Published in final edited form as:

Am J Ophthalmol. 2015 April ; 159(4): 777–787.e1. doi:10.1016/j.ajo.2015.01.011.

THE AFRICAN DESCENT AND GLAUCOMA EVALUATION STUDY (ADAGES): PREDICTORS OF VISUAL FIELD DAMAGE IN GLAUCOMA SUSPECTS

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Abstract

Purpose—To evaluate racial differences in the development of visual field (VF) damage in glaucoma suspects.

Design—Prospective, observational cohort study.

Methods—Six hundred thirty six eyes from 357 glaucoma suspects with normal VF at baseline were included from the multicenter African Descent and Glaucoma Evaluation Study (ADAGES). Racial differences in the development of VF damage were examined using multivariable Cox Proportional Hazard models.

Results—Thirty one (25.4%) of 122 African descent participants and 47 (20.0%) of 235 European descent participants developed VF damage ($p=0.078$). In multivariable analysis, worse baseline VF mean deviation, higher mean arterial pressure during follow up, and a race *mean intraocular pressure (IOP) interaction term were significantly associated with the development of VF damage suggesting that racial differences in the risk of VF damage varied by IOP. At higher mean IOP levels, race was predictive of the development of VF damage even after adjusting for

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Financial Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and the following were reported. Drs. Khachatryan, Bowd, Sample, Sharpsten and Hammel have no financial disclosures.

Contributions of Authors: Involved in Design and conduct of the study (NK, FAM, CB, PAS, JML, CAG, RNW, NH, LMZ); Collection, management, analysis, and interpretation of the data (NK, FAM, CAG, LS, CB, AM, RNW, LMZ); Preparation, review, or approval of the manuscript (NK, FAM, PAS, JML, CAG, RNW, LS, CB, AM, NH, LMZ).

potentially confounding factors. At mean IOPs during follow-up of 22, 24 and 26 mmHg, multivariable hazard ratios (95%CI) for the development of VF damage in African descent compared to European descent subjects were 2.03 (1.15–3.57), 2.71 (1.39–5.29), and 3.61 (1.61–8.08), respectively. However, at lower mean IOP levels (below 22 mmHg) during follow-up, African descent was not predictive of the development of VF damage.

Conclusion—In this cohort of glaucoma suspects with similar access to treatment, multivariate analysis revealed that at higher mean IOP during follow-up, individuals of African descent were more likely to develop VF damage than individuals of European descent.

INTRODUCTION

Primary open angle glaucoma (POAG) is the leading cause of irreversible blindness in the African-American population.^[1–3] Studies in the United States and Africa suggest that the prevalence of POAG is 4–5 times higher among individuals of African descent than those of European descent,^[2–5] and that there is more visual impairment and faster progression of the disease in individuals of African descent than in other racial groups.^[5–7] There is also consistent evidence that healthy individuals of African descent have, on average, thinner corneas and greater optic disc and neuroretinal rim area, larger cups, larger cup-to-disc ratio measurements and thicker retinal nerve fiber layer than European descent individuals.^[8–11] However, it remains unclear what clinical, ocular, genetic, demographic and socio-economic factors explain the racial differences in the development of glaucoma and subsequent severity of the disease.^[12–14] For example, in the Ocular Hypertension Treatment Study, African ancestry was not predictive of the development of glaucoma when corneal thickness, cup-to-disc ratio and other clinical and demographic predictive factors were included in the final multivariable model.^[9]

The African Descent and Glaucoma Evaluation Study (ADAGES)^[8] is a prospective, multicenter, observational cohort study of glaucoma patients, glaucoma suspects and healthy participants of African and European descent. ADAGES evaluates participants with a variety of measures of optic nerve head structure and visual function, while documenting clinical, ocular, systemic, and socio-demographic predictive factors. The overall aim of ADAGES is to better identify, describe and categorize these ocular, clinical and socio-demographic factors that explain differences in glaucoma onset and rate of progression found between individuals of African descent and those of European descent after providing similar access to treatment.

The present ADAGES report compares the incidence and identifies predictive factors for the development of visual field (VF) damage among African descent and European descent glaucoma suspects.

METHODS

Study Population

This was an observational cohort study of glaucoma suspects. Participants included in this study were selected from the ADAGES and Diagnostic Innovations in Glaucoma Study (DIGS).^[8, 11, 15] The multi-center ADAGES includes participants from the Hamilton

Glaucoma Center at the Department of Ophthalmology, University of California, San Diego; the New York Eye and Ear Infirmary; and the Department of Ophthalmology, University of Alabama at Birmingham. DIGS includes participants recruited at the University of California, San Diego. By design, the procedures and testing relevant to this report are identical in ADAGES and DIGS. The protocols for DIGS and ADAGES were harmonized at study initiation so that the European descent participants in DIGS can be used as a comparison group for the primarily African descent participants enrolled in ADAGES.

All the methods adhered to the tenets of the Declaration of Helsinki and to the Health Insurance Portability and Accountability Act. The institutional review boards at the University of California, San Diego, New York Eye and Ear Infirmary and University of Alabama at Birmingham approved the methods. All participants of the study gave written informed consent. ADAGES and DIGS are registered as cohort clinical trials (<http://www.clinicaltrials.gov> (identifiers, NCT00221923 and NCT00221897; September 14, 2005)).

Enrollment in ADAGES took place between January 2003 and July 2006. Follow-up of this cohort is still ongoing. Detailed information about ADAGES is provided elsewhere.^[8] To be included in ADAGES/DIGS, at study entry participants were required to have best-corrected visual acuity of 20/40 or better, spherical refraction less than 5.0 diopters (D), cylinder correction less than 3.0 D, and open angles by gonioscopy. Those with coexisting ocular trauma, retinal disease, uveitis, non-glaucomatous optic disc neuropathy, or other diseases possibly affecting the VF were excluded from the study.

