Influence of Age, Race and Image Quality on Spectral Domain Optical Coherence Tomography (SDOCT) based measures of the Ganglion Cell Layer (GCL), Macular Thickness (MT), Retinal Nerve Fiber Layer (RNFL) and Neuroretinal Rim Area in healthy adult eyes.

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Objective: To determine how age, race and image quality affect the ganglion cell layer (GCL), macular, and retinal nerve fiber layer (RNFL) thickness, and neuroretinal rim area in healthy adult eyes measured using SDOCT.

Method: In a cross-sectional study, Cirrus SDOCT was used to collect optic nerve head images from 121 healthy adults of African descent (AD, 106 eyes) and European descent (ED, 122 eyes) and macular images from 74 healthy adults (AD 95 eyes, ED 49 eyes). All eyes had a normal appearing optic disc, an IOP < 22 mmHg, and no repeatable visual field damage. The effects of age, race and image quality, defined as signal strength, on GCL, macular and RNFL thickness and neuroretinal rim area were determined using univariate and multivariate linear mixed models.

Results: In univariate analysis, with increasing age, there was a decrease in average RNFL thickness of 0.19μm/year (p=0.002) and in average GCL thickness of 0.18 μm/year (p=0.002). Superior, inferior, and nasal macular thickness decreased with age.

AD participants had larger disc areas (p=0.026) and thinner inner macular thickness than ED participants. In multivariable analysis, age, race and signal strength were not associated with rim area. Age and signal strength were associated with both average RNFL thickness (p=0.002, p=0.020 respectively) and average outer macular thickness (p=0.013, p=0.05 respectively). Race was not found to be associated with average RNFL thickness (p=0.618), average outer macular thickness (p= 0.184), or average GCL thickness (p=0.768) in the multivariable analysis.

Conclusions: In this cross-sectional study of healthy participants, age was inversely associated with GCL, macular, and RNFL thickness regardless of race. Clinicians should consider the associations between age, RNFL, and GCL thickness to help differentiate between aging-related changes and glaucomatous progression.

BACKGROUND:

As the second leading cause of blindness in the United States, glaucoma affects over 60.5 million people worldwide. As the population ages, the rate of glaucoma increases disproportionately. In fact, it is estimated that the number of glaucoma cases will grow to 79.6 million worldwide by the year 2020 as the aging population rises [1]. Given that both aging and glaucoma can lead to similar characteristic changes in the optic disc and visual field, it is important for clinicians to not only understand age-related changes, but also differentiate between the two so that clinicians can provide proper diagnosis and treatment.

Numerous epidemiological studies have shown that the prevalence of glaucoma increases exponentially with age. Within the white population, the estimated prevalence of POAG is 1.2% for those between the age of 40-89 years [2]. The Barbados Eye Studies demonstrates a similar trend in a black population; the incidence rate increased from 1.2% at ages 40-49 years to 4.2% at ages 70 or more [3]. Similarly, Mukesh et al. reports that the incidence of possible, probable, and definite open angle glaucoma (OAG) increases from 0.5% of participants aged 40-49 to 11% of participants aged 80 years and older [4]. As a person ages, many physiological and biochemical changes can lead to long-term loss of nerve fibers. For instance, cribiform plate thickness and the density of

optic nerve fiber were found to be negatively associated with increasing age [5-7]. [8, 9]. Vascular bed resistance was found to be positively associated with age, which suggests poor vascular supply to the optic disc as one ages, making it more susceptible to glaucomatous damage [8, 9]. Similarly, the thickness of the macula has been reported to be negatively associated with age [10]. While the association between age and ONH measurements has been well documented in whites and blacks separately, our study will be the first to investigate this relationship in these two populations.

With a better understanding of how race affects age-related changes, clinicians can better differentiate between the healthy aging process of the eyes and glaucomatous damage in high-risk populations. A recent study demonstrates that the pattern of neuroretinal rim changes is very similar in both glaucoma and healthy aging participants. Although the rate of neuroretinal rim area changes is 7 times higher in glaucoma patients than in controls, the highest rate of change for both groups of participants is in the inferior temporal sector [11]. The similarities between glaucomatous and age-related changes have undoubtedly made diagnosis of glaucoma more difficult. Small, yet significant, differences between the healthy and the disease state can now, fortunately, be detected with more advanced instruments.

