaucoma (Table 3), personal history of glaucoma was independently associated with good or very good self-rated glaucoma knowledge (OR = 3.75 [95% CI 1.29–10.92],  $p = 0.02$ ), but none of the other covariates were independently associated with self-rated drop use ability. In the logistic regression for ability to use eyedrops (Table 4), no covariates were independently associated with good or very good self-rated ability to use eyedrops.

The mean objective knowledge score was  $11.8 \pm 2.2$  ( $59.0 \pm 11.0\%$  correct) out of 20. Regarding specific quiz items, 124/131 (94.7%) knew that glaucoma was treatable, 103/131 (78.6%) knew that glaucoma is often asymptomatic in its early stages, 95/131 (72.5%) knew that glaucoma causes permanent vision loss, 62/131 (47.3%) knew that glaucoma was related to elevated IOP, and 33/131 (25.2%) knew that glaucoma resulted from damage to the optic nerve. In the linear regression for objective knowledge score (Table 5), secondary school or greater education level was independently associated with a higher knowledge score ( $p = 0.03$ ), but age, sex, primary ethnicity, and personal history of glaucoma were not.

## DISCUSSION

Through a cross-sectional study, we sought to evaluate awareness and understanding of

**Table 3** Multivariable logistic regression analysis of self-rated good or very good knowledge of glaucoma among 131 participants with basic awareness of glaucoma

Variable	≥ Good self-rated knowledge		OR (95% CI)	<i>p</i>
	No./total	% (95% CI)		
Age (per 1 year increase)	–	–	1.00 (0.97–1.03)	0.93
Sex				0.74
Female	14/60	23.3 (12.6–34.0)	1 [reference]	
Male	23/71	32.4 (21.5–43.3)	1.17 (0.47–2.87)	
Primary ethnicity				
Amhara	11/49	22.4 (10.7–34.1)	1 [reference]	
Oromo	11/34	32.4 (16.7–48.1)	1.51 (0.50–4.57)	0.47
Gurage	6/22	27.3 (8.7–45.9)	1.26 (0.34–4.62)	0.73
Mixed or other	9/26	34.6 (16.3–52.9)	2.17 (0.70–6.75)	0.18
Education level				0.12
< Secondary	11/52	21.2 (10.1–32.3)	1 [reference]	
≥ Secondary	26/79	32.9 (22.5–43.3)	2.07 (0.82–5.19)	
Residence				0.63
Addis Ababa	26/91	28.6 (19.3–37.9)	1 [reference]	
Other	11/40	27.5 (13.7–41.3)	0.79 (0.30–2.09)	
History of glaucoma				0.02
No	22/101	21.8 (13.8–29.9)	1 [reference]	
Yes	15/30	50.0 (32.1–67.9)	3.75 (1.29–10.92)	

glaucoma among adults in an urban clinical setting of Addis Ababa, Ethiopia. Our study found that the prevalence of glaucoma awareness was 44.0%. This rate is slightly higher than other published studies from Ethiopia. In a 2017 study performed in Gondar Town, Northwest Ethiopia, the prevalence of glaucoma awareness was 35.1%, while a 2013 study from Addis Ababa determined the prevalence of glaucoma awareness was 28.4% [8, 9]. This variance between studies could represent substantive increases in glaucoma awareness over time but could also reflect differences in methodology and/or clinical setting. Interestingly, a third study performed in southwestern Ethiopia found that only 2.4% of participants were aware

of glaucoma [10]. However, that particular study defined awareness as knowing something about glaucoma beyond having simply heard of the condition and was conducted in a rural environment where access to educational material might not be as readily available. Regardless, these investigations all demonstrate that awareness of glaucoma is well below optimal levels in Ethiopia.

While it is difficult to directly compare levels of awareness because of methodologic differences between studies, the prevalence of glaucoma awareness noted in the current study is similar to that measured in many other countries. A study of non-clinical, administrative staff at a Nigerian hospital found that just

**Table 4** Multivariable logistic regression analysis of self-rated good or very good ability to use eye drops among 131 participants with basic awareness of glaucoma

