African Descent and Glaucoma Evaluation Study (ADAGES)

II. Ancestry Differences in Optic Disc, Retinal Nerve Fiber Layer, and Macular Structure in Healthy Subjects

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Objective: To define differences in optic disc, retinal nerve fiber layer, and macular structure between healthy participants of African (AD) and European descent (ED) using quantitative imaging techniques in the African Descent and Glaucoma Evaluation Study (ADAGES).

Methods: Reliable images were obtained using stereoscopic photography, confocal scanning laser ophthalmoscopy (HRT II; Heidelberg Engineering, Inc, Heidelberg, Germany) and optical coherence tomography (OCT) for 648 healthy subjects in ADAGES. Findings were compared and adjusted for age, optic disc area, and reference plane height where appropriate.

Results: The AD participants had significantly greater optic disc area on HRT (2.06 mm²; P < .001) and OCT (2.47 mm²; P < .001) and a deeper HRT cup depth than the ED group (P < .001). Retinal nerve fiber layer thickness was greater in the AD group except within the temporal region, where it was significantly thinner. Central macular thickness and volume were less in the AD group.

Conclusions: Most of the variations in optic nerve morphologic characteristics between the AD and ED groups are due to differences in disc area. However, differences remain in HRT cup depth, OCT macular thickness and volume, and OCT retinal nerve fiber layer thickness independent of these variables. These differences should be considered in the determination of disease status.

Trial Registration: clinicaltrials.gov Identifier: NCT00221923


Several epidemiologic studies have demonstrated a greater susceptibility to primary open-angle glaucoma and higher rates of blindness in populations of African descent (AD) compared with those of European descent (ED). These racial differences in the susceptibility to glaucomatous injury prompted the initiation of the National Eye Institute–funded African Descent and Glaucoma Evaluation Study (ADAGES). ADAGES enrolled AD and ED individuals who were healthy or who had suspected glaucoma, ocular hypertension, or glaucoma.

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ADAGES is the first prospectively designed observational cohort study to follow up a well-characterized AD patient population covering all stages of glaucoma (excluding end-stage disease). Each ADAGES participant undergoes a variety of measures of visual function and optic nerve and retinal nerve fiber layer (RNFL) structure and documentation of clinical, ocular, systemic, and demographic risk factors. The 3-site collaboration includes the Department of Ophthalmology and the Hamilton Glaucoma Center at the University of California, San Diego (UCSD), which served as the data coordinating center; the Department of Ophthalmology, New York Eye and Ear Infirmary (NYEE); and the Department of Ophthalmology, University of Alabama, Birmingham (UAB). The baseline characteristics and study design have been described in a previous publication.

The present study evaluated differences in optic disc topography, RNFL, and macular measurements obtained with confocal scanning laser ophthalmoscopy using Heidelberg retina tomography (HRT) (HRT II; Heidelberg Engineering, Inc, Heidelberg, Germany) and optical coherence tomography (OCT) (Stratus OCT; Carl Zeiss Meditec, Inc, Dublin, California) between healthy AD and ED subjects to determine structural differences between these groups in ADAGES.
The methods for ADAGES have been described in the baseline study design article. The methods relevant to this particular study are reviewed in this section.

Baseline data from participants in the National Eye Institute–funded Diagnostic Innovations in Glaucoma Study (DIGS) and ADAGES who did not have ocular disease were used for all the analyses in the present study. The methods followed in DIGS and ADAGES are identical. All participants gave written informed consent. The institutional review boards at all 3 sites approved the study methods. Methods adhere to the tenets of the Declaration of Helsinki and to the Health Insurance Portability and Accountability Act. Healthy control subjects for ADAGES and DIGS were recruited to join the present study by advertisement, from family members of patients, and from primary eye care clinics.

Each healthy control underwent a complete ophthalmological examination that included medical history, measurement of Snellen best-corrected visual acuity, Early Treatment Diabetic Retinopathy Study visual acuity, color vision, central corneal thickness, axial length, slitlamp biomicroscopy, gonioscopy, applanation tonometry, lens opacity estimation with version III of the Lens Opacities Classification System grading system, keratometry, dilated funduscopy, stereoscopic ophthalmoscopy of the optic disc with a 78-diopter (D) lens, and simultaneous stereoscopic fundus photography. Standard and visual function–specific perimetry tests were performed. However, only standard automated perimetry was used to define normality for inclusion in this study. Information regarding systemic conditions, medications, and several risk factors associated with glaucoma were also obtained, including blood pressure measurement, family history, highest known intraocular pressure (IOP), age, and history of diabetes mellitus, heart disease, and vascular disease. In addition to photography, the structure of the optic disc, RNFL, and macula were quantified using HRT and OCT.

