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Relationship between Glaucoma and Admixture in Postmenopausal African American Women

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Abstract

Objective—To investigate the association between African admixture and glaucoma prevalence amongst African American women.

Design, Setting, Participants—Participants included 11616 African American women from the Women's Health Initiative Study (WHI) for whom admixture information was available and included 2548 who self-reported a diagnosis of glaucoma.

Main Outcome Measures—Glaucoma.

Results—Significant association was observed between self-identified glaucoma status and admixture. However, this association was not significant in a model that included neighborhood socioeconomic status (NSES), hypertension, diabetes and body mass index (BMI). Self-identified glaucoma status was associated with diabetes that persisted after adjustment for admixture, NSES, hypertension, and BMI. Lower NSES was also associated with higher glaucoma risk but this association was marginal in the fully adjusted model and neither hypertension nor BMI showed association. When glaucoma status was limited to those reporting use or no use of appropriate ophthalmologic medication, no associations were observed in any of the models.

Conclusion—This study failed to find an independent association of glaucoma status and African admixture and these findings suggest that the higher frequency glaucoma in African Americans may be largely due to other factors.

Keywords

Admixture; Glaucoma; African American women

INTRODUCTION

Glaucoma is a leading cause of vision loss in elderly American adults.[1] In the US, a recent report estimated that the prevalence of glaucoma for adults aged 50 years and older was

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6.4% and the prevalence was highest for African Americans (9.9%), followed by Hispanics (7%) and European Americans (5.7%).[2]

Risk factors for primary open angle glaucoma include race, hypertension, age, family history of glaucoma, intraocular pressure, and structure of the optic disk.[3] The prevalence of glaucoma is reportedly approximately four times higher in African Americans than in European Americans over the age of 40[4] with multiple studies suggesting a strong relationship between self-reported ethnicity and the incidence or prevalence of open angle glaucoma.[4–7] Glaucoma is amongst the leading causes of blindness and visual impairment amongst African Americans and this risk increases with age.[8]

A recent meta-analysis of European glaucoma studies has identified multiple genetic risk factors including SNPs within CDKN2B, ATOH7 and SIX1 that are associated with primary open-angle glaucoma (POAG).[9] This finding supports the hypothesis that underlying genetic factors are important in determining the susceptibility to POAG and suggests that further exploration of race/ethnic differences might yield important information. We hypothesized that glaucoma prevalence may be associated with sub-Saharan African admixture and that neighborhood socioeconomic status, hypertension, diabetes and measures of adiposity may also be independent risk factors for the development of glaucomatous disease.

MATERIALS AND METHODS

Study Design and Participants

Study participants included women enrolled in the WHI Observational (OS) and Clinical Trial (CT) arms. In brief, the WHI includes160, 000 post-menopausal women aged 50–79 drawn from 40 different sites across the United States.[10,11] Within this cohort, 11,616 women are self-identified as African Americans for whom admixture information regarding European (EUR) and African (AFR) ancestry was determined based on analyses of ancestry informative markers (AIMs) as reported previously.[12–15] All studies were conducted with appropriate informed consent and in agreement with established Human Institutional Review Board procedures at the University of California Davis and along with the principles of the Helsinki Declaration.

Phenotypes and Covariates

Glaucoma status was recorded for greater than 90% of study participants based upon the response to the question: “Has a doctor told you that you have any of the following conditions or have you had any of the following procedures: Glaucoma?” Analyses to validate the self-reporting of glaucoma were aided by the self-reported use of ophthalmic beta-blocker medications used to lower intraocular pressure in individuals with glaucoma. The false negative rate as represented by the proportion of individuals who self-reported using ophthalmic beta-blocker medications but denied a diagnosis of glaucoma was 0.6% for the entire WHI study. Amongst those self-reporting glaucoma at baseline, however, only 20% acknowledged use of ophthalmic beta-blocker medications. Therefore we measured glaucoma status in the following two ways, 1. Glaucoma status (1): Participants who self-

reported glaucoma (n=11,616); and 2. Glaucoma status (2): Self-reported glaucoma and use of ophthalmic beta-blocker medications (n=8,978).