Spectral domain optical coherence tomography (SDOCT) is a new commercially available advanced optical imaging instrument that provides reproducible measures of the optic disc in vivo. With this new technology, clinicians have the potential to detect small anatomic changes in the optic disc that might be mistaken for disease progression. The greater scanning speed and superior image resolution compared to time-domain OCT enables the acquisition of more scans in a single imaging session, thereby reducing the need for data interpolation. The Cirrus (Zeiss Meditec inc, Dublin CA) is such SDOCT device. To our knowledge, this study is the first to use the Cirrus SDOCT to evaluate the effect of race on age-related neuroretinal rim, ganglion cell layer, and RNFL measurements.

The objective of this study was to determine how race, and image quality affect age-related changes of the neuroretinal rim, RNFL and GCL in healthy adult eyes using the Cirrus spectral-domain optical coherence tomography (SDOCT).

METHODS:

This was a cross-sectional study of participants included in the Diagnostic Innovations in Glaucoma Study (DIGS) and the African Descent and Glaucoma Evaluation Study (ADAGES), which are prospective longitudinal studies designed to evaluate optic nerve structure and visual function differences between individuals of African and European descent. Participants were recruited from 3 collaborating sites: the Hamilton Glaucoma Center, University of California – San Diego, La Jolla, New York Eye and Ear Infirmary, and the Department of Ophthalmology, University of Alabama, Birmingham. Both studies include normal, suspected glaucoma, and glaucoma subjects. Written informed consent was obtained from all the participants and all the methods adhered to the tenets of the Declaration of Helsinki for research involving human subjects.

Subjects:

To be eligible, a participant must have at least one eye that meets all inclusion criteria at the qualification visit and no exclusion criteria at the qualification visit and each subsequent visit. Inclusion criteria were open angles on gonioscopy, a best-corrected visual acuity of 20/40 or better, a spherical refraction within ± 5.0 diopters, and a cylindrical correction within ± 3.0 diopters. All participants were over 18 years of age and had at least 1 good-quality stereophotograph as well as two reliable (false-negative errors, false-positive errors, and fixation losses are lower or equal to 33%) standard automated perimetry (SAP) tests at baseline. Diabetic participants with healthy retinas and participants with a family history of glaucoma were included. At baseline, each participant received a complete ophthalmological examination, including medical history, visual acuity, slitlamp biomicroscopy, gonioscopy, Goldmann applanation tonometry, and simultaneous stereoscopic disc photography.

Participants who were considered healthy subjects all have an intraocular pressure (IOP) lower than 22mmHg, no history of IOP medications, a normal stereophoto assessment, and a normal SAP Visual Field Test result. Two independent, trained, masked observers graded each stereophotograph according to a standard protocol. As for the visual field, a normal SAP must have a pattern standard deviation (PSD) and a

Glaucoma Hemifield Test within normal limits. Patients did not have repeatable abnormal results in any of these tests.

Participants are excluded if they have any disqualifying ocular and non-ocular disease or conditions, have any congenital color vision defects, receive particular ocular procedures, have poor quality photos at baseline, or take any disqualifying systemic medications listed in the ADAGES Manual of Procedures. Cirrus scans with quality < 5 dB are also excluded from our analysis.

Instrumentation:

In this study, we used the Cirrus HD-OCT (software version 6.0, Carl Zeiss Meditec) to acquire our data and included only healthy participants. The protocol used for RNFL and ONH thickness evaluation was the optic disc cube. This protocol is based on a 3 dimensional scan of a 6 X 6 mm^2 area centered on the optic disc where information from a 1024 (depth) X 200 X 200-point cuboid is collected. Then, a 3.46-mm diameter circular scan is automatically placed around the optic disc, and the information about parapapillary RNFL thickness is obtained. To be included, all images were reviewed for non-centered scans and had to have signal strength ≥ 5 dB. For participants with multiple exams or multiple dates, we selected the last exam date for each eye [12].

Statistical Analysis

Descriptive analyses were calculated for each variable individually and by race. Wilcoxon Rank-Sum tests compared continuous variables such as Average C/D Ratio, Vertical C/D Ratio, Cup Volume, Average RNFL Thickness, Rim Area, and Disc Area, and Fisher's Exact Tests compared categorical variables including Age, Primary Race, Signal Strength, Gender, and Axial Length. Spearman's Correlation was used to compare the association between Age and Average RNFL Thickness, Rim area, Macular Thickness, and GCL Thickness as well as between Signal Strength and Average RNFL Thickness, Rim area, Macular Thickness, and GCL Thickness. Regarding the inclusion and exclusion criteria that are allowed to be in the analysis, we only include eligible participants; 17 subjects and 31 eyes were removed due to ineligibility and poor scan quality.