INCLUSION/EXCLUSION CRITERIA

All participants were older than 18 years. Eligible participants had open angles, a best-corrected visual acuity of 20/40 or better, and refractive error up to 5.0 D sphere and 3.0 D cylinder. All stereoscopic photographs had to be of readable quality for the subject to be included. The previous publication describes the photographic grading technique. Diabetic participants with no evidence of retinal involvement were included. A family history of glaucoma was allowed. Participants were excluded if they had a history of intraocular surgery (except for uncomplicated cataract surgery), elevated IOP (>22 mm Hg) at the time of the study, a history of elevated IOP, previous use of glaucoma medication, other intraocular eye disease, other diseases affecting the visual field (eg, pituitary lesions, demyelinating diseases, human immunodeficiency virus seropositivity, or AIDS), or problems other than glaucoma affecting color vision. At baseline, we required 2 reliable test results on 24-2 threshold standard automated perimetry (Carl Zeiss Meditec) using the Swedish Interactive Thresholding Strategy for inclusion in the study. Reliability was defined as less than 33% false-positive and false-negative findings and fixation losses. All fields are reviewed by the UCSD Visual Field Assessment Center (described in the previous publication). A field was considered normal if the pattern standard deviation was not triggered at 5% or less, the glaucoma hemifield test results were within normal limits, and the field showed no sign of glaucomatous defect based on subjective evaluation from the enrolling clinician. The appearance of the disc on clinical examination on enrollment or stereoscopic photographic evaluation was not used to define normality in the present study to eliminate the effect of differential misclassification bias due to the large cup-disk ratio (CDR) described in AD groups. This may result in the inclusion of some patients with early glaucoma without achronic visual field defects. However, because glaucoma is a low-prevalence condition, the effect is likely small, and the results of stereoscopic photographic evaluation are available to estimate the significance of this effect.

IMAGE ACQUISITION AND PROCESSING

Optic nerve stereoscopic photography, HRT, and OCT were performed. Photography and HRT were performed on both eyes; however, to reduce participant burden, OCT was performed only on the study eye.

OPTIC NERVE STEREOSCOPIC PHOTOGRAPHS

All color stereoscopic photographs were taken using a commercially available camera (Stereo Camera Model 3-DX; Nidek Inc, Palo Alto, California) after maximal pupil dilation. All photographic evaluations were performed using a simultaneous stereoscopic viewer (Asahi Pentax Stereo Viewer II; Asahi Optical Co, Tokyo, Japan) with a standard fluorescent lightbulb. Certified photograph graders from the UCSD Imaging Data Evaluation and Analysis Center evaluated all photographs. The certification process is detailed in the baseline publication.

HEIDELBERG RETINAL TOMOGRAPHY

The HRT II device (using software version 3.0) uses a diode laser and confocal imaging to produce 3-dimensional measurements of optic disc topography. Image acquisition, processing, and reproducibility of HRT measurements have been described in detail elsewhere. An experienced operator evaluated image quality and outlined the disc margin (ie, the contour line that defines the reference plane used for some analyses) with the aid of available stereoscopic photographs of the optic disc.

HRT ANALYSIS STRATEGY

We use the HRT internal software version 3.0 for all analyses. The HRT II includes a comprehensive software analysis package that provides stereometric topographic measures of the optic disc measured relative to the reference plane or the curved surface. Also available are several automated discriminant analysis functions and Moorfields regression analysis (MRA) comparing rim area adjusted for disc area with a normative database that designates each eye as probable “glaucoma,” “borderline,” or “normal.” The new software includes the glaucoma probability score (GPS), which does not rely on technician-dependent contour line placement or the reference plane. The GPS uses 6 optic disc measurements as input into a machine-learning classifier to describe the shape of the optic nerve head (ONH) as a probability from 0% (no glaucoma) to 100% (definite glaucoma). The new software also includes a larger ethnic-specific normative database of 700 eyes from ED subjects and 200 eyes from AD subjects that has been applied to the new GPS analysis and existing MRA.

