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# The African Descent and Glaucoma Evaluation Study (ADAGES): *Design and Baseline Data*

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## Abstract

**Objective—**To identify factors accounting for differences in glaucoma onset and rate of progression between individuals of African descent and European descent.

**Design—**A prospective, multicenter observational cohort study of 1221 participants of African descent and European descent with no glaucoma (normal), suspected glaucoma, and glaucoma. Six hundred eighty-six patient participants in the African Descent and Glaucoma Evaluation Study will be followed up longitudinally. Four hundred thirty-six participants of European descent from the Diagnostic Innovations in Glaucoma Study (DIGS) were also included. Baseline demographics, visual function (standard automated perimetry, short-wavelength automated perimetry, frequency doubling technology perimetry), optic nerve structure (retina tomography, optical coherence tomography), clinical status, and risk factors were measured.

**Results—**Individuals of African descent had (1) thinner corneas ($P<.001$) across all diagnostic groups, (2) a higher percentage of reported diabetes mellitus ($P<.001$) and high blood pressure ($P<.001$) and a lower percentage of reported heart disease ($P=.001$), and (3) worse pattern standard deviation for standard automated perimetry fields overall ($P=.001$) and within normal limits ($P=.01$) than individuals of European descent. No differences were present for mean intraocular pressure ($P=.79$).

**Conclusions—**Significant baseline differences were found in a number of clinical findings between persons of African descent compared with European descent. Longitudinal data from the

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**Additional Information:** The eTable is available at http://www.archophthalmol.com.

African Descent and Glaucoma Evaluation Study will be important for determining which baseline features are important and predictive for accurate diagnosis and follow-up in this high-risk group.

The African Descent and Glaucoma Evaluation Study (ADAGES) was begun to provide information regarding the high prevalence and rapid progression of primary open-angle glaucoma (POAG) in persons of African ancestry.[1–3] The results from ADAGES will be evaluated to assist in understanding published results from population-based studies that show that individuals of African descent are disproportionately affected by POAG.[4,5] The National Eye Institute–sponsored Baltimore Eye Survey found the prevalence estimates of POAG were 4 to 5 times higher in persons of African descent compared with those of European descent, ranging from 1.2% in individuals of African descent aged 40 to 49 years to 11.3% in those 80 years or older.[2] The Barbados Eye Study confirmed the high prevalence and rapid progression in African descent populations[6] and found the 4-year incidence rate of POAG was 2.2% overall and 5.8% among persons of African descent with ocular hypertension, which is more than 5 times higher than the estimated incidence in a predominantly European descent population.[7] Primary open-angle glaucoma progresses more rapidly[8] and appears approximately 10 years earlier in this population,[1,8,9] making glaucoma the leading cause of irreversible blindness in Americans of African descent.[1,3,10] These findings, coupled with the prevalence estimates of glaucoma obtained from population-based surveys and the United Nations aging trends, make it clear this is a growing problem. The trends suggest that 44.7 and 58.6 million people worldwide will be affected by POAG by 2010 and 2020, respectively.[11,12] This number will increase to 3.36 million US citizens by 2020 because of the rapid aging of the population.

To our knowledge, ADAGES is the first prospectively designed observational cohort study to follow up a well-characterized African descent patient population covering all stages except end-stage glaucoma. ADAGES evaluates participants with a variety of measures of optic nerve structure and visual function, while documenting clinical, ocular, systemic, and demographic risk factors.

The overall aim of the study is to identify clinical factors that explain the differences in glaucoma onset and rate of progression found between individuals of African descent and those of European descent. ADAGES was designed to determine whether accounting for these differences can help optimize algorithms for detection of glaucoma by providing important information about the similarities and differences in normal optic nerve structure and function among different populations and the changes that occur in these populations as glaucoma progresses. ADAGES progression monitoring takes into account ancestry, as well as optic disc morphology, corneal thickness, and other known risk factors.

Briefly, the specific aims of ADAGES are:

1. To document the presence or absence of any differences between healthy-eyed individuals of African descent and European descent.
2. To quantify differences in visual function and optic disc and retinal nerve fiber layer structure and progressive changes in these measures between patients of African descent and European descent with glaucoma or suspected glaucoma compared with participants without glaucoma (normal). Differences in normative values could lead to misinterpretation of results from diagnostic instruments that currently have normative databases consisting primarily of persons of European descent. Current methods for analyzing progression also have been developed primarily in European descent populations. Monitoring a well-defined cohort of African descent patients will help us to improve our understanding of standard and visual function–specific perimetry in African descent patients and to improve algorithms for analyzing disease progression.

3. To combine information from structural imaging and visual function testing to help explain reported differences between African descent and European descent eyes in the onset and rate of progression of glaucoma.

Measuring the rate of glaucomatous damage is essential to improving our ability to identify patients at the highest risk of developing visual impairment due to glaucoma. Certain characteristics of glaucomatous optic neuropathy (GON) and visual field loss may progress at different rates. Delineation of the rate and patterns of glaucoma damage and their possible relationship to risk factors should improve understanding of the pathophysiology of the disease and provide evidence for specific hypotheses of glaucoma damage.

The study design, methods, enrollment, baseline demographics, and baseline clinical findings are reported herein. More complete analyses of all the visual function and optic nerve structural measurements tested in ADAGES will be reported separately.