For this report, only ADAGES/DIGS participants of African descent or European descent classified as “suspect glaucoma” at the baseline visit with a minimum of 2 years of follow-up, and at least 4 good quality VF visits were included in the analysis. Eyes with suspected glaucoma had a history of elevated IOP (ocular hypertension, OHT) and/or an optic disc appearance suspicious of glaucoma but normal visual fields at study entry. Elevated IOP was defined as IOP > 21 mm Hg or a history of ocular hypotensive treatment. Participants with evidence of consecutive repeatable VF damage at study entry in either eye were excluded.

Ocular Exam

The ocular testing completed for ADAGES and DIGS has been described elsewhere.^[8, 11, 15] In brief, participants underwent a comprehensive ophthalmic examination, including annual review of medical history, best-corrected visual acuity, slit lamp biomicroscopy, intraocular pressure (IOP), dilated funduscopy examination, pachymetry, simultaneous stereoscopic optic disc photography, standard automated perimetry (SAP) with 24-2 Swedish Interactive Threshold Algorithm (Carl Zeiss Meditec, Inc., Dublin, CA), and Heidelberg Retina Tomograph (HRTII; Heidelberg Engineering, Inc, Heidelberg, Germany). At each bi-annual follow-up visit, VF testing, IOP measurements and HRT imaging were completed.

Structural Damage

An optic disc appearance suspicious of glaucoma was defined as suspicion of neuroretinal rim thinning or notching, localized or diffuse retinal nerve fiber layer defect, or a between-eye asymmetry of the vertical cup-disc ratio more than 0.2. Two graders, masked to the participants' race, age, and clinical diagnosis, evaluated the simultaneous stereo-photographs (Kowa WX3D, Kowa Optimed, Inc, Torrance, CA or Nidek 3Dx, Nidek Inc, Fremont, CA), according to a standard protocol using a stereoscopic viewer. In case of discrepancies between the 2 graders, adjudication was completed by a third experienced grader. Only photographs of adequate quality were used for evaluation. Participants with optic disc appearance suspicious of glaucoma in one or both eyes, but no VF damage, were included in the study.

Functional damage

Normal SAP visual fields were defined as a mean deviation (MD) and pattern standard deviation (PSD) within the 95% confidence limits and a glaucoma hemifield test (GHT) result within the 99% normal limits. Reliable tests had 33% or less fixation losses and false-negatives and 25% or less false positives. Trained reviewers from the University of California, San Diego-based Visual Field Assessment Center (VisFACT) ensured that each VF test included in ADAGES and DIGS was of good quality without lid or rim artifacts, evidence of learning effects or other artifacts.

SAP visual fields were defined as abnormal if PSD was $\geq 5\%$ and/or GHT was "outside normal limits." Eyes that developed a repeatable VF defect, defined as 3 consecutive abnormal VF tests, were defined as developed VF damage. The development of VF damage was reviewed by an ophthalmologist (NK) to confirm that the damage was glaucomatous and the location of damage was consistent on all 3 visual fields.

Study Endpoint: Development of Visual Field Damage

A participant reached study endpoint when at least one eye developed repeatable VF damage (i.e., abnormal VFs as defined above) at 3 consecutive visits.^[13] In order to analyze the data based on participant, rather than eye, eyes that did not develop repeatable glaucomatous VF damage were excluded from the analysis if their fellow eye developed repeatable visual field damage during follow-up.

Clinical History and Socio-demographic Information

Standardized interviews were conducted to obtain socio-demographic information including age, gender, and race. Clinical information including history of glaucoma treatment and history of systemic hypertension was obtained from medical charts.

A participant was considered to have systemic hypertension if any of the following criteria were met: (a) history of high blood pressure obtained from medical charts, (b) history of treatment for systemic hypertension obtained from medical charts (c) measured average readings of systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg in a sitting position during a follow up visit using DINAMAP® PRO Monitor Model 100 (Critikon, USA). Blood pressure measurement cutoffs were selected based on the guidelines

of the International Society of Hypertension/World Health Organization.^[16] Mean systolic, diastolic pressure, and arterial pressure during follow up were calculated using measurements at baseline and each follow up visit. Mean arterial pressure was estimated using the following formula: mean arterial pressure = (2/3) diastolic pressure + (1/3) systolic pressure.^[17] Only mean arterial pressure was included in the model.

The following ocular parameters were included in the univariate analysis as they have been reported to be significantly associated with the risk of developing glaucomatous damage:^[13, 18, 19] baseline axial length, central corneal thickness (CCT), spherical equivalent refraction, HRT measured disc area and rim area, photography-based horizontal and vertical cup-to-disc ratios, and VF MD. Overall mean IOP during follow up was calculated using measurements at baseline and at each follow up visit.

By design, ADAGES is an observational cohort that likely reflects current best practices of treatment decision-making. Most IOP-lowering medications were provided at no cost to participants. A participant was considered to have a history of “glaucoma treatment” if his/her medical record indicated use of IOP-lowering medication and/or any glaucoma-related procedure during follow-up. Treatment decisions were not dictated by the study and were made at the discretion of the treating ophthalmologist at each site.