OPTICAL COHERENCE TOMOGRAPHY

The operation of the OCT has been described in detail in previous publications. In brief, the Stratus OCT device uses low coherence interferometry to measure the time delay of backscattered light reflected from the tissue of interest to determine tissue thickness providing 2-axis resolution of approximately less than 10 μm. The following 3 types of scans are acquired in ADAGES on the study eye of each participant annually after dilation: fast RNFL, fast ONH, and fast macula scan. The protocol for image acquisition, including the assessment of quality by the UCSD Imaging Data Evaluation and Analysis Center, has been de-
The associations between age and optic disc structure (HRT and OCT) were evaluated in both ancestry groups (using generalized estimating equation models for HRT and OCT, respectively). The AD group was younger than the ED group, adjustment for age was used in the comparison of all further structural variables. There were no significant differences in sex between groups. The AD group had a significantly higher proportion of individuals with a diagnosis of hypertension but not diabetes. Because the higher prevalence of diabetes mellitus in the AD group approached significance and an association between diabetes and RNFL measurements has been previously described, separate multivariable models were also run that included diabetes as a covariate in the analysis. This analysis provided results similar to the final models shown.

General ocular characteristics are given in Table 2. The AD group had larger optic discs on HRT and OCT.  

### Table 1. Demographic Data

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>AD Group (n=326)</th>
<th>ED Group (n=322)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>45.1 (13.3)</td>
<td>47.7 (15.9)</td>
<td>.03</td>
</tr>
<tr>
<td>Female, %</td>
<td>64.7</td>
<td>64.6</td>
<td>.73</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>30.7</td>
<td>19.6</td>
<td>.003</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>6.1</td>
<td>3.1</td>
<td>.10</td>
</tr>
</tbody>
</table>

Abbreviations: AD, African descent; ED, European descent. *Significant values are given in boldface type.

### Table 2. Ocular Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>AD Group (n=326)</th>
<th>ED Group (n=322)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disc area on HRT, mm²</td>
<td>2.06 (0.47)</td>
<td>1.77 (0.39)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Disc area on OCT, mm²</td>
<td>2.47 (0.45)</td>
<td>2.26 (0.43)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Reference plane height, mm</td>
<td>0.36 (0.11)</td>
<td>0.32 (0.11)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Intraocular pressure, mm Hg</td>
<td>15.2 (2.8)</td>
<td>15.1 (2.6)</td>
<td>.49</td>
</tr>
<tr>
<td>MD, dB</td>
<td>-0.32 (1.23)</td>
<td>-0.15 (1.16)</td>
<td>.07</td>
</tr>
<tr>
<td>PSD, dB</td>
<td>1.58 (0.40)</td>
<td>1.53 (0.36)</td>
<td>.03</td>
</tr>
<tr>
<td>CTD, µm</td>
<td>534 (33)</td>
<td>552 (37)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Axial length, mm</td>
<td>23.70 (0.95)</td>
<td>23.71 (0.97)</td>
<td>.94</td>
</tr>
<tr>
<td>Photographic vertical CDR</td>
<td>0.47 (0.16)</td>
<td>0.42 (0.16)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Photographic horizontal CDR</td>
<td>0.46 (0.16)</td>
<td>0.42 (0.16)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Classified as glaucoma</td>
<td>5.5</td>
<td>5.4</td>
<td>.90</td>
</tr>
</tbody>
</table>

Abbreviations: AD, African descent; CCT, corneal central thickness; CDR, cup-disc ratio; ED, European descent; HRT, confocal scanning laser ophthalmoscopy (Heidelberg retinal tomography); MD, mean defect; OCT, optical coherence tomography; PSD, pattern standard deviation.  
*Unless otherwise indicated, data are expressed as mean (SD). bFor MD, PSD, CCT, axial length, CDR, and disc area on HRT, 620 eyes of AD individuals and 601 eyes of ED individuals; for disc area on OCT, 309 eyes of AD individuals and 268 eyes of ED individuals.  
**Significant values are given in boldface type.