We considered the following baseline covariates when examining the relationship between admixture and glaucoma: Age, neighborhood socioeconomic status (NSES), hypertension, diabetes and body mass index (BMI). BMI was computed as measured weight (kg) divided by the square of measured height (m^2). Systolic hypertension status (hypertensive or normotensive) was determined based on the participants' baseline blood pressure as previously defined.[13] We also adjusted for socioeconomic status (SES) using a standardized geocoding protocol[16] that linked individual WHI participant addresses to year 2000 U.S. Census Federal Information Processing Standards (FIPS) codes and tract-level socioeconomic data. A summary measure of each subject's neighborhood socioeconomic environment was estimated from the tract-level data using six variables representing several dimensions of wealth and income: 1) natural log (median household income); 2) natural log (median value of housing units); 3) percentage of households receiving interest, dividend, or net rental income; 4) percentage of adults > 25 years of age who had completed high school; 5) percentage of adults > 25 years of age who had completed college; and 6) percentage of employed persons > 16 years of age in executive, managerial, or professional specialty occupations. These six variables were converted into standardized (z) scores by subtracting the population-specific mean from the value associated with each participant's Census tract and then dividing the difference by the population-specific standard deviation. The transformation was performed separately within the OS and CT and generated six z scores, each of which indicated the deviation of the tract level value from the corresponding, population-specific mean and summed to zero across the population. A neighborhood summary z score was then constructed by summing the six z scores.

Ancestry Informative Markers (AIM's)

We estimated the proportion of African and European admixture using a validated set of ancestry informative markers (AIMs).[17,18] This marker set included 92 SNPs that enable the accurate estimation of admixture proportions in African Americans.[12,17,18] Genotyping was performed as previously described[17] and all AIM SNPs were in Hardy Weinberg equilibrium (P>.005) in parental populations. Using this SNP set, the mean width of the 90% Bayesian confidence intervals (CIs) was 0.2 for admixture estimates in our studies of groups of African Americans, Mexican Americans and Puerto Ricans.[17] For the current study we did not include assessment of Amerindian Admixture since the African American participants showed a very low frequency of admixture from this population (Amerindian admixture, mean = 0.019, standard deviation = 0.025).

The percentage African and European admixture contribution (ranging from 0% to 100%) to each self-identified African American woman was assessed using STRUCTURE (v2.3.3) [19] analyses of AIM genotyping results as previously described.[12] The results were consistent, demonstrating a less than 0.02 difference between each of the three independent runs.

Statistical Analyses

The outcome variable for all analyses was glaucoma status 1 (self-reported glaucoma) and glaucoma status 2 (self-reported glaucoma and self-reported use of ophthalmic beta-blocker medications). Descriptive variables including age, NSES, diabetes, hypertension, and BMI were categorized by glaucoma status 1 and glaucoma status 2. Chi-square testing was used to compare the frequencies of diabetes and hypertension while a t-test was used to compare the means of each continuous variable between individuals who self-reported as having, versus not having glaucoma.

We used logistic regression to study the associations between glaucoma status 1 and glaucoma status 2 and African admixture. All analyses included age of study entry as a covariate and were performed with and without adjustment for NSES, diabetes, hypertension, and BMI. For the main analyses, we examined each model (NSES, diabetes, hypertension, and BMI) separately and also together. Continuous variables, such as BMI, were first standardized and then entered into our models. Odds ratios (OR) and 95% CI were obtained for each of the admixture variables based on different models.

Logistic regression models were used to study the associations between glaucoma status 1 and glaucoma status 2 and NSES, hypertension, diabetes and measures of adiposity (BMI) adjusting for admixture. Odds ratios (OR's) and 95% confidence intervals (CI's) were obtained for each of the different models.