Univariate and multivariable random effects regression analyses were performed to determine the association between outcome variables such as Average RNFL thickness, Rim Area, and Disc Area and covariates such as age, race, axial length, and signal strength from the Cirrus. To adjust for the correlation of multiple scans per eye and intra-eye correlation within patients, a nested random effects model for clustered data was used. Age and signal strength variables were centered around the sample mean. P-values less than 0.05 were considered statistically significant, and there were no adjustments made for multiple comparisons. The statistical software R (version 2.10.0) was used (http://www.r-project.org) for the analyses.

Results

Characteristics of healthy participants with ONH scans are given in **Table 1.** Age, disc area, RNFL thickness, and signal strength (image quality) were significantly different between the African descent group and the European descent group. Female gender proportion and rim area, however, were not significantly different between the two groups. **Table 2** lists the characteristics of healthy participants with macular thickness and ganglion cell thickness scans. Age, female gender proportion, and ganglion cell thickness were not significantly different between the African descent and the European descent groups, but the inner and outer macular were significantly thicker in the European group.

Figure 1-5 are generated using the mixed effect model. The linear line in the plot is generated using the univariate mixed effect model. Individual data plot is color-coded based on each participant's primary race. For example, red data plots represent measurements taken from African descent subjects while blue data plots represent measurements taken from European descent subjects. Based on ONH cube scan, age was negatively association with average RNFL thickness ($p = 0.0018$)(**Figure 1**) while signal strength was positively associated with average RNFL thickness ($p = 0.03$)(**Figure 2**). In the multivariate analysis, age and signals strength remained associated with average RNFL thickness ($p=0.002$, $p=0.020$ respectively). Race, however, was not found to be associated with average RNFL thickness ($p=0.618$).

Based on our macular cube scan univariate analysis, age was found to be negatively associated with average outer macular thickness (p = 0.008) as well as with average ganglion cell layer thickness. (p = 0.002)(**Figure 3**). Signal strength was found to be negatively associated with average outer macular thickness (p =0.028). However, there was no association between signal strength and average inner macular thickness (p = 0.103)(**Figure 4**). Age is negatively associated with average inner macular thickness (p = 0.008)(**Figure 5**). Race was associated with average inner macular thickness (p=0.007), but not with outer macular thickness (p=0.143) or average GCL thickness (p=0.728).

Based on the macular cube scan multivariate analysis, age and signal strength remained associated with average outer macular thickness (p=0.013, p=0.05 respectively). Race was not associated with average outer macular thickness (p=0.184) or average GCL thickness (p=0.786), but it was associated with average inner macula thickness (p=0.008). **Table 3** provides a summary of Figure 1-5, including the P-values and coefficient. For other results that were not reported above, see table 3.

Table 1. Characteristics of Healthy Participants with ONH Scans

	European Descent 122 eyes of 65 participants	**African Descent** 106 eyes of 56 participants	**p-value**
Age (yrs)	58.6 (48.7 – 67.9)	52.4 (45.6 – 60.0)	0.008
Females	46 (54%)	39 (46%)	>0.99
Disc Area (mm^2)	1.77 ± 0.30	1.92 ± 0.37	0.0014
Rim Area (mm^2)	1.29 ± 0.20	1.31 ± 0.21	0.22
RNFL thickness (µm)	91.62 ± 9.45	93.97 ± 9.01	0.027
Signal Strength	8.45 ± 1.36	8.35 ± 1.26	0.028

Table 2. Characteristics of Healthy Participants with Macular Thickness and Ganglion Cell Thickness Scans

	European Descent	**African Descent**	**p-value**
Participants	25	49	n/a
Eyes	49 (34%)	95 (67%)	n/a
Age (yrs)	49.7 (41.2 – 61.9)	50.1 (42.9 – 56.2)	0.83
Females	16 (31%)	35 (69%)	0.60
Ganglion Cell	81.96 ± 7.72	81.68 ± 5.53	0.27

Thickness(µm)			
Inner Macular Thickness(µm)	322.08 ± 17.42	311.67 ± 14.08	<0.001
Outer Macular Thickness(µm)	275.91 ± 14.63	271.42 ± 12.49	0.039

Figure 1. Strong negative association between age and average RNFL thickness (p = 0.0018). No association between age and rim area (p = 0.15)

Figure 2. Signal strength was positively associated with average RNFL thickness (p =0.03). No association between signal strength and rim area (p = 0.10)

Figure 3. Age was negatively associated with average outer macular thickness (p =0.008) and with average ganglion cell layer thickness (p = 0.002).