### RESULTS

Of the 634 eyes of 326 AD subjects and 630 eyes of 322 ED subjects, 620 eyes (97.8%) in the AD group and 601 eyes (95.4%) in the ED group had HRT examinations that met the quality control criteria. The OCT examinations were performed only in the randomly selected study eye. Six hundred five eyes met the quality control criteria, with 290 of 308 eyes (94.2%) with the fast macula and fast RNFL included from the ED group and 315 of 320 eyes (98.4%) from the AD group. Three hundred nine AD eyes and 268 ED eyes had good-quality fast ONH scans included in the analysis. Although the differences in the number of included eyes was significant between AD and ED groups for the 3 OCT scan types (*P*<.001), most of the exclusions were owing to missing test data due to technical problems with 1 site and not because of poor quality. Basic demographic and medical characteristics of both groups are shown in Table 1. Because the AD group was younger than the ED group, adjustment for age was used in the comparison of all further structural variables. There were no significant differences in sex between groups. The AD group had a significantly higher proportion of individuals with a diagnosis of hypertension but not diabetes. Because the higher prevalence of diabetes mellitus in the AD group approached significance and an association between diabetes and RNFL measurements has been previously described, separate multivariable models were also run that included diabetes as a covariate in the analysis. This analysis provided results similar to the final models shown.

General ocular characteristics are given in Table 2. The AD group had larger optic discs on HRT and OCT. Mean
reference plane height was also higher in AD individuals. Thus, adjustment was performed for the HRT variables that are associated with these measures. There were no significant differences in IOP or axial length between groups. As expected, the AD group had thinner mean corneal thickness than the ED group. In addition, the AD group had a higher pattern standard deviation than the ED group. Visual functional measures and perimetry are the subject of a concurrent publication. Photograph-based CDR was larger vertically and horizontally for the AD group. However, a similar proportion of individuals were identified as having glaucomatous-appearing discs via masked grading of stereoscopic photographs.

Table 3 gives the comparisons of means and standard deviations for the standard HRT variables adjusted for age between racial groups. The *P* values associated with the interracial comparison of variables adjusted for age and disc area and for age, disc area, and reference plane height are provided for variables that are dependent on these measures (under the heading “Full Models” in Table 3). Although several HRT optic disc variables differed between groups in the age-adjusted models, only mean and maxi-
mum cup depth and the contour line modulation between the temporal and inferior regions of the disc differed significantly between groups in the full models. The HRT rim area and volume were greater in the AD group. However, these differences were largely explained by differences in disc area and reference plane height for rim area and rim volume. Figure 1 illustrates the mean regional differences in rim to disc area determined by HRT. Rim area was significantly thicker in the AD group in all regions except temporally. This result corresponds well to findings of regional variation in RNFL thickness between racial groups determined with HRT. Rim area was significantly thicker in the AD group, and these differences were highly significant between groups in the full models. For optic nerve variable estimates determined with the use of OCT, 4 eyes from the AD group and 14 eyes from the ED group were eliminated owing to a previously described error with the Stratus OCT24 optic disc variable estimate that yielded an incorrect estimate of rim area equal to zero in small crowded discs. Significantly thicker RNFL measurements were found in the AD group for the inferior and superior regions surrounding the optic disc adjusted for differences in disc area and age. Conversely, the temporal RNFL thickness corresponding to the papillomacular bundle was significantly thinner in the AD group. Vertical CDR and cup area were significantly different between groups. However, after adjustment for age and disc area, no OCT ONH variables differed between groups.

The mean (SD) OCT total macular volume (AD, 6.7 [0.4] mm³; ED, 6.8 [0.4] mm³; P = .001) and foveal thickness (AD, 152.0 [20.7] mm; ED, 167.2 [23.7] mm; P < .001) were significantly lower in the AD group compared with the ED group. In addition, for regional measures, all central macular thickness measurements were thinner in the AD group, and these differences were highly significant between groups.

The comparison of optic disc morphologic characteristics as determined by automated modeling of the optic cup and peripapillary retinal surfaces used to calculate the GPS are provided in Table 4. Although the overall GPS classification was similar between racial groups, all of the morphologic variables used in this classification except rim steepness were significantly different between groups.

Differences in OCT optic nerve variables and RNFL thickness between the AD and ED groups are given in Table 5 and Table 6, respectively, with regional differences in RNFL thickness demonstrated in Figure 2. For optic nerve variable estimates determined with the use of OCT, 4 eyes from the AD group and 14 eyes from the ED group were eliminated owing to a previously described error with the Stratus OCT24 optic disc variable estimate that yielded an incorrect estimate of rim area equal to zero in small crowded discs. Significantly thicker RNFL measurements were found in the AD group for the inferior and superior regions surrounding the optic disc adjusted for differences in disc area and age. Conversely, the temporal RNFL thickness corresponding to the papillomacular bundle was significantly thinner in the AD group. Vertical CDR and cup area were significantly different between groups. However, after adjustment for age and disc area, no OCT ONH variables differed between groups.