Variable	≥ Good self-rated drop ability		OR (95% CI)	<i>p</i>
	No./total	% (95% CI)		
Age (per 1 year increase)	–	–	1.00 (0.97–1.03)	0.96
Sex				0.18
Female	42/60	70.0 (58.4–81.6)	1 [reference]	
Male	58/71	82.0 (73.1–90.9)	1.86 (0.74–4.64)	
Primary ethnicity				
Amhara	40/49	81.6 (70.8–92.5)	1 [reference]	
Oromo	28/34	82.4 (69.6–95.2)	0.82 (0.23–2.87)	0.75
Gurage	14/22	63.6 (43.5–83.7)	0.35 (0.10–1.21)	0.10
Mixed or other	18/26	69.2 (51.5–86.9)	0.49 (0.16–1.54)	0.22
Education level	38/52	73.1 (61.1–85.2)	1 [reference]	
< Secondary	62/79	78.5 (69.4–87.6)	1.05 (0.42–2.60)	
≥ Secondary				0.92
Residence				0.97
Addis Ababa	68/91	74.7 (65.8–83.6)	1 [reference]	
Other	32/40	80.0 (67.6–92.4)	1.02 (0.36–2.86)	
History of glaucoma				0.74
No	76/101	75.2 (66.8–83.6)	1 [reference]	
Yes	24/30	80.0 (65.7–94.3)	1.22 (0.38–3.95)	

29.2% had heard of glaucoma [11]. Other recent studies from urban settings in India, Pakistan, and Iran found prevalence rates of glaucoma awareness of 45%, 48.7%, and 46.6%, respectively [12–14]. Given the relatively higher contribution of glaucoma to overall blindness in east SSA countries (11.7%) relative to South Asian (5.81%) or Middle Eastern countries (6.89%), the comparable awareness levels found in Ethiopia suggest a disconnect between glaucoma awareness and willingness to undergo treatment.

Our study suggests that increasing age and having at least some secondary school education are independently associated with awareness of glaucoma. This is consistent with the

findings in the study performed in Gondar [8]. In all three of the aforementioned awareness studies performed in Ethiopia, a significant association between level of education and glaucoma awareness was found [8–10]. This is consistent with studies from other countries as well [15–17]. Our current study, however, did not find any association between awareness of glaucoma and sex, primary ethnicity, or residence in Addis Ababa. In the present study, 28.2% of participants rated their knowledge of glaucoma as good or very good. Again, it is challenging to make direct comparisons, especially since this study assessed self-reported glaucoma knowledge while other studies utilized differing objective score measures, but this

**Table 5** Multivariable linear regression analysis of objective glaucoma knowledge score among 131 participants with basic awareness of glaucoma

Variable	Objective glaucoma knowledge score		<i>p</i>
	Coefficient	SE	
Intercept	10.52	0.83	< 0.0001
Age (per 1 year increase)	0.004	0.01	0.77
Sex			0.59
Female	0 <sup>a</sup>	0 <sup>a</sup>	
Male	0.22	0.41	
Primary ethnicity			
Amhara	0 <sup>a</sup>	0 <sup>a</sup>	
Oromo	0.49	0.52	0.35
Gurage	0.23	0.58	0.70
Mixed or other	0.48	0.53	0.36
Education level			0.03
< Secondary	0 <sup>a</sup>	0 <sup>a</sup>	
≥ Secondary	0.87	0.41	
Residence			0.87
Addis Ababa	0 <sup>a</sup>	0 <sup>a</sup>	
Other	−0.07	0.45	
History of glaucoma			0.08
No	0 <sup>a</sup>	0 <sup>a</sup>	
Yes	0.92	0.52	

<sup>a</sup> This parameter is set to zero because it is the reference

finding is similar to other studies in Ethiopia and in other countries.

In a recent study of adults in Gish Abay Town, Northwest Ethiopia, 16.8% of adults were found to have a good knowledge of glaucoma, as defined by a score > 50% on an objective quiz [18]. In another study from Addis Ababa, good glaucoma knowledge, defined as an ability to describe glaucoma and one risk factor and treatment, was found in just 12.1% of participants [9]. The average score on the objective knowledge quiz used in the current study was 59%, which would suggest a much better knowledge of glaucoma among

participants in our sample compared with these other studies in Ethiopia. However, our study was conducted in a clinical setting, and anyone who had not heard of glaucoma was not given the quiz. Thus, while our results might suggest an improvement in glaucoma understanding, they must be interpreted in context, and further investigation is warranted.