Analyses were carried out using SAS version 9.2 (SAS Institute, Cary, NC, USA). All statistical tests were two sided and $P<0.05$ was considered statistically significant.

Power estimates were obtained for both continuous covariates and categorical variables, using a significance level of 0.05 and two sample sizes 11,616 and 8,978, respectively.

RESULTS

Descriptive Statistics of age, NSES, hypertension, diabetes, and BMI

Table 1 displays the baseline characteristics of all study participants by glaucoma status 1 and glaucoma status 2. Participants with glaucoma 1 and glaucoma status 2 were significantly older, had a lower NSES, slightly lower BMI as well as a higher prevalence of diabetes and hypertension than participants without glaucoma.

Estimation of the association between Admixture and Glaucoma Status

We found a significant association between admixture and glaucoma status 1 (OR= 1.38, 95% CI= 1.02–1.86) adjusting for age only (Table 2). Including diabetes status in the multivariate logistic regression model resulted in no significant association between admixture and glaucoma status 1 (OR=1.29, 95% CI=0.96–1.74). Similarly, when NSES was added to the model, the association between admixture and glaucoma status 1 was no longer statistically significant (OR=1.28, 95% CI 0.94–1.73). No significant association was found when the other study covariates, hypertension and BMI, were added to this model.

Similarly, no significant association was found between admixture and glaucoma status 2 in unadjusted (OR=1.06, 95% CI=0.59–1.88) and fully adjusted models (OR=1.18, 95% CI=0.65–2.13).

Estimation of the association between Diabetes and Glaucoma Status

Diabetes status was significantly associated with glaucoma status with and without adjustment for admixture, NSES, hypertension, and body mass index BMI (Table 3). In the first model that only included age at entry, diabetes was significantly associated with glaucoma (OR= 1.51, 95% CI=1.37, 1.67). This association remained significant when NSES was added to the model (OR= 1.49, 95% CI= 1.35, 1.65) and also in the fully adjusted model that included all study covariates (OR= 1.52, 95% CI= 1.37, 1.69).

In contrast, no significant association was found between admixture and glaucoma status 2 in unadjusted (OR=1.17, 95% CI=0.96–1.43) and fully adjusted models (OR=1.20, 95% CI=0.98–1.47).

Estimation of the association of NSES on Glaucoma Status

Lower NSES was also significantly associated with higher risk of glaucoma (OR=1.07; CI=1.02, 1.12) (Table 4). This association remained when admixture (OR=1.06, 95% CI=1.01, 1.11) or diabetes status was added to the model (OR= 1.05, 95% CI=1.01, 1.10). In the fully adjusted model, which included AFR, DM, hypertension, and BMI, the association between NSES and glaucoma was marginally statistically significant (p= 0.04).

In contrast, no significant association was found between admixture and glaucoma status 2 in unadjusted (OR=1.08, 95% CI=0.99–1.17) and fully adjusted models (OR=1.08, 95% CI=0.99–1.19).

Estimation of the effect of hypertension and adiposity

We also conducted similar analyses for assessment of whether or not hypertension or adiposity as measured by BMI, were associated with glaucoma status 1 and glaucoma status 2. Neither showed an association when adjusting for age or in models incorporating the other covariates.

DISCUSSION

Our primary objective was to investigate the association between African ancestry and glaucoma prevalence in a large cohort of postmenopausal African American women. While greater African admixture was associated with self-reported glaucoma this association did not persist after adjustment for NSES and diabetes. In contrast, NSES and diabetes status were each independently associated with glaucoma status 1 (self-reported glaucoma) with diabetes showing the most robust association (fully adjusted OR = 1.52). However, association was not observed in any of the models using glaucoma status 2 (self-reported glaucoma and use of ophthalmic beta-blocker medications).