## METHODS

### STUDY CENTERS

The 3-site collaboration includes the Hamilton Glaucoma Center at the Department of Ophthalmology, University of California, San Diego (UCSD) (data coordinating center), the New York Eye and Ear Infirmary, and the Department of Ophthalmology, University of Alabama, Birmingham (UAB). The institutional review boards at all 3 sites approved the study methods for ADAGES. Methods adhere to the tenets of the Declaration of Helsinki and to the Health Insurance Portability and Accountability Act. All participants gave written informed consent. ADAGES is registered as a cohort clinical trial (clinical-trials.gov). Enrollment began January 2003 and ended July 2006. Data are centrally processed and analyzed at UCSD through established reading centers.

The data from ADAGES were compared and combined with data on an additional group of 436 European descent normal and patient individuals obtained through 2 ongoing prospectively designed longitudinal studies at UCSD, which together make up the Diagnostic Innovations in Glaucoma Study (DIGS).[13,14] With the exception of the targeted population for ADAGES, the protocols for ADAGES and DIGS are identical and patients are followed up longitudinally. DIGS does not limit enrollment based on race or ethnicity, but only persons of African descent and European descent are included in these analyses.

### PARTICIPANTS

Participants were asked to identify their ancestry by self-report using the National Eye Institute inclusion/enrollment system describing ethnicity and race (http://orwh.od.nih.gov/pubs/outreach.pdf [pages 120–121]). Information regarding a family history of glaucoma (biological mother, father, sibling, aunt, uncle, grandparent) was also obtained. Normal and patient participants were recruited from the glaucoma clinics and optometric practices at each of the 3 recruiting sites, by advertisement and community presentations, and by referral from other ophthalmologists in the community.

### INCLUSION CRITERIA AT BASELINE

All participants had open angles, a best-corrected visual acuity of 20/40 or better, and a refraction less 5.0 diopters sphere and 3.0 diopters cylinder. We required at least 1 good-quality stereophotograph and 1 reliable standard automated perimetry (SAP) Humphrey 24-2 field test result at baseline defined as less than 33% false positives, false negatives, and fixation losses. Analyses required 2 such SAP field test results where noted. Both eyes were included, except

in cases where only 1 eye met the study criteria. All participants were older than 18 years. Diabetic participants with no evidence of retinal involvement were included.

## EXCLUSION CRITERIA

Participants were excluded if they had a history of intraocular surgery (except for uncomplicated cataract surgery or glaucoma surgery); secondary causes of glaucoma (eg, iridocyclitis, trauma); other systemic or ocular diseases known to affect the visual field (eg, pituitary lesions, demyelinating diseases, human immunodeficiency virus, or AIDS); significant cognitive impairment; history of stroke, Alzheimer disease, or dementia; problems other than glaucoma affecting color vision; an inability to perform visual field examinations reliably; or a life-threatening disease that precluded retention in the study. Inclusion/exclusion criteria are reevaluated annually, but changes associated with progression of glaucoma or normal aging do not exclude participants from follow-up.

Some clinicians require both visual field loss and evidence of GON for a diagnosis of glaucoma, referring to those with only 1 of these findings as having suspected glaucoma. Others may consider the presence of GON or repeatable visual field loss sufficient to diagnose glaucoma. For this reason, we present the specific criteria used (Table 1) to classify participants into study groups for purposes of reporting baseline results. Changes to these classification criteria may occur if dictated by new developments in the field or for specific analyses. Depending on the particular objective of each analysis, bias may be reduced if we use either the presence of GON based on stereophotographs or the presence of standard visual field loss to classify patient groups when evaluating the ability of visual field testing or imaging, respectively, to differentiate between healthy and glaucomatous eyes.[15]

## PROCEDURES

Each participant underwent a complete ophthalmological examination at baseline, which included relevant medical history, blood pressure measurement, best-corrected visual acuity, slitlamp biomicroscopy, gonioscopy, Goldmann applanation tonometry, central corneal thickness measurement, dilated funduscopy, stereoscopic ophthalmoscopy of the optic disc with a 78-diopter lens, and simultaneous stereoscopic disc photography. In addition to photography, the structure of the optic disc and nerve fiber layer was measured with a variety of imaging devices, including the Heidelberg Retina Tomograph (Heidelberg Engineering, Heidelberg, Germany), GDx (Carl Zeiss Meditec, Dublin, California), and optical coherence tomography (Stratus OCT; Carl Zeiss Meditec). Tests of visual function included SAP, short-wavelength automated perimetry, and frequency doubling technology perimetry. See Table 2 for details of the examinations and tests completed at each visit. We tracked all systemic and ocular procedures and medications and any concurrent conditions that might affect vision.

This examination protocol is repeated annually for patients with glaucoma, ocular hypertension, and suspected glaucoma, who receive treatment and glaucoma medications at no cost at the discretion of their glaucoma specialist. Transportation is provided when needed.