Statistical analysis

We examined racial differences in socio-demographic characteristics, ocular, and systemic factors using the Wilcoxon rank-sum test and Fisher exact test. Univariate Cox proportional hazards models were used to determine whether race and other risk factors were predictive of the development of VF damage among glaucoma suspects and to account for the correlation between fellow eyes in the presence of censoring.^[20] A censored eye is one in which, as of the last visit, VF damage has not developed. In the multivariate model, variables were chosen for analysis based on their importance in previous publications and their statistical significance ($p < 0.05$) in the univariate models. In addition, we evaluated whether the effect of race varied by level of IOP by including a race-IOP interaction term in the multivariable model. An IOP*IOP interaction term was also included as a possible predictor as the relationship between IOP and VF change can be non-linear.^[21] We present a hazard ratio (and 95% confidence interval (CI)) for each predictor variable, which represents the increased or decreased risk of VF damage with respect to that predictor. Statistical analyses were performed using STATA software version 12 (Stata Co., College Station, TX).

RESULTS

The study included 636 eyes of 357 participants with a mean age at entry of 58.1 ± 12.3 years (mean $\pm$ standard deviation (SD)). Overall, 231 participants (65%) were female. Two hundred thirty five (67%) were of European descent and 122 (33%) were of African descent. The overall mean follow up time was 7.1 years (± 2.4 years); for African descent participants it was 7.0 years (± 2.4 years) and for European descent participants it was 7.1 years (± 2.4 years). Sixty-two (51%) of African descent and 137 (58%) of European descent

participants received ocular hypotensive treatment during the follow-up period; this difference was not statistically significant ($p=0.180$).

There were significant differences between African descent and European descent participants for several baseline ocular and non-ocular factors (Table 1). African descent participants had significantly larger HRT-measured disc area, thinner corneas, and higher blood pressure parameters (mean arterial pressure and diastolic pressure during follow up) than European descent participants (all p -values < 0.002 , significant after Bonferroni correction for multiple comparisons).

Overall, 101 eyes (16% of 636 eyes) of 78 participants (22% of 357 participants) developed repeatable VF damage during the follow-up period. Twenty-six participants developed VF damage in both eyes; 52 developed VF damage in one eye. Thirty-one African descent participants developed VF damage (25.4% (31/122) compared to 47 (20.0% (47/235)) European descent participants. The univariate Cox Proportional Hazards risk of developing VF damage of African descent compared to European descent participants was (HR, 1.43; 95% CI, 0.87–2.35) ($p=0.163$) (Table 2). Given that participants of African descent compared to European descent were younger at baseline (54.7 ± 13.1 vs 59.8 ± 11.5 years, respectively $p < 0.001$) and developed VF damage at an earlier mean age (59.9 ± 13.7 and 67.4 ± 9.6 years, respectively $p=0.016$), it became important to adjust for these age differences in the analysis. The association between race and the development of VF damage was statistically significant after adjusting for baseline age, (HR African descent, 1.66; 95% CI, 1.00 – 2.74, $p=0.049$), and of borderline significance after adjusting for baseline age and VF MD in multivariable models (HR African descent, 1.57; 95% CI, 0.96 – 2.58, $p=0.073$).

Other factors that were positively associated with the development of VF damage based on univariate analysis included older age (HR per year, 1.03; 95% CI, 1.01–1.06), higher mean systolic pressure during follow up (HR per 1.0 mmHg, 1.02; 95% CI, 1.01–1.04), higher mean diastolic pressure during follow up (HR per 1.0 mmHg, 1.03; 95% CI, 1.00–1.06), and higher mean arterial pressure during follow up (HR per 1.0 mmHg, 1.04; 95% CI, 1.01–1.06) (Table 2). Lower baseline VF MD (HR per 0.1 dB, 1.04; 95% CI, 1.02–1.05), larger photograph-based vertical cup-to-disc ratio (HR per 0.1, 1.21; 95% CI, 1.01–1.46), and lower spherical equivalent refraction (HR per 1.0 D, 1.14; 95% CI, 1.00–1.29) were among the ocular parameters predictive of VF damage.

The multivariable model included self-described race, CCT, disc area, mean IOP during follow-up, the interaction between self-described race and mean IOP and the variables listed above with $p < 0.05$ in univariate Cox Proportional Hazards analysis. This multivariable model (Table 3) suggests that in this ADAGES cohort of glaucoma suspects, worse baseline VF MD (HR per 0.1 dB, 1.04; 95% CI, 1.02–1.06) and higher mean arterial pressure during follow-up (HR per 1.0 mmHg, 1.03; 95% CI, 1.00–1.06) were associated with the development of VF damage. The significance of the race-IOP interaction term ($p=0.003$) suggests that racial differences in the probability of developing VF damage varied depending on mean IOP during follow-up, while the IOP-IOP interaction term ($p < 0.0001$) suggests a non-linear relationship between IOP and the development of VF damage. For this

reason we calculated the multivariable HR for race at different IOP levels (Table 3). We found that at the highest quartile of mean IOP level during follow-up (IOP > 21 mmHg), African descent was predictive of the development of VF damage; at the lowest 3 quartiles of mean IOP levels during follow-up (< 21 mmHg), African descent was not predictive of the development of VF damage (Figure 1). Specifically, at IOP levels of 22 mm Hg, 24 mmHg and 26 mmHg, the multivariable hazard ratios (HR African descent compared to European descent (95% CI)) for developing VF damage were 2.03 (1.15–3.57), 2.71 (1.39–5.29), and 3.61 (1.61–8.08), respectively, even after controlling for CCT, baseline age and VF MD, disc area and other systemic and ocular factors (Figure 2). However, when we did not specify the IOP in the model, the mean IOP of the entire cohort (approximately 17.8 mm Hg) is used as the default IOP. Using the default mean IOP during follow-up value in the multivariable model, race was not associated with the development of VF damage (HR African descent (95% CI)) 1.12. (0.66–1.90).