The current study had good power to detect ancestry association with self-reported glaucoma (glaucoma status 1) and less but reasonable power to detect an association with

admixture when the criteria included responses to the use of ophthalmic medication (glaucoma status 2). We estimated that we had 80% power to detect ORs of 1.12 and 1.26 for glaucoma status 1 and 2, respectively. These ORs are exceeded in our previous studies of ancestry association of several other traits in WHI[12–15].

Similar to previous studies, we found that diabetes was strongly associated with glaucoma status 1 in African American women.[20] Although diabetes itself was noted to be associated with African admixture in this study population[14], the association of diabetes with glaucoma was not attenuated when admixture was considered as a covariate. Our findings were consistent with those from the Black Women's Health Study[21] where diabetes was found to be associated with glaucoma, independent of other risk factors. Other recent studies have suggested contributing roles of both hypertension and diabetes together and independently on glaucoma risk.[22] However we note, that in our study glaucoma status 2 was not associated with diabetes in both unadjusted and adjusted models. Whether this result is simply a reflection of decreased power or whether it is due to errors in self-reporting of glaucoma is unclear as further discussed below.

There is general consensus from several studies that socioeconomic status, smoking and alcohol consumption are not risk factors for glaucoma.[23–25] In contrast, our analysis found neighborhood socioeconomic status (NSES) to be an independent risk factor for glaucoma status 1 in African Americans. Ophthalmic experts have proposed a conceptual model that links visual impairment with NSES.[26] Specifically, visual impairment may be due to lower access to care, limited knowledge regarding the disease, and a negative attitude towards' receiving eye care. It has been postulated that low NSES may result in delayed identification and treatment of glaucoma.[26]

We found no association between adiposity, as assessed by BMI, and glaucoma status. Studies examining BMI and glaucoma have shown varying results, with some showing a protective effects[23,27] others showing no such association;[21,28] and yet others showing an association between BMI and glaucoma which is dependent on IOP.[29]

Our analysis showed no statistically significant association between hypertension and glaucoma status 1 and glaucoma status 2. The Barbados Incidence Study of Eye Diseases (BISED), a population based survey of participants who were primarily of African ancestry found a protective effect of baseline hypertension with regard to incident glaucoma over a four year period.[30] These investigators hypothesized that hypertension initially protects retinal ganglion cells but over time, high blood pressure may have a harmful effect, especially in the more advanced stages of POAG.[31]

Perhaps, the most noteworthy result from our study is the lack of an independent association between African admixture and glaucomatous disease. Our initial hypothesis was that the variability in glaucoma prevalence between different groups of African Americans might be partially due to ancestral differences within an African American cohort. Ancestry has been postulated to be an important factor in determining glaucomatous disease in Black populations such as that ascertained in a landmark study conducted in St. Lucia, West Indies [30] which found a higher prevalence of glaucoma (8.8%) with presumed higher sub-

Saharan African admixture relative to the Black population of Baltimore, Maryland[4] where the prevalence of glaucoma was noted to be 4.18%. Since the WHI was conducted in the United States, one would expect that the African American ancestry from this study would more closely resemble that found in the Baltimore relative to St. Lucia with the U.S. population showing greater European ancestry relative to those residing in the West Indies. One can hypothesize that this greater European admixture United States may diminish the genetic influence of African ancestry in terms of glaucoma risk and that other factors such as diabetes and NSES may play a more pronounced role compared to the West Indies.

This study has several limitations the most significant of which is that glaucoma status was self-reported and medical records were not available to confirm the presence or absence of this disease. This limitation would be particularly problematic if the presence or absence of other factors included in our multivariate model were associated with the likelihood of subjects correctly self-identifying themselves as having or not having glaucomatous disease. It is noteworthy, however, that large prevalence survey in Los Angeles found that self-reporting for glaucoma was highly specific (96.3%) but not sensitive (37.7%).[33] As discussed above, we also used a second glaucoma definition (glaucoma status 2) that required the self-reported use of appropriate ophthalmic medication, however, this criterion decreased the sample size and the lack of association of diabetes and NSES with this definition may reflect decreased power rather than a more accurate glaucoma definition. Additional studies will be necessary to clarify this issue.