All color simultaneous stereophotographs were taken using a Nidek Stereo Camera Model 3-DX (Nidek Inc, Palo Alto, California) after maximal pupil dilation. All photograph evaluations were performed using a simultaneous stereoscopic viewer (Asahi Pentax Stereo Viewer II; Pentax, Tokyo, Japan) with a standard fluorescent light bulb. Certified photograph graders evaluated all photographs. To be certified, individuals were trained and then tested on separate standardized sets of stereophotographs depicting (1) glaucomatous and healthy eyes and (2) progressing and nonprogressing eyes. Recent evidence from the Ocular Hypertension Treatment Study (OHTS) and the European Glaucoma Prevention Study indicated that

reproducibility of stereophotograph assessment is good when graders have been trained using this type of formal protocol.[16,17]

Each photograph was graded by 2 independent graders according to a standard protocol using the standard photographs as reference. Each grader was masked to the participant's identity, diagnostic status, study, race, and other results. In cases of disagreement, a third senior grader adjudicated. All photographs were graded for quality and evidence of glaucoma damage. To assess between-grader reproducibility, 80 randomly chosen stereophotographs graded by IDEA (Imaging Data Evaluation and Analysis) Center personnel were evaluated for consensus between 2 graders; 73 of 80 (91%) were assigned the same diagnostic classification of glaucoma or healthy both times. Among the same 80 photographs, IDEA Center graders agreed on a vertical cup-disc ratio within 0.2 mm 70 of 80 times (87%). Adjudication of baseline photos was required in 31% of African descent and 28% of European descent eyes.

## DEFINITION OF GLAUCOMATOUS OPTIC DISC DAMAGE

Glaucomatous optic disc damage was defined as evidence of excavation, 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.

## ASSESSING VISUAL FUNCTION

Three commercially available perimetric procedures using standardized techniques were used to assess visual function for each participant.[14,18,19] Each test type took approximately 5 minutes per eye. All procedures required fixation by the patient, tested within the central 30° of the visual field, and had 52 test locations using a program 24-2 (the 2 locations near the blind spot were excluded from analysis). Proper refraction was established for each device. All required a 3-mm or larger pupil or dilation was used and recorded. The order of testing was randomized for each participant and that order was followed for each subsequent visit for that participant. Each visual field test was performed twice at baseline within a 3-month period, with repeats as necessary to replace unreliable visual field test results or those with artifacts affecting accuracy. Patients were given practice on all field types if they had no experience with them prior to their baseline testing. All field results were evaluated for adherence to study protocol, for reliability, and to rule out the presence of artifacts or evidence of field loss due to a disorder other than glaucoma. A description of the 3 visual field tests follows:

1. Standard automated perimetry used the Swedish interactive thresholding algorithm[20] on the Humphrey Visual Field Analyzer II (Carl Zeiss Meditec).
2. Short-wavelength automated perimetry, both the full-threshold algorithm and Swedish interactive thresholding algorithm (both on the Humphrey Visual Field Analyzer II), was used at baseline depending on time of enrollment.
3. Frequency doubling technology perimetry was measured on the commercially available Matrix perimeter developed by Welch-Allyn (Skaneateles, NY) and marketed by Carl Zeiss Meditec. The test was a grating contrast detection task using a Zippy Estimation by Sequential Testing algorithm.[21]

Visual field results of ADAGES participants were evaluated using statistical analysis packages available for each commercially available device. Global indexes, including mean deviation and pattern standard deviation (PSD), along with point-wise deviations (decibel values and probability maps) were provided. The ADAGES independent cohort of normal participants was used to assess any differences from expected specificity that occurred between the African descent and European descent groups.

## DEFINITION OF ABNORMAL STANDARD VISUAL FIELD

Standard automated perimetry visual field results were considered abnormal if the PSD was triggered at the 5%, 2%, 1%, or 0.5% levels or the Glaucoma Hemifield Test result was "outside normal limits." Abnormality had to be confirmed with an additional field result. A small subset of eyes had only 1 useable baseline SAP field result. If this 1 field result was normal, the participant was included in Table 3 and Table 4. If the 1 SAP field result was abnormal and the abnormality could not be verified, these eyes were excluded from the analyses reported in these 2 tables.

## ASSESSING OPTIC NERVE STRUCTURE

Imaging of the optic disc and retinal nerve fiber layer with the Heidelberg Retina Tomograph II (Heidelberg Engineering), Stratus OCT, and GDx with variable corneal compensation and enhanced corneal compensation was performed annually.[22] Details of the GDx variable corneal compensation and enhanced corneal compensation instruments and protocols have been published elsewhere[13,15,23,24] and will be provided in more detail in subsequent publications comparing in detail retinal nerve fiber layer results in African descent and European descent participants.

For the current analysis, images from the Heidelberg Retina Tomograph II (software version 3.1.5) were analyzed using HRT 3.0 software to obtain measurements of the optic disc. An experienced operator evaluated image quality and outlined the disc margin with the aid of available stereoscopic photographs of the optic disc.

## CORNEAL THICKNESS MEASUREMENT

Measurement of central corneal thickness provided information regarding glaucoma risk and intraocular pressure (IOP). Thinner corneas tend to show lower IOPs, while thicker corneas show higher IOPs.[25,26] This is of particular interest in view of reports showing lower central corneal thickness in African American individuals.[27–29] Corneal thickness was measured using a Pachette 2 ultrasonic pachymeter (DGH Technology Inc, Exton, Pennsylvania). A mean of 3 measurements taken at the center of the pupil was used.