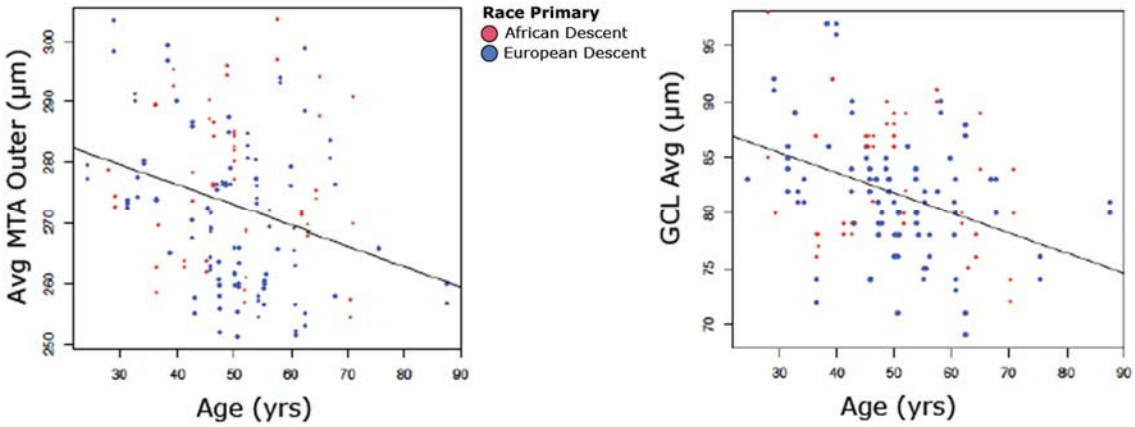


Figure 4. Signal strength was negatively associated with average outer macular thickness (p = 0.028). No association between signal strength and average ganglion cell layer thickness (p = 0.563).

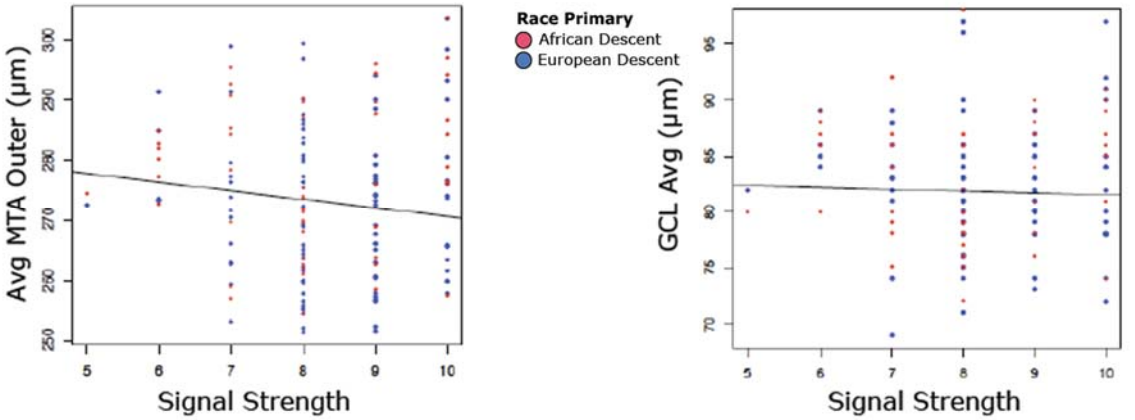
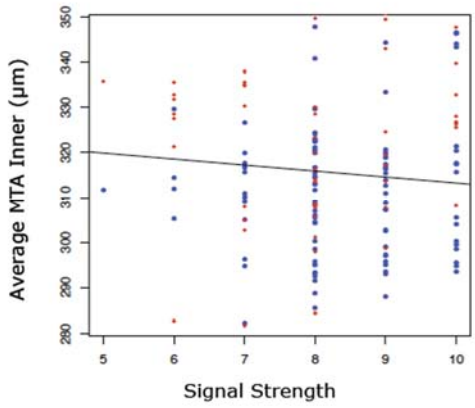


Figure 5. Signal strength was not associated with average inner macular thickness (p = 0.103). Age is negatively associated with average inner macular thickness (p = 0.008).