DISCUSSION

In this ADAGES observational cohort of glaucoma suspects, African descent participants were younger and developed VF damage at a significantly earlier age than European descent participants. When adjusted for these age differences, African descent participants were 1.66 times more likely to develop VF damage than European descent participants ($p=0.047$).^[1–5, 12, 22] It was also important to address the possibility that some glaucoma suspects may have early visual field damage – even though the visual fields were considered normal by generally accepted criteria.^[13] When we adjusted for both baseline age and VF MD, participants of African descent were still 1.57 times more likely to develop VF damage than European descent participants ($p=0.073$). Moreover, we found that at higher levels of mean IOP during follow-up, individuals of African descent were more likely to develop VF damage than individuals of European descent, even after controlling for age, CCT, baseline VF MD, disc area and other systemic, and ocular factors in a multivariable model (Table 3). For example at a mean IOP of 22 mmHg, individuals of African descent were twice more likely to develop VF damage than European descent participants ($p=0.014$), at an IOP of 26 mmHg, individuals of African descent were 3.6 times more likely to develop VF damage ($p=0.002$). At lower levels of mean IOP during follow-up, race was not predictive of the development of VF damage.

It should be noted that the important association between race and development of VF damage is missed when the race-IOP interaction term is not included in the model and when the effect of race is not evaluated at different levels of IOP. When the default IOP value (mean IOP of the cohort in most statistical software) is included in the model, race was not predictive of the development of VF damage. In addition, the IOP*IOP term was highly significant ($p<0.001$) confirming prior evidence that the relationship between IOP during follow-up and VF progression is often non-linear.^[21]

Our results are consistent with population-based studies reporting higher prevalence and earlier onset of POAG among individuals of African descent.^[1–5, 12, 22] When the default IOP value is included in the multivariable model, our results are also consistent with the Ocular Hypertension Treatment Study (OHTS) which suggested that the “increased risk of

POAG associated with participants who self-identified as African American appears largely attributable to differences in specific clinical factors and not race itself^[7] and that African descent individuals have similar 10-year incidences of POAG within the same tertile of risk as non- African descent individuals.^[23] Specifically, although the OHTS reported that the incidence of POAG was significantly higher among African descent participants compared with other participants (univariate HR=1.59; 95% CI, 1.09–2.32), self-described race was not predictive of the development of POAG after adjusting for clinical and demographic factors such as age, cup-to-disc ratio and corneal thickness (multivariable HR, 0.98; 95% CI, 0.65–1.46).^[7, 13] Similarly, in another study, self-described race was no longer a significant predictor of “fast VF progression,” defined as a component decay rate of $\geq 36\%/y$, when baseline cup disc ratio and VF parameters were included in the multivariable model.^[23, 24] These studies did not specifically examine the interaction between race and IOP in predicting the development of VF damage.

Another possible explanation for the lack of racial differences in the development of VF damage in these studies^[7, 13, 24] was that both groups had similar access to treatment. Population-based studies^[2, 4, 5, 8–10, 22] have shown that individuals of African descent have a higher prevalence of POAG, develop glaucoma at an earlier age, and have more severe glaucoma than other groups. African descent individuals also report barriers to obtaining care, including cost of care or lack of insurance, transportation, and trusting the health care system.^[25–27] In order to reduce the effect of possible socioeconomic disparities and access to treatment, ADAGES participants were provided with glaucoma medications and transportation (as needed) at no cost to the participant. These results suggest that on average with similar access to treatment, glaucoma suspects of African descent may not be at greater risk of developing VF loss and European descent individuals. However, our results are consistent with population-based studies in that at higher levels of IOP, presumably with less controlled IOP, glaucoma suspects of African descent are more likely to develop VF damage than individuals of European descent. In population-based studies it is likely that the proportion of African descent individuals with access to treatment is lower and IOP is higher, so that racial differences are more pronounced. The ADAGES is unique as it represents best practices for glaucoma management while providing access to treatment.

The incidence of VF damage in our study was higher than reported in the Ocular Hypertension Treatment Study (OHTS)^[13] and the European Glaucoma Prevention Study (EGPS).^[19] The OHTS^[13] and the EGPS,^[19] randomized clinical trials of ocular hypertensive individuals, reported five-year incidences of POAG in the treated group of 4.4% and 13.4%, respectively and, in the untreated and placebo groups of 9.5% and 14.1%, respectively (overall incidence, 7.6% and 9.8%, respectively). The incidence in these trials was even lower if one includes only eyes reaching a VF endpoint, as done in the current study. This may be due in part to the inclusion of glaucoma suspects and not just OHT subjects in the current cohort. However, in our subgroup of OHT participants without suspicious appearing optic discs at study entry, the 5 year-incidence of the development of VF damage was higher (17.3%) than previous reports. The cause for this remains to be determined.

