

# Retinal Vascular Caliber, Iris Color, and Age-Related Macular Degeneration in the Irish Nun Eye Study

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**PURPOSE.** To evaluate the relationship between retinal vascular caliber (RVC), iris color, and age-related macular degeneration (AMD) in elderly Irish nuns.

**METHODS.** Data from 1233 participants in the cross-sectional observational Irish Nun Eye Study were assessed from digital photographs with a standardized protocol using computer-assisted software. Macular images were graded according to the modified Wisconsin Age-related Maculopathy Grading System. Regression models were used to assess associations, adjusting for age, mean arterial blood pressure, body mass index, refraction, and fellow RVC.

**RESULTS.** In total, 1122 (91%) participants had gradable retinal images of sufficient quality for vessel assessment (mean age: 76.3 years [range, 56–100 years]). In an unadjusted analysis, we found some support for a previous finding that individuals with blue iris color had narrower retinal venules compared to those with brown iris color ( $P < 0.05$ ), but this was no longer significant after adjustment. Age-related macular degeneration status was categorized as no AMD, any AMD, and late AMD only. Individuals with any AMD (early or late AMD) had significantly narrower arterioles and venules compared to those with no AMD in an unadjusted analysis, but this was no longer significant after adjustment. A nonsignificant reduced risk of any AMD or late AMD only was observed in association with brown compared to blue iris color, in both unadjusted and adjusted analyses.

**CONCLUSIONS.** Retinal vascular caliber was not significantly associated with iris color or early/late AMD after adjustment for confounders. A lower but nonsignificant AMD risk was observed in those with brown compared to blue iris color.

**Keywords:** retinal vascular caliber, age-related macular degeneration, iris color

In recent years, studies have shown that noninvasive measurement of retinal blood vessels may offer insights into certain systemic diseases,<sup>1–8</sup> highlighting the eye as a unique window through which to view microvascular health elsewhere within the body. This opportunity may afford clinicians and other health professionals mechanistic insight into diseases with a microvascular component.<sup>5</sup>

Previous studies have examined ethnic and racial variation in retinal microvascular characteristics, identifying an association between retinal vascular caliber (RVC) and ethnicity, principally on the basis of a darker iris color.<sup>9–12</sup> The reason for the observed racial and ethnic differences in RVC is uncertain, but several underlying factors have been proposed, including genetic variation, anthropometric and ocular biometrics, varying susceptibility to vascular risk factors, or perhaps measurement error as a result of reduced vessel contrast against a more pigmented epithelium.<sup>10</sup> Furthermore, it was also reported that individuals with a lighter iris color were more likely to have a higher prevalence and a greater likelihood of progression to late AMD than those with a darker iris color.<sup>13</sup>

Age-related macular degeneration (AMD; Mendelian Inheritance in Man no. 603075) is the most common form of visual impairment among older people of European descent,<sup>14</sup> accounting for more than half of all new cases of registered

blindness.<sup>15</sup> Several epidemiologic studies have suggested common mechanistic processes and risk factors shared between AMD and cardiovascular disease (CVD)<sup>16–18</sup> and some have examined the relationship between RVC and AMD, although the findings reported have been inconsistent.<sup>19–25</sup> It has been suggested that changes in RVC may be a risk factor for AMD, and that factors involved in the pathogenesis of AMD such as inflammation may influence RVC at an earlier stage before AMD manifestations are observed clinically. As such, changes in RVC may potentially provide some prognostic indication for better risk stratification in individuals with an increased risk of developing AMD later in life.

Thus we sought to evaluate the relationship between RVC, iris color, and AMD status using cross-sectional data from the Irish Nun Eye Study (INES), which included 1233 white participants aged 56 to 100 years.

## METHODS

### Study Population

The INES was a cross-sectional observational study of eye health in white Irish nuns selected from convents across Ireland, with recruitment between 2007 and 2009. It was

designed specifically to examine the prevalence of AMD in a population with a restricted lifestyle and also to examine the relationship between light exposure and AMD.