## READING CENTERS

All data were processed through the ADAGES Coordinating Center, the VisFACT (Visual Field Assessment Center), and the IDEA Center, housed at the Hamilton Glaucoma Center, UCSD. VisFACT processed and reviewed the quality of all visual field test results from both standard and visual function–specific perimetry tests according to standard protocols. The IDEA Center processed and reviewed the quality of all simultaneous stereophotographs and also the results from a variety of retinal imaging devices according to standard protocols.[17,18] These reading centers also handled all data from DIGS and other National Eye Institute– or industry-sponsored trials. Both centers are responsible for certifying visual field and imaging technicians and photo graders, processing any data-related queries to and from each site, and requesting that tests be repeated when needed.

## STATISTICAL METHODS

Patient-specific categorical variables were compared using the Fisher exact test and continuous variables, with the *t* test. The generalized estimating equation approach[30] was used to adjust for the possible correlation in measurements between eyes from the same patient when comparing results from diagnostic tests. An exchangeable working correlation structure modeled the correlation between eyes. To test the hypothesis that there were differences in diagnostic test results between African descent and European descent patients, a contrast for the means from the 2 patient groups was computed univariately (without adjustment of any

other covariates) and multivariately via least squares means (to adjust for the effects of other covariates). The following covariates were included in the multivariable model: age, disc area, central corneal thickness, diabetes mellitus, high blood pressure, and heart disease. Models with age alone as a covariate were also examined. Differences owing to 3 different sites were examined via analysis of variance for continuous measurements and Fisher exact test for categorical outcomes. A $P$ value <.05 was considered statistically significant. Multiple testing corrections were not applied. Statistical analyses were performed in SAS (version 9.1; SAS, Cary, North Carolina) and R (version 2.6.2; http://www.r-project.org/).

ADAGES is sufficiently powered to compare the damage between African descent and European descent groups. The study typically has greater than 80% power to detect clinically interesting differences in the means of various abnormalities between African descent and European descent groups when compared using a 2-sided, 2-sample $t$ test with α set to .05. For example, for Heidelberg Retina Tomograph disc area, there was 89% power to detect a 0.27-$mm^2$ difference in means overall. For SAP PSD, there was 80% power to detect a 0.2-dB difference in means overall. For IOP, in the ocular hypertension group, there was 88% power to detect a 1.8–mm Hg difference.

# RESULTS

## PARTICIPANTS

ADAGES obtained baseline clinical, visual function, and optic nerve structure data on 803 individuals of African descent and 418 individuals of European descent. Table 5 shows the breakdown of all participants who provided consent (ADAGES only) by participation status, self-reported race, and subject category (normal or patient). One thousand eight hundred thirty-five individuals were screened and 1668 passed screening; of these, 1525 provided informed consent for participation in the study. Three hundred four of these 1525 declined after starting testing, did not meet inclusion criteria, or discontinued participation if we were unable to obtain reliable, good-quality key test results, such as standard visual field results (n=10), stereophotographs (n=5), or both (n=1). One thousand two hundred twenty-one participants were eligible and completed baseline testing (1110 participants eligible on both eyes and 111 on 1 eye). Of these, the 676 suspect and patient participants are being followed up longitudinally. Also, there were an additional 436 European descent participants, a subset from DIGS, for comparison at baseline (Table 6, UCSD European descent) and 307 of these (the suspects and patients) are being followed up longitudinally. Results in Tables 3, 4, and 6 include both the ADAGES and the DIGS participants.

In the ADAGES study cohort, 888 eyes (473 African descent and 415 European descent) entered the study after screening for inclusion as normal controls. Of these individuals who reported no ocular disease or eye problem history, 278 had abnormal findings at baseline, 35% African descent and 27% European descent. These participants are being followed up longitudinally to rule out false-positive results.

To be included in any baseline analysis, individuals had to be eligible for the study, complete ophthalmological examinations, and have at least 1 reliable, useable SAP visual field test result at baseline on at least 1 eye. Table 6 shows the participant demographic characteristics for the 1221 eligible ADAGES participants along with 436 DIGS participants of European descent who were included in the analyses. A group of European descent participants were enrolled in New York and Alabama to rule out site-specific differences in populations within each racial group (Table 6). Results are shown overall and by site.

Overall, the European descent participants were older than the African descent participants by approximately 4.5 years ($P$<.001). Fisher exact test results indicated that African descent

participants were significantly younger at UAB compared with those at UCSD in the normal (*P*<.001) and GON only (*P*=.01) groups. European descent participants were younger at both UAB and the New York Eye and Ear Infirmary compared with UCSD in the normal (*P*<.001) and visual field only (*P*<.001) groups. Age was the only site-specific difference found for any of the results reported herein. For this reason, age was included as a covariate in the models.

A significantly higher percentage of participants of African descent reported having been diagnosed with diabetes or high blood pressure and a lower percentage reported heart disease compared with those of European descent. The percentage of diabetes and heart disease was small in both groups (<13%). The direction of difference was consistent across all 3 sites for diabetes and high blood pressure. In normal participants only, blood pressure was significantly lower at UAB compared with UCSD (*P*=.03 for African descent; *P*=.03 for European descent). This difference may be due to the greater representation of older ages at UCSD. There was no difference overall in reported percentage with family history of glaucoma.