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significant (Figure 3). These differences were less pronounced in the outer macular region and significant only in the nasal inferior region of the outer macula. These regional differences are illustrated in Figure 3.

There were a few small intrasite differences in structural variables measured by the HRT and OCT in the AD group but not in the ED group, possibly reflective of increased heterogeneity in recently admixed AD populations in the United States. Specifically, HRT disc area was significantly smaller in AD individuals from NYEE (1.97 [0.4] mm²) compared with UCSD (2.18 [0.4] mm²; P=.003) and UAB (2.08 [0.47] mm²; P=.054), whereas OCT RNFL thickness was slightly larger in individuals recruited at UCSD (57.11 [13.69] mm²) compared with NYEE (52.15 [10.30] mm²; P=.007) and UAB (54.63 [10.05] mm²; P=.09). Although these structural differences may relate to regional variation in genetic admixture among the southern, eastern, and western United States, when site was included as a covariate in the models examining differences in optic disc or RNFL variables, similar results were obtained. Thus, these differences are unlikely to have significantly affected the results.

Table 7 provides the comparison of HRT diagnostic classification methods between racial groups adjusted for age and interocular correlations. Significant racial differences were seen in some previously published discriminant functions developed to provide a composite measure from HRT variables. Functions developed by Burk et al13 and Bathija et al10 showed significant differences consistent with a more glaucomatous categorization. Other functions developed by Mardin et al14 and Mikelberg et al15 did not show a difference in categorization between racial groups. A similar proportion of eyes between racial groups were identified as outside normal limits by the MRA and GPS techniques. However, in both groups the GPS technique identified a greater proportion of individuals to be glaucomatous than did the MRA technique.

With increasing disc area, rim area (OCT or HRT) and RNFL thickness measured (OCT) significantly increased (P < .001) in both racial groups for all variables. The associations of disc area with rim area and RNFL thickness were similar in both groups, with no significant differences in the associations between disc area and HRT rim area (P=.11), OCT rim area (P=.88), or OCT RNFL thickness (P=.60).

The relationships between increasing age with optic nerve and RNFL variables are shown in the eTable (http://www.archophthalmol.com). There were significant negative associations between age and OCT rim area, cup area, CDR, macular volume, and RNFL thickness in both groups. Scatterplots in eFigure 1 and eFigure 2 illustrate the slope of association with age for RNFL thickness and CDR measured by OCT for each racial group. Although age was significantly associated with optic nerve and RNFL variables within each racial group, across racial groups there were no significant differences in the slope of association between age and any structural variable.

In contrast, the HRT variables did not show an association with age in either racial group. Because there was a significant interaction between reference plane height with age, race, and each of the HRT variables, general linear models used to determine whether the associations with age differed between racial groups included the following explanatory variables: age, racial classification, interaction between age and racial classification, refer-

Table 7. OCT Diagnostic Functions

<table>
<thead>
<tr>
<th></th>
<th>AD Group (n=620)</th>
<th>ED Group (n=601)</th>
<th>P Value a</th>
</tr>
</thead>
<tbody>
<tr>
<td>OCT discriminant function, mean (SD), [units], by source</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mardin et al14, 1999</td>
<td>0.15 (1.38)</td>
<td>0.26 (1.15)</td>
<td>.16</td>
</tr>
<tr>
<td>Burk et al15, 1999</td>
<td>-0.17 (0.87)</td>
<td>-0.42 (0.96)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Bathija et al10, 1998</td>
<td>0.84 (0.89)</td>
<td>0.55 (0.74)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Mikelberg et al15, 1995</td>
<td>8.0 (3.7)</td>
<td>8.1 (3.6)</td>
<td>.82</td>
</tr>
<tr>
<td>OCT classification, % abnormal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global MRA</td>
<td>1.8</td>
<td>1.0</td>
<td>.26</td>
</tr>
<tr>
<td>Global GPS</td>
<td>12.1</td>
<td>11.1</td>
<td>.83</td>
</tr>
</tbody>
</table>