In the multivariable analysis of predictive factors for the development of VF damage, the current ADAGES results are consistent with other studies that worse VF MD at baseline (multivariate, HR 1.04, 95% CI:1.02–1.06) is predictive of the development of glaucomatous progression.^[14, 28] The multivariable analysis also suggests that higher mean arterial pressure is also predictive of glaucomatous VF damage, even after including mean IOP in the multivariable model. Moreover, when we controlled for systemic hypertension treatment in our model, higher arterial pressure remained significantly associated with the development of VF damage. Our results are consistent with a number of cross sectional and case-control studies reporting a significant correlation between glaucoma and high blood pressure.^[29–32] In contrast, several studies have linked glaucoma with low blood pressure while other prospective studies have not reported an association between either systolic or diastolic blood pressure and the incidence of glaucoma.^[12, 14, 33–37] Interestingly, the Los Angeles Latino Eye Study showed that both low diastolic and high systolic blood pressure were associated with an increased prevalence of open-angle glaucoma.^[38] This U-shaped relationship between blood pressure and glaucoma could be explained, at least in part, by several factors including that patients with low blood pressure may suffer from low ocular perfusion pressure and those with chronic hypertension may develop atherosclerosis over time leading to increased vascular resistance and compromised vascular autoregulation, resulting in ischemia of the ONH tissue and development of glaucoma.^[34, 39–41] However, as Khajawa et al demonstrate, it is impossible to tease out the independent contribution of IOP and ocular perfusion pressure in multivariable models.^[42] Specifically, if IOP is held constant as assumed in multivariable models, then HR per mm Hg increase in ocular perfusion pressure (blood pressure - IOP) will represent increase in blood pressure rather than ocular perfusion pressure. Therefore we focused on the association of IOP and blood pressure parameters on the development of VF damage. An advantage of the current longitudinal study is that blood pressure and IOP were measured throughout the follow-up period.

Several studies have reported that thinner CCT is predictive of the development of POAG, with multivariable HRs ranging from 1.25 to 2.07.^[13, 14, 19] In the current study, although participants with thinner CCT tended to have a higher risk of developing VF damage in univariate (HR per 40 μ m thinner 1.22, 95% CI: 0.95–1.57, $p=0.112$) and multivariable models (HR per 40 μ m thinner 1.18, 95% CI: 0.86–1.60, $p=0.302$), the association was not statistically significant. It is possible that with a larger sample size, the higher risk of developing VF damage in eyes with thinner corneas may reach statistical significance. In addition, the reduced effect of CCT could be due, at least in part, to the fact that the OHTS, which first published results documenting CCT as a predictive factor in 2002), influenced treatment of glaucoma suspects in our ADAGES cohort (with enrollment between 2003 and 2006). It is possible that ADAGES participants with thinner corneas have been treated and/or monitored more “aggressively” and therefore were not more likely to develop VF damage in this cohort.

Several limitations to this study should also be mentioned. First, our study is not a population-based study so one cannot generalize to the population of African and European descent individuals suspected of having glaucoma. Although ADAGES recruited participants primarily from academic glaucoma specialty practices, its relatively large

sample size and inclusion of patients from 3 geographic locations provides a fairly diverse cohort of African and European descent participants.^[8] The majority of African descent participants in our study were from Alabama (n=50, 41%) and from New York (n=41, 34%). We know that the ethnic background of the African American community in Alabama consists mostly of individuals born in the South of the United States, while the New York City population consists of a diverse group of immigrants including persons from the United States, the Caribbean, South America, and Africa.^[43] However, it is possible that there may be unidentified confounding or bias in the referral to academic centers that effects the results.

Second, in our study we used self-described race to categorize individuals. This categorization consists of a mixture of bio-genetic, geographic, socio-economic and cultural factors.^[15, 27, 44, 45] In order to investigate the racial admixture, ADAGES obtained blood samples for analysis of biogeographic ancestry. Among ADAGES African descent participants, the median estimated African proportion was 92.0% (IQR: 75.4–97.5%). Among European descent participants, the median estimated African proportion was 0.54% (IQR: 0.39–0.98%). (Girkin CA, et al. IOVS 2014;55:ARVO E-Abstract 2144) These results suggest that in the ADAGES cohort, self-described race is in close agreement with genetically defined biogeographic ancestry.

Finally, although ADAGES was designed to minimize racial differences in access to glaucoma treatment, it is possible that there were differences by self-described race in the treatment received or adherence to it. However, we found no evidence that African descent participants were less likely to be treated than European descent participants; the proportion of participants receiving glaucoma treatment was similar in both groups and the mean IOP was not higher in African descent participants. In fact, the mean IOP during follow-up was lower in African descent compared to European descent participants, possibly due in part to the thinner central corneas in African descent participants which result in lower measured IOP. African descent participants with lower mean IOP during follow-up, likely due in part to access and adherence to treatment, had similar or lower rates of VF damage compared to European descent participants. However, among glaucoma suspects with higher, presumably less well-controlled levels of IOP, perhaps due to poorer adherence, less aggressive treatment or other factors, African descent participants were more likely to develop VF damage than European descent participants, even after adjusting for CCT, baseline VF MD and other factors.

In conclusion, in this ADAGES cohort of African and European descent glaucoma suspects with similar access to treatment, participants of African descent with higher mean IOP during follow-up were more likely to develop VF damage than individuals of European descent even when controlling for CCT, disc area and other demographic and ocular factors. At lower levels of IOP, African descent participants were not at higher risk of developing VF damage than European descent participants. Further research is needed to evaluate the complex interaction of ophthalmic, genetic, systemic and other factors to improve our understanding of racial differences in the earlier onset of glaucoma and its progression at various levels of IOP.

ACKNOWLEDGEMENTS

Funding/Support: Supported by National Eye Institute, Eyesight Foundation of Alabama (Birmingham, Alabama, USA), the Edith C. Blum Research Fund of the New York Glaucoma Research Institute (New York City, New York, USA), Japan Eye Bank Association, Overseas Research Grant (Tokyo, Japan), Research to Prevent Blindness, an unrestricted grant (New York City, New York, USA), P30EY022589, EY08208 (LMZ), U10EY14267 (LMZ), EY019869 (LMZ), EY11008 (LMZ), EY021818 (FAM), EY022039 (CB), and EY13959. Alcon Laboratories Inc. (Fort Worth, Texas, USA), Allergan Inc. (Irvine, California, USA), Pfizer Inc. (New York City, New York, USA), Merck Inc. (Whitehouse Station, New Jersey, USA), Santen Inc. (Osaka, Japan) provided the participants' glaucoma medications at no charge.