## OCULAR FINDINGS

Table 3 shows the mean ocular findings within each diagnostic category by eye adjusted using the generalized estimating equation approach to control for within-participant correlations between eyes. Both ADAGES and the subset of DIGS participant eyes are included. Baseline findings on SAP are reported herein to demonstrate the range of disease included. For comparison with Table 3, Table 4 gives the percentage of individuals from both ADAGES and the DIGS subset in each diagnostic classification based on the participant's worse eye. Three *P* values (unadjusted, age-adjusted, and multiple covariate–adjusted) are shown in Table 3. In general, the necessary adjustment for age due to the younger African descent group caused the difference between racial groups to become more pronounced for many of the variables. The additional adjustment for other potentially influential covariates reduced the effect for some variables, such as cup-disc ratio. This is most likely because this multivariate model included disc area as one of the covariates. The age-adjusted *P* values are used in the following text.

Individuals of African descent had slightly lower refractive error than those of European descent, primarily in the normal group. As reported previously (see "Comment"), eyes from African descent individuals had significantly thinner corneas (Table 3) overall and in all groups. Slightly larger vertical and horizontal cup-disc ratios were also seen in persons of African descent compared with those of European descent in the normal, ocular hypertensive, and visual field only groups. No differences were present overall for mean IOP between African descent and European descent individuals. Of the patient participants (ocular hypertensive, GON only, visual field only, and visual field+GON groups), 54% of African descent and 58% of European descent patients were already using IOP-lowering medications at enrollment.

Table 3 also gives the SAP results for the normal group, the visual field+GON group, and overall by ancestry. The results for the other groups can be found in the eTable (http://www.archophthalmol.com). Mean deviation (*P*<.001) and PSD (*P*<.001) were significantly poorer in African descent compared with European descent individuals overall. Pattern standard deviation was also poorer in African descent individuals for the normal, ocular hypertensive, and GON only eyes, although these differences were small and values were within the normal range of the Humphrey Field Analyzer internal normative database by definition for these diagnostic groups. The distributions across all participants for mean deviation and PSD demonstrate the inclusion of a broad range of functional status from normal to severe loss in this study cohort. The mean deviation range was +3.69 to −30.40 dB (African descent) and +2.91 to −28.59 dB (European descent). Pattern standard deviation ranged from 0.91 to 17.19 (African descent) and 0.85 to 16.11 (European descent).

## COMMENT

The diagnosis of POAG is based on an assessment of the optic nerve appearance, visual field results, and other clinical signs and risk factors. Any characteristic difference in the African descent population with regard to these diagnostic measures needs to be addressed if an accurate diagnosis of glaucoma is to be made in this group. ADAGES baseline differences associated with ancestry were consistent with those reported in the literature showing that persons of African descent had higher refractive error, thinner corneas, larger cup-disc ratios, and larger disc and rim areas. Differences were seen even in healthy eyes. Such differences in optic nerve parameters between African descent and European descent groups are well documented. Larger optic disc areas have been observed in normal,[31–36] ocular hypertensive,[37] postmortem,[38] and glaucomatous[39,40] African descent eyes compared with European descent eyes. Further, healthy persons of African descent reportedly have larger optic cup volumes,[31,32,36] deeper optic cups,[32,41] and larger cup-disc ratios, although these differences should be interpreted with caution in light of reports that after adjusting for disc size, differences in other optic disc parameters are no longer significant.[32,37]

At baseline, ADAGES normal, ocular hypertensive, and GON only eyes from individuals of African descent had significantly worse PSD values on SAP than those of European descent. Although these differences might not be considered clinically significant, a joint analysis of the OHTS and Early Glaucoma Prevention Study untreated arms showed that the predictive factors for developing glaucoma included both SAP PSD and stereophotograph cup-disc ratio even when the visual field results and optic discs were considered normal.[42] Wilson and colleagues[8] showed that visual field defects were more likely to develop in participants of African descent with open-angle glaucoma who initially had normal Goldmann visual field results than in participants of European descent. They also found that visual field defects progressed in a higher percentage of persons of African descent. In the Salisbury Eye Evaluation Project, 60° Humphrey visual field tests showed that participants of African descent of all ages had worse visual field test results than those of European descent.[43] In a large cohort of individuals with ocular hypertension, Gordon and Kass[44] analyzed data from Humphrey 30-2 visual field tests. Although normal and reliable visual field test results in both eyes were an inclusion criterion in this study, the visual field mean deviation was significantly poorer in the African descent group, with similar standard deviations in both groups. Healthy individuals of African descent also had worse mean deviations on frequency doubling technology perimetry than those of European descent.[35]

There is evidence that individuals of African descent differ from those of European descent with respect to several risk factors associated with glaucoma, although there are studies in each case that counter this view. Differences in IOP and family history of glaucoma, diabetes, and systemic hypertension have been found between the groups. See Racette and colleagues[4] for a complete review giving findings in support for or against these differences. Overall, ADAGES baseline findings show that more individuals of African descent had high blood pressure and diabetes than those of European descent. No differences were found for level of IOP.

Studies have also shown that African descent individuals report specific barriers to obtaining care.[45,46] These include cost of care or lack of insurance,[45,46] transportation,[45] trusting the health care system,[45] and not having symptoms.[46] ADAGES controls for some of these issues by providing complete ophthalmological examinations by glaucoma specialists, glaucoma medications, and transportation(as needed) at no cost. We assign each participant a specific study contact person to answer questions and to greet the participant at each visit whenever possible. The physicians and technicians provide information about glaucoma and the testing involved to the participants.