Abbreviations: AD, African descent; ED, European descent; GPS, glaucoma probability score; MRA, Moorfields regression analysis; OCT, optical coherence tomography.

a Significant values are given in boldface type.
This study describes the differences in optic nerve morphologic characteristics, RNFL thickness, and macular thickness between healthy AD and ED participants in DIGS and ADAGES. Although several HRT topographic variables are significantly different between groups, after adjustment for disc area and reference plane height for measurements associated with these variables, these differences were nonsignificant or greatly reduced. Racial differences independent of disc area exist for HRT cup depth, with a significantly deeper cup in the AD group. In addition, some residual differences in the contour line modulation variables remained after adjustment for racial differences in disc area. Although the OCT RNFL was thicker in the AD group, the temporal region corresponding to the papillomacular bundle was thinner. Macular thickness and volume also were less in the AD group, especially in the central macular region.

Except for a few smaller studies, previous studies using quantitative optic nerve instruments have been performed in predominantly ED populations and have not included adequate numbers of AD subjects to evaluate the role of quantitative optic nerve analysis and the variables that are most predictive of glaucoma. Moreover, previous studies have not addressed the optimum analysis strategies for detection of glaucoma in this at-risk population in which open-angle glaucoma is more common, more refractory to treatment, and more severe, with higher rates of blindness. To date, no large-scale multicenter study used quantitative imaging devices to examine the difference between AD and ED groups in optic disc, macular, and RNFL anatomy.

A few small histological studies have been performed that examine racial differences in the morphologic characteristics of the lamina cribrosa and ONH connective tissue architecture. Quigley et al performed a postmortem histological study of 30 ED and 30 AD donors and demonstrated a larger, more oval optic disc in the AD group. In addition, Dandona and colleagues used digital laminar photography to examine 7 ED and 9 AD donor eyes. They found a larger pore size in the superior and inferior poles of the optic disc and a larger number of pores in the African American group. However, when the larger disc area in the AD group was taken into account, the ratio of connective tissue to pore area was similar.

Several clinical studies have characterized racial differences in optic disc structure between AD and ED groups, finding a larger disc area, CDR, and cup and a similar rim volume across several imaging techniques. Quantitative evaluation of conventional optic disc photography from the Baltimore Eye Survey demonstrated that mean optic disc area was 12% larger in the African American population. Cup area was also larger. Although the global rim area was similar in both racial groups owing to the relatively larger optic disc in African Americans, there was a decrease in rim to disc area, indicating that there may be a thinner rim and RNFL relative to disc size in this population. Smaller studies using the Rodenstock optic disc analyzer and the first generation of HRT have also demonstrated a similar rim area between racial groups.

In contrast to the Baltimore Eye Survey, which evaluated optic disc photographs, the ADAGES healthy AD participants demonstrated a larger overall HRT rim area and volume compared with ED participants. After adjustment for disc area, these differences were reduced and not significant. These findings are similar to those obtained in a previous HRT study that used a similar method and was conducted as part of a longitudinal study that preceded ADAGES at UAB. That early study indicated that with more precise quantitative techniques, the size of the neuroretinal rim relative to disc area is similar or slightly greater in AD individuals compared with ED individuals. The OCT rim area also did not differ between groups before and after adjustment for the larger optic disc area in the AD group. In addition, although the rim area (measured by both HRT and OCT) and RNFL thickness were significantly associated with disc area in both groups, the differences in these associations were not significant between racial groups. These results contradict those previously suggested by the Baltimore Eye Survey.

In addition to global variations in RNFL thickness, regional variations of the racial differences in RNFL thickness were found. There was a surprisingly thinner RNFL in the region of the papillomacular bundle in the AD group, which has not been previously reported. The thinner papillomacular bundle and the finding of a thinner macula in the AD groups imply that differences may exist in the amount of retinal nerve fibers in this region in AD individuals. These differences were independent of racial differences in disc area, implying that simply including individuals in normative databases with a wide range of disc sizes may not be adequate, and race-specific normative databases may be needed to optimize detection techniques when using RNFL or macular imaging. Kelty et al have recently demonstrated thinner measurements of the inner macula with the OCT in AD individuals.