Dr. Zangwill receives research support from Carl Zeiss Meditec Inc. (Dublin, California, USA), Heidelberg Engineering GmbH (Heidelberg, Germany), Optovue Inc. (Fremont, California, USA), Topcon Medical Systems Inc. (Oakland, New Jersey, USA), Nidek Inc. (Fremont, California, USA). Dr. Weinreb receives research support from Aerie (Bedminster, New Jersey, USA), Carl Zeiss Meditec Inc. (Dublin, California, USA), Genentech (San Francisco, California, USA), Heidelberg Engineering GmbH (Heidelberg, Germany), National Eye Institute (Bethesda, Maryland, USA), Nidek Inc. (Fremont, California, USA), Novartis (Basel, Switzerland), Quark (Fremont, California, USA), Topcon Inc. (Tokyo, Japan). Dr. Weinreb provides consultancy to AcuMEMS (Menlo Park, California, USA), Amatek (Depew, New York, USA), Aerie (Bedminster, New Jersey, USA), Alcon Laboratories Inc. (Fort Worth, Texas, USA), Allergan Inc. (Irvine, California, USA), Aquesys (Orange County, California, USA), Bausch&Lomb (Bridgewater, New Jersey, USA), Topcon Inc. (Tokyo, Japan). Dr. Medeiros receives research support from Alcon Laboratories Inc. (Fort Worth, Texas, USA), Bausch & Lomb (Bridgewater, New Jersey, USA), Carl Zeiss Meditec Inc. (Dublin, California, USA), Heidelberg Engineering, GmbH (Heidelberg, Germany), Merck Inc. (Whitehouse Station, New Jersey, USA), Allergan Inc. (Irvine, California, USA), Sensimed (Lausanne, Switzerland), Topcon Inc. (Tokyo, Japan), Reichert, Inc. (Depew, New York, USA), National Eye Institute (Bethesda, Maryland, USA). Dr. Medeiros also provides consultancy to Allergan, Inc. (Irvine, California, USA), Carl-Zeiss Meditec, Inc. (Dublin, California, USA), Novartis (Basel, Switzerland). Dr. Leibmann receives research support from Allergan, Inc. (Irvine, California, USA), Bausch & Lomb, Inc. (Bridgewater, New Jersey, USA), Carl Zeiss Meditec, Inc. (Dublin, California, USA), Diopysis, Inc. (Pine Brook, New Jersey, USA), Heidelberg Engineering, GmbH (Heidelberg, Germany), Optovue, inc. (Fremont, California, USA), Quark Pharmaceuticals, Inc. (Fremont, California, USA), Sensimed, Inc. (Lausanne, Switzerland), Topcon, Inc. (Tokyo, Japan), Reichert, Inc. (Depew, New York, USA). Dr. Leibmann provides consultancy to Alcon Laboratories Inc. (Fort Worth, Texas, USA), Allergan, Inc. (Irvine, California, USA), Bausch & Lomb, Inc. (Bridgewater, New Jersey, USA), Carl Zeiss Meditec, Inc. (Dublin, California, USA), Diopysis, Inc. (Pine Brook, New Jersey, USA), Heidelberg Engineering, GmbH (Heidelberg, Germany), Merz Pharmaceuticals, Inc. (Greensboro, North Carolina, USA), Valeant Pharmaceuticals, Inc. (Laval, Quebec, Canada). Dr. Girkin receives research support from Carl Zeiss Meditec, Inc. (Dublin, California, USA), Heidelberg Engineering, GmbH (Heidelberg, Germany), SOLX (Waltham, Massachusetts, USA). Dr. Miki provides consultancy to Nidek (Gamagori, Japan).

Other Acknowledgments: None

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Biography

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Figure 1.

The African Descent and Glaucoma Evaluation Study (ADAGES) Survival Analysis: Racial differences in the development of visual field damage vary by intraocular pressure. (Right) Multivariable survival curves indicate that at the highest quartile of intraocular pressure during follow-up (intraocular pressure > 21 mmHg) African descent glaucoma suspects had a significantly (Log rank, $p < 0.001$) lower probability of survival (not developing repeatable visual field damage) (grey line) than European descent participants (dashed line). (Left) At lower mean intraocular pressure during follow-up, no racial differences were found.

Figure 2.

The African Descent and Glaucoma Evaluation Study (ADAGES) Cox Proportional Hazards Analysis: The risk of developing visual field damage among glaucoma suspects of African descent is significantly higher than those of European descent at mean intraocular pressures during follow-up of 22, 24 and 26 mmHg. At lower mean intraocular pressures, race was not predictive of the development of visual field damage. Age, central corneal thickness, spherical equivalent refraction, disc area, stereophotograph-based vertical cup-disc ratio, visual field mean deviation, mean arterial pressure, and a race*mean intraocular pressure interaction term and a mean intraocular pressure*mean intraocular pressure interaction term were included in the multivariable model. Mean= Mean intraocular pressure during follow-up of the cohort (17.8 mmHg).

The African Descent and Glaucoma Evaluation Study (ADAGES). Demographic, Systemic and Ocular Characteristics for African Descent and European Descent Glaucoma Suspects.