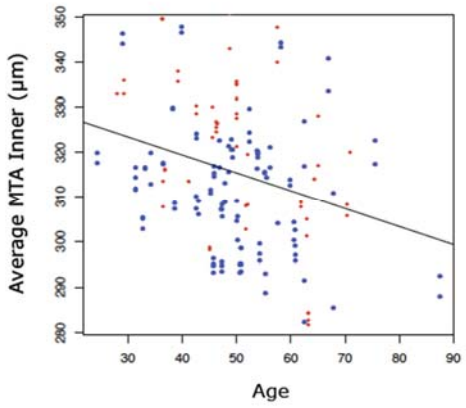


Table 3. Univariate Analysis Coefficients and P-values of the Effect of Age, Signal Strength and Race on ONH, MTA, and GCL Variables.

Univariate Analysis variables	Age		Signal Strength		Race	
	Coefficient	P-value	Coefficient	P-value	Coefficient	P-value
ONH						
Rim Area	-0.002	0.15	-0.015	0.10	-0.011	0.744
Avg RNFL thickness	-0.19	0.0018	0.70	0.03	-1.9	0.271
MTA						
Avg MTA Outer	-0.34	0.009	-1.45	0.028	10.2	0.007
Avg MTA Inner	-0.40	0.008	-1.34	0.10	4.78	0.144
GCL						
GCL Avg	-0.18	0.002	-0.17	0.56	0.53	0.728

Discussion

This study demonstrated that there was a negative association between age and ganglion cell layer thickness, average RNFL thickness, and superior, inferior, and nasal macular thickness, regardless of race.

Ganglion cell layer (GCL) thickness has been suggested to decrease in glaucomatous eyes. Together with macular nerve fiber layer thickness (mNFL), inner plexiform layer thickness (mIPL), and inner nuclear layer thickness (mINL), GCL thinning can be seen in glaucoma patients even before detectable visual field changes

occur[13]. Combining the 3 layers most affected by glaucoma, (mNFL, mGCL, and mIPL), has the potential to serve as an effective strategy for early detection of the disease. As a diagnostic tool, GCL thickness was comparable, if not superior, to retinal nerve fiber layer (RNFL) thickness in its ability to distinguish between glaucoma and healthy participants [1, 14, 15]. While the effect of glaucoma on GCL thickness has been studied extensively, the relationship between GCL and aging is still a newly explored territory. Our study illustrated a decrease in average GCL thickness of 0.18 μm per year, which was similarly reported by *Ooto et al [16]*. They found GCL to be thinner in the temporal sector than in the nasal sector within regions 1-3 mm from the central fovea [16]. With the possibility of using GCL together with RNFL thickness to better assess for glaucoma, we first must understand how GCL thickness changes with age. This knowledge would likely facilitate the development of a better diagnostic tool and criteria.

Similar to previous findings, our study found that superior, inferior, and nasal macular thickness significantly decreased with increasing age. *Song et al.* found that overall average macular thickness, average inner macular thickness, average outer macular thickness, and overall macular volume were negatively associated with increasing age [17]. This trend was quantified by *Sung et al.* and they went further to show that inner sectors appear to thin out with age slower than outer sectors [18]. In terms of regional thinning, our results were consistent with previous studies; we found that retinal thinning is not uniform across the macula and that this decrease in thickness was not significant in the foveal region [19-22]. There are several studies that did not find a correlation between macular thickness and age using Time Domain-OCT, which has been reported to underestimate the RNFL thickness [23, 24]. This discrepancy was further exacerbated once age was taken into consideration [25]. Differences in instrumentations and subject characteristics could possibly account for the disagreement between previous results and our current findings.

We found RNFL thickness to be negatively correlated with age, which was consistent with previous works [16, 20, 26]. Our study illustrated that RNFL thickness decreased at a rate of 0.19μm per year, a rate similarly reported by past studies [16, 27-29]. Even with different instruments like Stratus TD-OCT and scanning laser polarimeter, RNFL thickness has been shown to decline with age [30, 31]. Two recent longitudinal

studies illustrated a similar trend [32, 33]. The trend between average RNFL thickness and age is seen not only in African and European descent participants, as suggested in our study, but also in Indian, Hispanic, Japanese, and Chinese populations [18, 27]. *Kergoat et al* argued that the decrease in RNFL thickness with age was mainly a result of age rather than refractive error because there is a significantly lower rate of myopia in older controls compared to younger ones [26]. Aside from age, other systemic variables such as blood pressure, lipids, serum glucose, and smoking status did not appear to influence RNFL measurements [27].