Another study limitation is that while WHI participants were queried annually regarding their glaucoma status, the specific glaucoma classification was not ascertained. The most frequent category of glaucoma in the United States is POAG [32,34,35] and the frequency of POAG increases with age. POAG is also, by far, the dominant form of glaucoma in sub-Saharan Africans and accounts for 94% of all glaucomatous diseases based on large studies conducted in Ghana.[36, 37] Thus, the assumption that most study participants reported to have glaucoma had POAG is unlikely to severely impact the interpretation of our results. Finally, although we attempted to control for known risk factors for glaucoma we may have omitted other unrecognized risk factors for this disease.

Despite these limitations, this study represents the largest epidemiological analysis of risk factors for glaucoma among postmenopausal African American women. The WHI is a well-designed, longitudinal and powerful multi-site study providing ample power and participant data to robustly explore the relationships between the aforementioned risk factors and glaucoma in the African American population. While the results of the admixture analysis did not confirm our hypothesis with regard to an association with glaucomatous disease, other significant associations identified in this work continue to add to the body of literature demonstrating that general systemic conditions such as diabetes, as well as socioeconomic status, are associated with a greater prevalence of glaucomatous disease. Given the devastating consequences of progressive glaucoma that include significant vision loss and blindness, identification of populations at high risk may assist public health efforts aimed at combating this disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Baseline Characteristics of the Women's Health Initiative (WHI) Study Population by Self-Reported Glaucoma Status

	Self-identified Glaucoma (n=11,616)					Self-identified Glaucoma and Ophthalmic Beta-Blocker Medications (n=8,871)				
	No Glaucoma (n= 9068)		Glaucoma (n= 2548)			No Glaucoma (n= 8344)		Glaucoma (n= 527)		
Variable[a]	**Mean**	**SEM**[b]	**Mean**	**SEM**[b]	**p value**[c]	**Mean**	**SEM**[b]	**Mean**	**SEM**[b]	**p value**[c]
AGE	61	0.07	63.5	0.14	<.0001	61.18	0.08	65.00	0.31	<.0001
NSES	−0.90	0.01	−0.98	0.02	<.0001	−0.90	0.01	−0.85	0.05	<.0001
BMI	31.14	0.07	31.00	0.13	<.0001	31.24	0.07	30.60	0.27	<.0001
	n	**%**	**n**	**%**	**p value**[c]	**N**	**%**	**n**	**%**	**p value**[c]
HTN										
yes	5139	56.67	1545	60.6	0.0003	4857	58.21	338	64.1	0.0074
no	3929	43.33	1003	39.4		3487	41.79	189	35.9	
DM										
yes	2043	22.53	789	31.0	<.0001	1975	23.67	143	27.1	0.070
No	7025	77.47	1759	69.0		6369	76.33	384	72.9	

[a] Age: in years, NSES = neighborhood socioeconomic status, BMI = body mass index, HTN = hypertension, DM = diabetes status.

[b] SEM = Standard Error of the Mean.

[c] The p values were obtained from two-sample t-test for continuous variables and from Chi-squared test for categorical variables.

Table 2

Logistic Regression Analysis of the Association of African Admixture on Glaucoma

	Self-identified Glaucoma (no glaucoma n=9068, glaucoma n=2548)				Self-identified Glaucoma and Ophthalmic Beta-Blocker Medications (no glaucoma n=8344, glaucoma n=527)			
Model[a]	**OR**[b]	**95% CI**		**p value**	**OR**[b]	**95% CI**		**p value**
1. Sub-Saharan African Admixture (AFR)	1.38	1.02	1.86	0.035[c]	1.06	0.59	1.88	0.85
2. AFR, Diabetes (DM),	1.29	0.96	1.74	0.095	1.04	0.58	1.85	0.90
3. AFR, Neighborhood Socioeconomic (NSES)	1.28	0.94	1.73	0.113	1.18	0.65	2.13	0.59
4. AFR, DM, NSES	1.22	0.90	1.66	0.197	1.16	0.64	2.10	0.62
5. AFR, DM, NSES, Hypertension (HTN)	1.23	0.91	1.67	0.187	1.16	0.64	2.09	0.63
6. AFR, DM, NSES, HTN, BMI	1.24	0.91	1.68	0.168	1.18	0.65	2.13	0.59