Table 1

Risk Factors	African Descent Participants (subjects, n=122)		European Descent Participants (subjects, n=235)		P- value ^c	
	Developed Visual Field Damage (n=31)	No Visual Field Damage (n=91)	Total African Descent (n=122)	Developed Visual Field Damage (n=47)	No Visual Field Damage (n=188)	Total European Descent (n=235)
Demographic						
	Mean±SD		Mean±SD			
Baseline Age, years	57.5±14.0	53.7±12.7	54.7±13.1	64.1±9.8	58.8±11.7	59.8±11.5
Follow-up time, years	7.5±2.0	6.8±2.5	7.0±2.4	8.3±2.0	6.9±2.4	7.1±2.4
Follow-up time from baseline to development of visual field damage, years	2.4±2.0	N/A		3.4±2.5	N/A	0.088 ^d
Age at first abnormal visual field, years	59.9± 13.7	N/A		67.4± 9.6	N/A	0.016 ^d
	N(%)	N(%)	Total	N(%)	N(%)	Total
Gender:	Female 22(71)	63(69)	85(70)	30(64)	116(62)	146(62)
	Male 9(29)	28(31)	37(30)	17(36)	72(38)	89(38)
Ocular at baseline						
	Mean±SD		Mean±SD			
Central Corneal Thickness ^a , μm	537.4±38.0	538.4±38.0	538.1±37.9	558.5±41.7	562.3±35.3	561.5±36.6
Spherical equivalent refraction ^a , D	-0.11±1.42	-0.77±1.86	-0.61±1.77	-0.33±2.19	-0.59±1.95	-0.53±2.00
Axial Length ^a , mm	23.82±0.81	24.13±1.01	24.05±0.97	23.98±1.12	23.79±1.07	23.83±1.08
Rim Area ^a , mm2	1.33±0.42	1.35±0.26	1.34±0.30	1.24±0.32	1.31±0.25	1.30±0.26
Stereophotograph-based Vertical Cup-Disc Ratio ^a	0.64±0.15	0.64±0.14	0.64±0.14	0.67±0.16	0.59±0.15	0.61±0.16
Stereophotograph-based Horizontal Cup-Disc Ratio ^a	0.63±0.16	0.64±0.15	0.64±0.15	0.64±0.15	0.58±0.16	0.59±0.16
Disc Area ^a , mm2	2.30±0.40	2.30±0.58	2.30±0.54	2.08±0.51	1.97±0.40	2.00±0.42
Visual Field Mean Deviation ^a , dB	-1.17±1.68	-0.29±1.24	-0.51±1.4	-0.84±1.20	-0.31±1.21	-0.42±1.23
Pattern Standard Deviation ^a , dB	1.85±0.25	1.58±0.25	1.65±0.27	1.72±0.24	1.53±0.26	1.57±0.26
Intraocular Pressure, mmHg	17.7±6.2	16.8±5.7	17.0±5.8	18.1±7.7	18.5±5.9	18.4±6.3

Risk Factors		African Descent Participants (subjects, n=122)			European Descent Participants (subjects, n=235)			P-value ^c
		Developed Visual Field Damage (n=31)	No Visual Field Damage (n=91)	Total African Descent (n=122)	Developed Visual Field Damage (n=47)	No Visual Field Damage (n=188)	Total European Descent (n=235)	
		N(%)	N(%)	Total	N(%)	N(%)	Total	
Diagnostic Groups:	Ocular Hypertension	12(39)	42(46)	54(44)	16(34)	86(46)	102(43)	0.911
	Optic Disc Appearance Suspicious of Glaucoma	19(61)	49(54)	68(56)	31(66)	102(54)	133(57)	
<i>Ocular during Follow-up</i>		<i>Mean±SD</i>			<i>Mean±SD</i>			
Mean Intraocular Pressure ^b , mmHg		19.0±4.9	16.5±3.4	17.2±4.0	17.9±5.1	18.4±3.9	18.3±4.2	0.010
		N(%)	N(%)	Total	N(%)	N(%)	Total	
Glaucoma Treatment		17(55)	45(50)	62(51)	30(64)	107(57)	137(58)	0.180
<i>Systemic (during follow-up)</i>		<i>Mean±SD</i>			<i>Mean±SD</i>			
Mean Arterial Pressure ^b , mmHg		100.9±11.1	95.5±9.2	96.9±9.9	92.9±9.6	91.8±8.7	92.0±8.7	<0.001
Mean Systolic Pressure ^b , mmHg		141.2±17.7	133.1±14.2	135.1±15.3	133.1±15.5	129.6±13.7	130.3±14.1	0.005
Mean Diastolic Pressure ^b , mmHg		80.8±10.5	76.8±8.3	77.7±9.0	72.9±8.3	72.9±8.0	72.9±8.0	<0.001
		N(%)	N(%)	Total	N(%)	N(%)	Total	
Systemic Hypertension		28(90)	70(77)	98(80)	32(68)	143(76)	175(74)	0.238

^a Average of the two eyes used^b Measured at follow up visits from baseline to the last visit or first abnormal visual field in 3 consecutive abnormal visual fields^c p-value comparing total African descent participants to total European descent participants, using Fisher's exact test for categorical variables, Wilcoxon rank-sum test for continuous variables. If adjusting for multiple comparisons using Bonferroni correction, significant p-value are defined as 0.002^d p-value comparing African descent participants who developed visual field damage to European descent participants who developed visual field damage

Table 2

The African Descent and Glaucoma Evaluation Study (ADAGES). Univariate and Baseline Age and Visual Field Adjusted Cox Proportional Hazards Models Evaluating the Relationship Between Race, Ocular and Systemic Factors and the Development of Visual Field Loss Among Glaucoma Suspects.