Average RNFL thickness, as shown in our study and others, has been demonstrated to positively associate with the quality of the OCT scan as measured by signal strength [27, 34]. The relationship between RNFL thickness and signal strength appeared to vary regionally with the superior and nasal RNFL measurements being influenced the most by image quality [35]. Signal strength has also been observed to affect other ONH measurements such as rim measurements and cup measurements [36]. Keeping in mind the effects of image quality, clinicians should be aware of the potential reduction in RNFL thickness measurement when OCT images have low signal strengths. Taking even a step further, when clinicians detect a change in RNFL thickness over time, they should attempt to rule out the possibility that the changes were due to a change in signal strength.

Consistent with previous findings, we did not find correlation between rim area and age [37-39]. However, there are studies that have found a negative correlation between rim area and age [16, 20, 27, 40]. Inconsistency in literatures could be partly due to differences in study populations, instruments, and participant demographics. Additionally, it has been suggested that rim area is not as reproducibly measured; measurements by different instruments can be highly variable [41]. Optic disc area variance was reported to be the most important factor responsible for rim area variability in OCT and that confocal scanning laser ophthalmoscopy (CSLO) demonstrates higher measurement reproducibility for rim area compared with OCT [42]. Perhaps, the high variability of rim area is the reason why it is not influenced by age. Certainly, the source of disagreements and the effect of rim area on the detection of glaucoma progression require further study.

Comparing ONH and macular parameter differences between AD and ED participants, our study demonstrated that AD participants had significantly larger disc areas and thinner inner macular thickness than ED participants. This is consistent with previous investigations on disc area [40, 43-46] and macular thickness [18, 43, 47]. Using the Spectral Domain OCT (RTVue), *Girkin et al* reported that ED participants had significantly smaller optic disc area than AD participants and other racial groups such as Japanese, Hispanic, and Indian. AD participants also had thinner inner retinal thickness in the macula than ED participants in their study. Similar to our study, rim area was not significantly different between AD and ED participants [18]. These racial differences are essential in defining the range of normal variation not only in the overall population, but also within specific populations. Furthermore, our study goes on to highlight our interest in the cross-sectional rate of change estimated by race. Such knowledge can aid clinicians in identifying disease states and improving patient care within a particular population.

Previously, most researchers have investigated either the macula or the optic disc measurements. With the Cirrus, we are now able to obtain both GCL measurements. Our findings provided the first data on ONH measurements collected from healthy participants with Cirrus (version 6.0). The finding of an age-related decline of RNFL, GCL, and macular thickness regardless of race carries important clinical implications. It is often difficult for clinicians to differentiate between glaucomatous and non-glaucomatous eyes. Detecting a negative relationship between these measurements and age alone is not sufficient to diagnose early glaucomatous changes. As shown in our study, with increasing age, there was a significant decrease in average RNFL thickness of 0.19μm/year and a decrease in average GCL thickness of 0.18 μm/year. These measurements not only confirm previous findings, but also help consolidate our knowledge of the normal aging process of the human visual system. Since these age-related changes can be detected in RNFL, GCL, and macula thickness, this finding highlights the importance of using multiple measurements to differentiate between pathological from non-pathological processes. Future clinicians, most likely, will be able to diagnose glaucoma earlier and more accurately by trending not one or the other, but both the macula and the ONH measurements over time.

Nevertheless, there were several limitations to our study, including a relatively small sample size and the use of self-reported race. *Boehmer et al.* demonstrated that between 22.9% - 23.6% of self-reported Whites and between 31.1% and 31.6% of self-reported African Americans were incorrectly reported and classified [48]. Similar to most investigations on this area of interest, the relationships between aging and these factors are unclear due to the cross-sectional nature of our data. Longitudinal studies of healthy participants are needed to elucidate age-related RNFL, GCL, and macula thickness changes. Note also that optic nerve head and macular measurements were acquired from AD and ED participants between the ages of 24 and 91, a range relevant to most ophthalmic diseases.

While many previous studies have demonstrated changes in either ONH or macula parameters across different ages and racial groups, few have studied all three parameters (ONH, Macula, and Ganglion Cell Layer) within one study using the Cirrus SD-OCT. Our study demonstrated that there was a significant association between age and ganglion cell layer, macular, and RNFL thickness regardless of race. Similarly, the effect of age and signal strength on RNFL, rim area, macular thickness and ganglion cell layer thickness also did not differ by race. A significant negative trend alone is not sufficient to diagnose glaucomatous progression. It needs to be compared to the normal ranges of age-related decline. With that in mind, clinicians can hope to better differentiate between glaucomatous damages and normal aging changes by observing the trend of the ONH, the macula, and the ganglion cell layer measurements.

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