Medical researchers and clinicians often categorize patients and research subjects by race to recognize differences in susceptibility to disease, determine differing medical needs, and highlight health disparities.[47,48] However, there are questions as to the validity of racial classification in any strict biologic sense.[49,50] Most of the epidemiologic literature uses self-description to define racial differences. Clearly, there are limitations with using this definition and *self-described race* is a term that represents an amalgam of cultural, geographic, socioeconomic, and biologic characteristics and is at best a suboptimal summary of human biodiversity that cannot be interpreted in the strict biologic sense.[51] However, there exists incontrovertible evidence of racial distinctions in many aspects of life, such as access to education, employment, and health care. These distinctions undoubtedly contribute to race-associated differences in health outcomes and as long as these health disparities exist, we must continue to collect data by race, however imprecise that measure may be.[50] In addition, self-reported race has demonstrated dependent and independent associations to glaucoma along with several other ocular and systemic conditions, it correlates highly with genetic admixture results,[52] and it remains an important and relatively accessible factor.[2] ADAGES is collecting additional demographic information and genetic material on ADAGES and DIGS patients and will be reporting these results in the near future.

ADAGES is complementary to other clinical studies. The National Eye Institute–sponsored OHTS, a multi-center study that began enrollment in 1994 of patients with ocular hypertension and no other evidence of glaucoma, has 25% African American participation (408 eyes).[44] The OHTS has been invaluable in determining risk for glaucoma and the beneficial effect of IOP-lowering treatments and documenting the higher incidence of POAG in African American individuals.[53] Although self-identified African American race was significantly associated with a 71% increase in risk of developing POAG compared with other participants in the univariate analysis, when other risk factors, including corneal thickness, cup-disc ratio, and visual field PSD, were included in a multivariable model, race was no longer statistically associated with POAG. This result differs from the evidence cited earlier from population-based studies that suggested an increased risk for individuals of African descent for both the development and progression of glaucoma and the need to study this issue further.

ADAGES includes participants across the glaucoma spectrum, except end-stage disease, and will provide important estimates of the rate of progression for African descent individuals that are currently lacking in the literature. The extensive measures of visual function, optic nerve structure, and clinical risk factors should facilitate the development of models to determine the relative importance of self-reported race and other risk factors in the progression of glaucoma. The inclusion of healthy eyes in ADAGES is important for understanding any normal differences that should be taken into account when interpreting data from individuals of African descent vs those of European descent, such as the well-documented differences in the size of the optic disc.

A major emphasis of ADAGES is the longitudinal follow-up using a variety of measures to document glaucomatous progression, when present. Progressive change in optic disc appearance has been suggested as the best available reference standard for glaucoma diagnosis.[15] While several qualitative differences in the optic nerve have been reported between eyes of persons of African descent and European descent, there is relatively little quantitative data and very little information about possible differences in visual field results, especially for automated perimetry. There is no information about possible differences among the newer perimetric procedures for assessing progression and the few longitudinal studies that evaluate these newer tests have participants predominantly of European descent. A test that is good at detecting early damage may not necessarily be the best for detecting progression at later stages of the disease.

Defining glaucomatous damage in an African descent population using quantitative structural measures and selective tests of visual function, such as those used in ADAGES, could improve clinical management of this disease. A better understanding of damage in this group may be crucial for development of better clinical end points that can facilitate clinical studies of neuroprotective agents in this at-risk minority population.

In conclusion, the findings from ADAGES will have direct impact on the management of glaucoma in this at-risk minority population, providing the clinician with critical information currently not known or well understood, especially as it relates to the newer and innovative methods for measuring visual function, optic nerve and retinal nerve fiber layer structure, and progression of the disease.

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**Table 1**

Criteria for Classification of Participants for Analyses Shown in Subsequent Tables

| Diagnostic Category | IOP < 22 mm Hg[a] | | Photo Grade | | SAP Visual Field Test Result |
|---|---|---|---|---|---|
| Normal (recruited or referred as normal) | Yes and no IOP-lowering medications | AND | Normal | AND | Normal |
| Suspect by source (referred as patient) | Yes and no IOP-lowering medications | AND | Normal | AND | Normal |
| Ocular hypertension | No or taking IOP-lowering medications | AND | Normal | AND | Normal |
| Abnormal visual field test result only | NA | AND | Normal | AND | Glaucomatous (repeatable) |
| Glaucomatous optic neuropathy only | NA | OR | Glaucomatous | AND | Normal |
| Abnormal visual field test result and glaucomatous optic neuropathy | NA | AND | Glaucomatous | AND | Glaucomatous (repeatable) |

Abbreviations: IOP, intraocular pressure; NA, not applicable; SAP, standard automated perimetry.

[a]Intraocular pressure 22 mm Hg or higher measured as such on baseline ocular examination or documented history of such.