Predictive Factors	Hazard Ratio (95% CI)		
	Univariate	Adjusted for baseline age	Adjusted for baseline age and visual field mean deviation
<i>Demographic</i>			
African Descent	1.43 (0.87–2.35)	1.66 (1.00 – 2.74)	1.57 (0.96 – 2.58)
Older Age per year	1.03 (1.01–1.06)	1.03 (1.01–1.06)	1.02 (1.00 – 1.05)
Male Gender	0.87 (0.52–1.45)		
<i>Ocular (at baseline)</i>			
Diagnostic Group: Optic Disc Appearance Suspicious of Glaucoma versus Ocular Hypertension	1.55 (0.94–2.56)	1.44 (0.87– 2.38)	1.39 (0.84–2.30)
Axial Length (per 1.0 mm greater)	0.96 (0.79–1.16)		
Central Corneal Thickness (per 40 μ m thinner)	1.22 (0.95–1.57)	1.26 (0.97–1.64)	1.29 (0.99–1.68)
Lower Spherical Equivalent Refraction (per 1.0 D greater)	1.14 (1.00–1.29)	1.06 (0.92–1.22)	1.11 (0.96–1.28)
Disc Area (per 0.4 mm ² greater)	1.17 (0.98–1.39)	1.24 (1.03–1.48)	1.23 (1.02–1.48)
Stereophotograph-based Vertical Cup-Disc Ratio (per 0.1 greater)	1.21 (1.01–1.46)	1.22 (1.02–1.46)	1.18 (1.00–1.41)
Rim Area (per 0.2 mm ² greater)	0.86 (0.10–7.54)		
Baseline Visual Field Mean Deviation (per 0.1 dB lower)	1.04 (1.02–1.05)	1.03 (1.02 –1.05)	1.03 (1.02–1.05)
<i>Ocular (during follow up)^a</i>			
Mean Intraocular Pressure (per 1.0 mmHg greater)	1.01 (0.93–1.09)	1.01 (0.93–1.09)	1.01 (0.93–1.09)
Mean Intraocular Pressure * Mean Intraocular Pressure	1.02 (1.01–1.02)	1.02 (1.01–1.02)	1.01 (1.01–1.02)
<i>Systemic (during follow up)^a</i>			
Mean Arterial Pressure (per 1.0 mmHg greater)	1.04 (1.01–1.06)	1.03 (1.01–1.06)	1.04 (1.02–1.07)
Mean Systolic Pressure (per 1.0 mmHg greater)	1.02 (1.01–1.04)		
Mean Diastolic Pressure (per 1.0 mmHg greater)	1.03 (1.00–1.06)		
Systemic Hypertension	1.00 (0.57–1.77)		

^a Measured at follow up visits from baseline to the last visit or first abnormal visual field in 3 consecutive abnormal visual fields

Table 3

The African Descent and Glaucoma Evaluation Study (ADAGES) Multivariable Analysis: Racial Differences in The Risk of Development of Visual Field Damage Vary by Mean Intraocular Pressure During Follow-up.

Predictive Factors	Multivariable Hazard Ratio (95% CI)
<i>Demographic</i>	
African Descent (Hazard Ratio varies by level of intraocular pressure)	
@ Intraocular Pressure =10 mmHg	0.36 (0.13–1.01)
@ Intraocular Pressure =12 mmHg	0.48 (0.20–1.15)
@ Intraocular Pressure =14 mmHg	0.64 (0.31–1.33)
@ Intraocular Pressure =16 mmHg	0.86 (0.47–1.57)
@ Intraocular Pressure =18 mmHg	1.14 (0.67–1.93)
@ Intraocular Pressure =20 mmHg	1.52 (0.91–2.54)
@ Intraocular Pressure =22 mmHg	2.03 (1.15–3.57)
@ Intraocular Pressure =24 mmHg	2.71 (1.39–5.29)
@ Intraocular Pressure =26 mmHg	3.61 (1.61–8.08)
@ Mean Intraocular Pressure of Cohort (17.8 mmHg)	1.12 (0.66–1.90)
Older Age per year	1.02 (0.99–1.04)
<i>Ocular (at baseline)</i>	
Central Corneal Thickness (per 40 µm thinner)	1.18 (0.86–1.60)
Lower Spherical Equivalent Refraction (per 1.0 D greater)	1.11 (0.84–1.34)
Disc Area (per 0.4 mm² greater)	1.06 (0.84–1.34)
Stereophotograph-based Vertical Cup-Disc Ratio (per 0.1 greater)	1.25 (0.99–1.57)
Baseline Visual Field Mean Deviation (per 0.1 dB lower)	1.04 (1.02–1.06)
<i>Ocular (during follow up)^a</i>	
Mean Intraocular Pressure^a (per 1.0 mmHg greater)	0.97 (0.92–1.03)
Mean Intraocular Pressure * Mean Intraocular Pressure	1.01 (1.01–1.02)
Race and Mean Intraocular Pressure Interaction	1.15 (1.05–1.27)
<i>Systemic (during follow up)^a</i>	
Mean Arterial Pressure (per 1.0 mmHg greater)	1.03 (1.00–1.06)

^a Measured at follow up visits from baseline to the last visit or first abnormal visual field in 3 consecutive abnormal visual fields

* Model included race, age, central corneal thickness, spherical equivalent refraction, disc area, baseline stereophotograph-based vertical cup-disc ratio, baseline visual field mean deviation, mean intraocular pressure during follow-up, mean arterial pressure, and a mean intraocular pressure*mean intraocular pressure interaction term and a race*mean intraocular pressure interaction term