Studies from other African countries have found varying rates of glaucoma knowledge. A study in Nigeria found a prevalence of good knowledge of glaucoma, as defined by a score > 50% on a basic glaucoma knowledge test, of just 6.7% in a rural community [19]. A study from



Ghana found that just 27% of glaucoma patients in an eye clinic had accurate knowledge of the disease [20]. Our study found that a personal diagnosis of glaucoma was associated with self-rated good or very good knowledge of glaucoma. Since patients who have been diagnosed with glaucoma have undergone an eye examination in the past, this finding is consistent with other studies that have shown that a history of previous eye examinations is correlated with knowledge of glaucoma [8, 18]. We also found that a higher education level was associated with an increased objective knowledge of glaucoma, which is a finding consistent with other studies [8, 12, 16, 18].

It should be noted that our linear regression model suggests that while significant, the effect of secondary education is relatively small with regard to increased objective knowledge of glaucoma, as the coefficient of 0.87 suggests a < 1-point improvement in score with at least a secondary education. This seemingly small effect can be explained by the fact that individuals who were not aware of glaucoma were not given the objective knowledge quiz. Of those individuals who did not have awareness of glaucoma, a much larger percentage had only a primary school education than those who had heard of glaucoma (68.9% vs. 39.7%). However, this dynamic is not reflected in the linear regression model, which therefore suggests that the effect of education is likely larger than reported. Therefore, this result suggests that regional and national efforts to advance education could have a direct impact on health-related behaviors. Public awareness campaigns and clinically based patient education may be particularly beneficial in environments with less access to higher education and lower literacy rates.

This study did not find any covariates that were associated with a self-rated good or very good ability to use eyedrops. Further investigation is needed to better identify those who will benefit the most from eyedrop instillation teaching. Other studies have been performed to better understand medication adherence patterns among glaucoma patients. Factors such as higher education level, younger age, a higher frequency of follow-up visits, milder disease

stage, and a financial ability to pay for medications have been associated with better adherence in Ethiopian populations [21–23]. While our study found a relatively high proportion of individuals who had confidence in their ability to administer eye drops, these results are limited by the fact that only those individuals who had heard of glaucoma were asked to rate their confidence. Furthermore, there was a significant discrepancy between the proportion of participants who felt they had a good or very good knowledge of glaucoma (28.2%) and the proportion of participants who expressed confidence in instilling eyedrops (76.3%). All of this underscores the importance of teaching patients about proper eye drop instillation, especially since multiple studies have established the connection between eye drop administration, patient self-efficacy, and adherence to treatment [24–26].

Any survey study is subject to limitations. The current study was performed in a tertiary medical center where people have access to medical care and are likely more knowledgeable about medicine in general. As such, the participants may have been biased towards an increased awareness and knowledge of glaucoma relative to other communities, especially those from rural areas where healthcare is less accessible. Furthermore, it is possible that interview bias affected responses, though the interpreters utilized in the study were trained optometrists and made efforts to reduce influencing participant responses.

The primary findings of this study—an overall low prevalence of glaucoma awareness, an association between completed education level and both awareness and knowledge of glaucoma, high patient confidence in the ability to self-administer eye drops, and a remarkably high level of patient willingness to undergo medical or surgical treatment for glaucoma—demonstrate that there is a significant gap in Ethiopia between glaucoma awareness and acceptance of treatment. Since population-based advances in general education are likely to take time, public health awareness campaigns and provider-patient educational efforts are likely to achieve a more immediate impact. Additionally, therapeutic treatments that

effectively achieve lower IOP while requiring less patient adherence and follow-up, such as selective laser trabeculoplasty, could play an increasing role in populations with decreased access to care or glaucoma medications [27, 28]. Patients' willingness to receive treatment in our study suggests that increasing awareness among those at highest risk of developing glaucoma (age > 40 years, positive family history) is likely to reduce the disease burden and its associated personal and public costs.

## CONCLUSIONS

In this clinic-based, cross-sectional study, awareness and knowledge of glaucoma within an Ethiopian population were generally poor. Awareness and knowledge of glaucoma were both associated with higher levels of education. This suggests that educational interventions at the public health and provider-patient levels may potentially improve awareness and understanding of glaucoma in a population that is amenable to treatment.

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**Compliance with Ethics Guidelines.** This study was approved by both the University of Michigan (HUM00148963) and St. Paul's Millennium Medical College Institutional Review Boards. This study was performed in accordance with the tenets of the Declaration of Helsinki and its later amendments. All subjects provided informed consent to participate in the study.

**Data Availability.** The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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