[a] Models included the variables listed and all models adjusted for entry age.
The models included neighborhood socioeconomic factors (NSES), sub-Saharan African admixture (AFR), diabetes (DM), systolic hypertension (HTN), and body mass index (BMI).

[b] The odds ratio (OR) and 95% confidence intervals (CI) are shown.

[c] Statistically significant ($p < 0.05$)

Table 3

Logistic Regression Analysis of the Association of Diabetes on Glaucoma

	Self-identified Glaucoma (no glaucoma n=9068, glaucoma n=2548)				Self-identified Glaucoma and Ophthalmic Beta-Blocker Medications (no glaucoma n=8344, glaucoma n=527)			
Model[a] (n=11616)	**OR[b]**	**95% CI**		**p value**	**OR[b]**	**95% CI**		**p value**
1. DM	1.51	1.37	1.67	<.0001[c]	1.17	0.96	1.43	0.13
2. DM, AFR	1.51	1.36	1.66	<.0001[c]	1.17	0.96	1.43	0.13
3. DM, NSES	1.49	1.35	1.65	<.0001[c]	1.19	0.97	1.45	0.10
4. DM, AFR, NSES	1.49	1.35	1.64	<.0001[c]	1.18	0.97	1.45	0.10
5. DM, AFR, NSES, HTN	1.50	1.36	1.66	<.0001[c]	1.18	0.96	1.45	0.11
6. DM, AFR, NSES, HTN, BMI	1.52	1.37	1.68	<.0001[c]	1.20	0.98	1.47	0.08

[a] Models included the variables listed and all models adjusted for entry age.
The models included neighborhood socioeconomic factors (NSES), sub-Saharan African admixture (AFR), diabetes (DM), systolic hypertension (HTN), and body mass index (BMI).

[b] The odds ratio (OR) and 95% confidence intervals (CI) are shown.

[c] Statistically significant ($p < 0.0001$)

Table 4

Logistic Regression Analysis of the Association of Neighborhood Socioeconomic Factors (NSES) on Glaucoma Status

	Self-identified Glaucoma (no glaucoma n=9068, glaucoma n=2548)				Self-identified Glaucoma and Ophthalmic Beta-Blocker Medications (no glaucoma n=8344, glaucoma n=527)			
Model[a] (n=11616)	**OR[b]**	**95% CI**		**p value**	**OR[b]**	**95% CI**		**p value**
1. NSES	1.07	1.02	1.12	0.004[c]	1.08	0.99	1.17	0.10
2. NSES, AFR	1.06	1.01	1.11	0.011[c]	1.08	0.99	1.18	0.08
3. NSES, DM	1.05	1.01	1.10	0.028[c]	1.08	0.99	1.18	0.07
4. NSES, AFR, DM	1.04	1.00	1.10	0.055[c]	1.09	1.00	1.19	0.06
5. NSES, AFR, DM, HTN	1.04	1.00	1.10	0.052[c]	1.09	1.00	1.19	0.06
6. NSES, AFR, DM, HTN, BMI	1.05	1.00	1.10	0.041[c]	1.09	0.99	1.19	0.08

[a] Models included the variables listed and all models adjusted for entry age.
The models included neighborhood socioeconomic factors (NSES), sub-Saharan African admixture (AFR), diabetes (DM), systolic hypertension (HTN), and body mass index (BMI).

[b] The odds ratio (OR) and 95% confidence intervals (CI) are shown.

[c] Statistically significant ($p < 0.05$)