**Table 2**

Schedule of Baseline and Follow-up Testing

| | Visit | | |
|---|---|---|---|
| | **Qualification/Baseline** | **Visual Field 2nd Baseline** | **Follow-up Annual** |
| Screening interview | X | | |
| Informed consent | X | | |
| Clinical examination and medical history | | | |
| Blood pressure | X | | X |
| Medical history | X | | X |
| Ocular examination | | | |
| Axial length, color vision, pachymetry, keratometry, gonioscopy[a] | X | | |
| Acuity, refraction, | X | X | X |
| Corneal viscoelasticity | X | X | X |
| Undilated and dilated ocular examination including slitlamp and direct and indirect ophthalmoscopy | X | | X |
| Goldmann applanation tonometry | X | | X |
| Lens opacity classification system | X | | X |
| Simultaneous stereophotographs | X | | X |
| Imaging | | | |
| Scanning laser polarimetry | X | | X |
| Retina tomography[b] | X | | X |
| Optical coherence tomography[c] | X | | X |
| Visual field testing | | | |
| Standard automated perimetry | X | X | X |
| Short-wavelength automated perimetry | X | X | X |
| Frequency doubling technology perimetry | X | X | X |

[a] Only done on the qualification visit, unless the participant had ocular surgery during the study.

[b] Heidelberg Retina Tomograph (Heidelberg Engineering, Heidelberg, Germany).

[c] Stratus OCT (Carl Zeiss Meditec, Dublin, California).

**Table 3**

Baseline SAP, HRT, and Ocular Finding Results by Self-reported Ancestry and Diagnostic Categories[a]

| | AD | | ED | | | | |
|---|---|---|---|---|---|---|---|
| | No. of Eyes | Mean (SD) | No. of Eyes | Mean (SD) | Unadjusted *P* Value | Age-Adjusted *P* Value | Multiple Covariate–Adjusted *P* Value[b] |
| **Normal** | | | | | | | |
| SAP | | | | | | | |
| Mean deviation, dB | 657 | −0.36 (1.26) | 645 | −0.21 (1.17) | .15 | .12 | .04 |
| Pattern standard deviation, dB | 657 | 1.61 (0.43) | 645 | 1.55 (0.38) | .02 | .01 | .01 |
| Ocular findings | | | | | | | |
| Spherical correction, D | 657 | −0.58 (1.41) | 645 | −0.87 (1.63) | .02 | .002 | .02 |
| IOP, mm Hg | 657 | 15.26 (2.77) | 645 | 15.10 (2.64) | .37 | .20 | .03 |
| Central corneal thickness, μm | 655 | 533.70 (33.56) | 638 | 551.67 (36.94) | <.001 | <.001 | |
| Stereophotograph-based cup-disc ratio (vertical) | 657 | 0.45 (0.15) | 645 | 0.41 (0.15) | <.001 | <.001 | .72 |
| Stereophotograph-based cup-disc ratio (horizontal) | 657 | 0.44 (0.15) | 645 | 0.41 (0.16) | <.001 | <.001 | .75 |
| **Abnormal VF Test Results and GON** | | | | | | | |
| SAP | | | | | | | |
| Mean deviation, dB | 185 | −7.20 (7.25) | 184 | −6.18 (5.58) | .10 | .17 | .08 |
| Pattern standard deviation, dB | 185 | 6.17 (3.77) | 184 | 6.41 (3.89) | .73 | .33 | .51 |
| Ocular findings | | | | | | | |
| Spherical correction, D | 185 | −0.76 (1.94) | 171 | −0.98 (1.94) | .39 | .02 | .03 |
| IOP, mm Hg | 185 | 16.76 (4.92) | 184 | 15.32 (4.76) | .05 | .12 | .21 |
| Central corneal thickness, μm | 185 | 520.52 (38.70) | 181 | 535.27 (40.16) | <.001 | <.001 | |
| Stereophotograph-based cup-disc ratio (vertical) | 185 | 0.80 (0.10) | 184 | 0.82 (0.10) | .23 | .14 | .02 |
| Stereophotograph-based cup-disc ratio (horizontal) | 185 | 0.75 (0.11) | 184 | 0.75 (0.13) | .51 | .74 | .16 |
| **All** | | | | | | | |
| SAP[c] | | | | | | | |
| Mean deviation, dB | 1496 | −1.59 (3.80) | 1588 | −1.17 (3.03) | .01 | <.001 | .003 |

| | AD | | ED | | | | |
|---|---|---|---|---|---|---|---|
| | No. of Eyes | Mean (SD) | No. of Eyes | Mean (SD) | Unadjusted *P* Value | Age-Adjusted *P* Value | Multiple Covariate–Adjusted *P* Value[b] |
| Pattern standard deviation, dB | 1496 | 2.50 (2.23) | 1588 | 2.28 (2.17) | .02 | <.001 | .01 |
| Ocular findings | | | | | | | |
| Spherical correction, D | 1520 | −0.57 (1.57) | 1559 | −0.81 (1.81) | .01 | <.001 | <.001 |
| IOP, mm Hg | 1523 | 16.26 (3.90) | 1602 | 16.45 (4.48) | .35 | .79 | .06 |
| Central corneal thickness, μm | 1520 | 531.71 (36.28) | 1588 | 552.67 (38.30) | <.001 | <.001 | |
| Stereophotograph-based cup-disc ratio (vertical) | 1523 | 0.55 (0.18) | 1602 | 0.53 (0.21) | .06 | <.001 | .08 |
| Stereophotograph-based cup-disc ratio (horizontal) | 1523 | 0.54 (0.18) | 1602 | 0.51 (0.20) | .01 | <.001 | .12 |

Abbreviations: AD, African descent; D, diopter; ED, European descent; GON, glaucomatous optic neuropathy; HRT, Heidelberg Retina Tomograph (Heidelberg Engineering, Heidelberg, Germany); IOP, intraocular pressure; SAP, standard automated perimetry; VF, visual field.