Racette et al compared the results of Stratus OCT between AD and ED healthy individuals as part of a study used in the planning of ADAGES and had similar findings with a thicker superior and inferior RNFL in the AD group. In addition, a previous study compared the results of scanning laser polarimetry and found reduced RNFL retardation in individuals of Afro-Caribbean ancestry compared with ED participants. However, that study used a fixed method for anterior segment compensation that is now known to generate artifacts in retardation measurements.

The present study also demonstrated larger (OCT and HRT) and deeper (HRT) optic disc cups in AD individuals. Tsai et al also found a deeper cup in AD individuals compared with ED individuals. In smaller previous studies performed in the development of ADAGES, HRT cup depth in the AD group was found to be significantly deeper compared with the ED group. Furthermore, in the present study, the cup depth determined on the basis of automated modeling of the optic disc used for the GPS was also significantly deeper in the AD group.
Recently, Zangwill and colleagues\(^{30}\) compared the baseline HRT I variables between 74 ocular hypertensive AD subjects and 365 ocular hypertensive subjects of non-African ancestry enrolled in the Ocular Hypertension Treatment Study. Subjects within this latter group included 329 ED subjects, 24 Hispanic subjects, and 12 subjects who were Native American, Alaskan, Asian, or Pacific Islander. Similar to our study of healthy subjects, the AD group had a significantly greater optic disc area and larger CDR, cup area, cup depth, and cup volume. Unlike our findings, their study in ocular hypertensive subjects found a lower rim area and rim volume in AD subjects. However, because ocular hypertensive patients were enrolled, it is likely that some early glaucomatous injury could have existed in this ocular hypertensive population and may have confounded the comparison of baseline structural measurements of the optic disc between racial groups.

Racial differences in optic disc structure can affect the ability of techniques to evaluate optic disc topography to detect glaucoma. Broadway et al\(^{40}\) demonstrated that the discriminating ability of the HRT varied depending on the phenotype of optic disc damage in that person. Furthermore, differences in optic disc area will have an effect on the diagnostic precision of quantitative optic nerve instruments.\(^{12,41,42}\) This is an important consideration in that one of the major differences in optic disc structure between AD and ED individuals is disc area. In addition, racial differences in HRT variables that are independently associated with early glaucomatous field loss have been demonstrated in AD and ED groups.\(^{27}\)

Racial differences in optic disc and RNFL anatomy need to be addressed when using techniques to discriminate between normal and glaucomatous eyes. Some discriminant functions with the HRT performed similarly across racial strata (Mardin et al\(^ {14}\) and Mikelberg et al\(^ {15}\)) whereas others did not (Bathija et al\(^ {10}\) and Burk et al\(^ {12}\)). The commonly used MRA and GPS performed similarly across racial groups. Although the MRA was developed using controls from a primarily European population, this technique adjusts for disc area, which accounts for most of the differences between racial groups. This is in agreement with a smaller previous study examining the effects of race on MRA classification.\(^ {10}\) Although many of the variables that are used in the GPS differed between racial strata, the overall GPS classification yielded a similar level of misclassification in the AD and ED groups, albeit significantly higher than MRA misclassification in both groups. The performance of these and other detection methods will be the subject of future research.

Despite the similar results for overall GPS classification, all GPS variables were more glaucomatous in the AD group compared with the ED group except rim steepness, with vertical and horizontal measures of RNFL curvature being more negative and with a deeper and larger cup in the AD group. The disparity between the similarity in GPS classification between groups and the difference in morphometry in the GPS modeling variables is likely caused by the inclusion of a specific African American normative database, and that racial classification is included in the selection of the normative data used in this technique.

Although little is currently known regarding the impact of variations in optic disc anatomy and susceptibility to glaucoma, preliminary computational modeling of the biomechanical behavior of the lamina cribrosa and posterior sclera suggest that the laminar connective tissues may experience greater IOP-related strain in eyes with larger and/or more oval optic discs.\(^ {43}\) Thus, the larger optic discs found in the AD group may relate to a greater strain at any given IOP compared with smaller discs in the ED group, which may explain some of the vulnerability to IOP-related injury seen in AD populations. Although the Baltimore Eye Survey found that larger disc area was weakly associated with glaucoma,\(^ {44}\) no prospective studies have demonstrated that larger optic nerves are at an increased risk for developing progressive glaucoma.\(^ {45}\)

The finding of a deeper optic cup in AD compared with ED groups could potentially have biomechanical significance as well. A deeper optic cup may imply that AD individuals may have a thinner lamina cribrosa or a more posterior insertion of the lamina cribrosa within the scleral canal. Simplified mathematical models of the lamina cribrosa have suggested that, all else being equal, ONHs with a thinner lamina undergo more IOP-induced deformation.\(^ {30}\)

For both groups, there were significant associations with age in several of the optic nerve variables in a direction suggesting that there is reduction in neural tissue with aging (ie, a lower rim area, reduced macular volume, thinner RNFL, larger cup area, and larger CDR in older individuals) with OCT but not HRT (eTable). The slopes of the associations of age with each OCT variable were not significantly different between AD and ED groups. However, the associations of RNFL loss with age must be interpreted with caution given that these associations were defined in cross-sectional data. The additional prospective follow-up in ADAGES will be helpful for validating these findings, which may affect the detection of progressive glaucomatous damage.

One limitation of this study, common to most clinical studies exploring racial differences in disease characteristics, is categorization using self-described race, a term that represents an amalgam of cultural, geographic, socioeconomic, and biological characteristics. Self-described race is at best a poor summary of human biodiversity that cannot be interpreted in the strict biological sense.\(^ {3}\) However, self-described race has demonstrated dependent and independent associations in several diseases; thus, it is an important risk factor. The shortcomings of this limitation are moderated, however, by the information being obtained in a standardized fashion. Fortunately, self-described race has demonstrated a high correlation with more sophisticated measures of racial classification using genetic admixture techniques and thus is likely an adequate surrogate measure.\(^ {47}\)

The need to define glaucoma based on visual field criteria alone, while necessary for the unbiased comparison of structural variables, introduces the possibility that a small number of eyes may have had early glaucoma without achromatic perimetric defects. However, given that the prevalence of glaucoma in the source population for the normal subjects is low, the effect is not likely to be significant. Furthermore, given that similar numbers of subjects
across racial strata were identified as having glaucomatous-appearing optic discs according to masked stereoscopic photograph grading (Table 2), this effect is not likely to be a differential across racial strata and therefore should not influence the between-group comparisons.

In summary, the present study found that healthy AD and ED participants in ADAGES differed significantly in several optic nerve variables. However, when optic disc area and reference plane height (for HRT) are taken into account, only slight differences remained, with a greater HRT cup depth, thicker overall OCT RNFL, and a thinner OCT papillomacular bundle and macula in the AD group. Although racial differences in disease-free populations should be considered when determining the limits of normality of the optic disc with HRT and OCT, many of these racial differences in optic disc topography may be accounted for by adjusting for disc area and reference plane height where appropriate. However, race-specific normative databases may be needed to optimize the performance of devices that use RNFL or macular imaging to detect glaucoma in AD and ED groups. The role of these findings in the predilection to develop glaucoma in AD individuals warrants further investigation.

Submitted for Publication: January 28, 2009; final revision received July 7, 2009; accepted August 13, 2009.

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Financial Disclosure: Dr Girkin received research support from Heidelberg Engineering, Inc and Carl Zeiss Meditec; Dr Sample received research support from Carl Zeiss Meditec, Haag-Streit, and Welch Allyn; Dr Liebmann received research support from Heidelberg Engineering, Inc; Dr Medeiros received research support from Heidelberg Engineering, Inc and Carl Zeiss Meditec; Dr Weinreb received research support from and is a consultant for Heidelberg Engineering, Inc and Carl Zeiss Meditec; and Dr Zangwill received research support from Heidelberg Engineering, Inc and Carl Zeiss Meditec.

Funding/Sponsor: This study was supported by grants U10 EY14267 (Drs Girkin, Sample, and Liebmann), EY08208 (Dr Sample), EY11008 (Dr Zangwill), and EY13959 (Dr Girkin) from the National Eye Institute; by the Eyesight Foundation of Alabama (Dr Girkin); by grants from Alcon Laboratories, Inc, Merck, Allergan, Pfizer, Inc, and ANTEN, Inc (for participants’ glaucoma medications); and by the New York Glaucoma Research Institute (Dr Liebmann).

Online-Only Material: The eTable and eFigures are available at http://www.archophthalmol.com.

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(CREPRINTED) ARCH OPHTHALMOL/VOL. 128 (NO. 3), MAY 2010 WWW.ARCHOPHTHALMOL.COM

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