[a] Additional diagnostic groups are shown in the eTable (http://www.archophthalmol.com).

[b] Adjusted by age, disc area, central corneal thickness, diabetes mellitus, high blood pressure, and heart disease.

[c] Forty-one eyes of 35 participants who did not have a repeated SAP to confirm the abnormal SAP results for either eye within the baseline visit not included.

**Table 4**

Breakdown of Diagnostic Categories by Ancestry[a]

| | No. (%) | | | |
|---|---|---|---|---|
| | Overall All Eyes | | Overall by Worse Eye[a] | |
| **Diagnostic Category** | **AD (n=1496)** | **ED (n=1588)** | **AD (n=797)** | **ED (n=850)** |
| Normal | 657 (44) | 645 (41) | 307 (39) | 303 (36) |
| Patient | 839 (56) | 943 (59) | 490 (61) | 547 (64) |
| Suspect by source | 120 (8) | 116 (7) | 53 (7) | 53 (6) |
| Ocular hypertension | 150 (10) | 243 (15) | 67 (8) | 109 (13) |
| Abnormal GON only | 157 (11) | 263 (17) | 80 (10) | 140 (17) |
| Abnormal VF only | 227 (15) | 137 (9) | 153 (19) | 106 (12) |
| Abnormal VF + GON | 185 (12) | 184 (11) | 137 (17) | 139 (16) |

Abbreviations: AD, African descent; ED, European descent; GON, glaucomatous optic neuropathy; VF, visual field.

[a]To determine worse eye, we assumed the order shown (best on top to worst on bottom).

**Table 5**

Distribution of Participants Who Gave Consent by Eligibility Status and Self-reported Ancestry

| | AD (n=1036) | | ED (n=489) | | |
|---|---|---|---|---|---|
| **Enrolled and Eligibility Determined** | **Normal** | **Longitudinal Participant** | **Normal** | **Longitudinal Participant** | **Total[a]** |
| Continue eligible | 307 | 496 | 170 | 248 | **1221** |
| Ineligible | 43 | 52 | 10 | 17 | **122** |
| Discontinue | 60 | 43 | 17 | 12 | **132** |
| Decline | 22 | 13 | 11 | 4 | **50** |
| **Total** | **432** | **604** | **208** | **281** | **1525** |

Abbreviations: AD, African descent; ED, European descent.

[a] African Descent and Glaucoma Evaluation Study participants only.

**Table 6**

Participant Demographics for the Full Eligible ADAGES and DIGS Cohorts Broken Down by Self-reported Ancestry and Site[a]

| | % | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | All (n=1657) | | | UAB (n=570) | | NYEE (n=476) | | UCSD (n=611) | |
| | AD (n=803) | ED (n=854) | *P* Value | AD (n=329) | ED (n=241) | AD (n=299) | ED (n= 177) | AD (n=175) | ED (n=436) |
| Age, y, mean (SD) | 51.1 (14.1) | 55.7 (15.5) | <.001 | 48.6 (13.9) | 50.2 (14.4) | 51.4 (13.8) | 50.3 (14.9) | 55.2 (14.0) | 61.0 (14.4) |
| ≤29 | 7.0 | 7.1 | | 6.4 | 7.5 | 8.7 | 14.1 | 5.1 | 4.1 |
| 30–39 | 13.0 | 8.3 | | 20.1 | 15.8 | 8.7 | 7.9 | 6.9 | 4.4 |
| 40–49 | 26.4 | 17.0 | | 31.6 | 27.8 | 22.7 | 19.8 | 22.9 | 9.9 |
| 50–59 | 26.5 | 23.9 | | 20.7 | 21.2 | 34.5 | 31.1 | 24.0 | 22.5 |
| 60–69 | 15.3 | 22.1 | | 10.3 | 16.2 | 15.4 | 17.0 | 24.6 | 27.5 |
| ≥70 | 11.8 | 21.6 | | 10.9 | 11.6 | 10.0 | 10.2 | 16.6 | 31.7 |
| Male | 35.4 | 40.5 | .03 | 30.4 | 39.4 | 39.5 | 37.3 | 37.7 | 42.4 |
| Hispanic ethnicity | 3.6 | 7.7 | <.001 | 0.0 | 0.0 | 9.0 | 20.3 | 1.1 | 6.9 |
| Heart disease | 7.4 | 12.3 | .001 | 10.6 | 11.6 | 3.0 | 4.5 | 8.6 | 15.8 |
| Family history of glaucoma | 39.9 | 39.8 | >.99 | 34.4 | 35.3 | 48.2 | 46.3 | 36.0 | 39.7 |
| Diabetes mellitus | 12.3 | 4.8 | <.001 | 12.5 | 5.8 | 10.0 | 2.8 | 16.0 | 5.0 |
| High blood pressure | 43.7 | 30.4 | <.001 | 45.0 | 28.2 | 36.1 | 26.0 | 54.3 | 33.5 |

Abbreviations: AD, African descent; ADAGES, African Descent and Glaucoma Evaluation Study; DIGS, Diagnostic Innovations and Glaucoma Study; ED, European descent; NYEE, New York Eye and Ear Infirmary; UAB, University of Alabama; UCSD, University of California, San Diego.

[a] ADAGES, N=1222; DIGS, N=436.