### Study Characteristics

Contact was made with 152 convents, of which 126 (82.9%) responded and agreed to participate. A total of 1500 nuns in these 126 convents were invited to take part in the study, and 1233 (82.2%) agreed. Those who did not participate tended to be ill or unavailable on the day of examination. The inclusion criteria mandated participants to be of Irish descent and aged over 55 years and to have lived in a convent for at least 25 years. There were no specific exclusion criteria. In order to maximize recruitment and minimize disruption to participant routines, all examinations were carried out within the community. The study was approved by the Institutional Review Board and the Office for Research Ethics Committee Northern Ireland and adhered to the tenets of the Declaration of Helsinki. Informed written consent was obtained from all participants prior to participation.

### Demographic Data

Demographic data were obtained from interviews by a trained field worker using a structured questionnaire. This study was specific to one ethnicity, as only white Irish nuns were included.

### Anthropometric and Blood Pressure Measurements

Blood pressure was measured in a seated position with an oscillometric blood pressure aneroid sphygmomanometer (Speidel and Keller, Jungingen, Germany) after the questionnaires had been completed. Mean arterial blood pressure (MABP) was calculated as one-third of the systolic (SBP) plus two-thirds of the diastolic blood pressure (DBP). Height, weight, and waist circumference were measured, and body mass index (BMI) was calculated as weight (in kilograms) divided by height (in meters) squared.

### Ocular Examination and Retinal Photography

Each individual underwent a comprehensive ophthalmic examination. Medical and ophthalmic questionnaires covered areas such as medical and ocular history and relevant risk factors for AMD. Iris color was determined from the undilated pupil of each eye by a single examiner (EM) and categorized by comparison with four standard photographs prior to pupil dilation as blue, brown, hazel, or green. Refractive error was recorded either from a recent prescription or from the participant's glasses. Where glasses were not available, corrected visual acuity was achieved by pinhole correction; refraction was not carried out. Each individual had anterior segment photography and photography of the skin around the eyes and forehead, and retinal findings were recorded by stereoscopic retinal imaging using the NIDEK AFC 210 digital camera (Aichi, Japan). Fields 1 and 2 were captured following dilation of the pupils with 1% tropicamide.

### AMD Characterization

All images were independently graded by the Network of Ophthalmic Reading Centres UK (NetwORC UK) in Belfast. Anonymized images were submitted to NetwORC UK, and trained graders followed a standardized procedure to identify the characteristics of early and late AMD using the definitions

of the Wisconsin Age-related Maculopathy Grading System.<sup>26</sup> The definitions for AMD were based on the International Classification for Age-related Macular Degeneration.<sup>27</sup> The presence of features within a 6000- $\mu\text{m}$  circle centered on the fovea was recorded. Drusen were classified according to size, characteristics of homogeneity of surface features, and outline. Pigmentary changes were classified into two categories, hyperpigmentation and hypopigmentation. These features were used to assign each eye to a severity grade as follows: no AMD, no features of AMD or the presence of soft distinct drusen ( $>63$  and  $\leq 125$   $\mu\text{m}$ ) or pigmentary abnormalities only; early AMD, soft, indistinct ( $\geq 125$   $\mu\text{m}$ ), or reticular drusen only or soft distinct drusen with pigmentary abnormalities; late AMD, either geographic atrophy (well-demarcated area of retinal pigment atrophy with visible choroidal vessels) or neovascular AMD (presence of any of the following: serous or hemorrhagic retinal or retinal pigment epithelial detachment, subretinal neovascular membrane, or periretinal fibrous scar).

### Retinal Vessel Caliber Assessment

Retinal arteriolar and venular calibers were measured using Interactive Vessel ANalysis software (IVAN; University of Wisconsin, Madison, WI, USA) according to a standardized protocol for all retinal vessels located between a half and one disc diameter distance from the optic disc margin in the digitized image. The revised Knudston-Hubbard formula<sup>28</sup> was used to summarize these measurements as CRAE (central retinal arteriolar equivalent) and CRVE (central retinal venular equivalent), which represent the average caliber of the arterioles and venules in each examined eye. A single trained grader (AM), blinded to the participants' characteristics, conducted all retinal measurements. Reproducibility of retinal vascular measurements was high, with intragrader reliability assessed in 200 randomly selected retinal photographs and an intraclass correlation coefficient (95% confidence interval) calculated as 0.975 (0.967–0.981) for CRAE and 0.993 (0.990–0.994) for CRVE, respectively. A high correlation between the right and left eyes in retinal vascular measurements has been reported elsewhere.<sup>28</sup> Data from the right eye were used and when unavailable was replaced by left eye data.

### Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics version 21 (IBM Corp., Armonk, NY, USA). Quantitative retinal vascular caliber was assessed as a continuous variable. One-way analysis of variance and multiple linear regression analyses were used to compare the mean CRAE and CRVE by iris color in both unadjusted (model 1) and adjusted analyses (models 2, 3, and 4). The minimally adjusted model (model 2) included covariates for refraction, age, BMI, and MABP. The model was not adjusted for sex, as all participants were female. The fully adjusted model (model 4) also included the covariates from the minimally adjusted model in addition to diabetes mellitus status, hypertension, ever smoker, ischemic heart disease (IHD), cerebrovascular accident (CVA), alcohol consumption (yes/no), and the fellow vessel (venule or arteriole) caliber (i.e., CRAE as a covariate in the analysis of CRVE and vice versa) as suggested previously.<sup>29</sup> The same approach was used to compare CRAE and CRVE according to AMD status with adjustment for potential confounders in a minimally and fully adjusted model as described for iris color. Logistic regression was used to assess the significance of iris color as a predictor of AMD status. Separate analyses of any AMD (early and late AMD) versus no AMD and of late AMD only versus no AMD were performed, each with adjustment for confounders. A *P* value  $< 0.05$  was regarded as statistically significant.

TABLE 1. Summary Statistics of Participants

Characteristic	All Participants	Gradable, <i>n</i> = 1122	Ungradable, <i>n</i> = 111	<i>P</i>
Mean age, <i>y</i> (SD)	77.1 (8.4)	76.3 (8.1)	84.8 (7.4)	<0.001
Mean BMI, kg/m <sup>2</sup> (SD)	24.5 (5.1)	24.6 (5.1)	23.8 (5.0)	0.09
Mean MABP, mm Hg (SD)	92.5 (10.6)	92.4 (10.4)	93.2 (12.3)	0.47
IHD, <i>n</i> (%)	137 (11)	120 (11)	17 (15)	0.20
CVA, <i>n</i> (%)	40 (3)	36 (3)	4 (3)	0.79
Ever smoked, <i>n</i> (%)	57 (5)	49 (4)	8 (7)	0.22
Diabetes, <i>n</i> (%)	37 (3)	34 (3)	3 (3)	1.00
Hypertension, <i>n</i> (%)	504 (41)	454 (40)	50 (43)	0.59
Chronic kidney disease (%)	705 (60)	623 (59)	82 (74)	0.004
Alcohol consumption (%)	81 (7.9)	77 (8.2)	4 (3.6)	0.20
1–7 measures/wk (%)	78 (7.6)	74 (7.9)	4 (3.6)	
>7 measures/wk (%)	3 (0.3)	3 (0.3)	0 (0)	
Osteoporosis (%)	402 (33)	365 (33)	37 (31)	0.78
Statins (%)*	482 (39)	448 (40)	34 (28)	0.01
Aspirin (%)*	420 (34)	369 (33)	51 (42)	0.03
Diuretics (%)*	281 (23)	240 (21)	41 (34)	0.001
Beta blockers (%)*	215 (17)	192 (17)	23 (19)	0.57
Calcium channel blockers (%)*	169 (14)	142 (13)	27 (22)	0.003
Ace inhibitors (%)*	145 (12)	134 (12)	11 (9)	0.37
Corticosteroids (%)*	66 (5)	62 (5)	4 (3)	0.31
NSAIDs (%)*	62 (5)	53 (5)	9 (7)	0.18

\* Medications with a frequency > 5%. NSAIDs, nonsteroidal anti-inflammatory drugs.

RESULTS

In total, gradable retinal images of sufficient quality for vessel assessment were available in 1122 (91%) of the 1233 participants. Images were not available for 111 participants, in part as a consequence of difficulties with image acquisition due to postural complications with the elderly participant, poor pupillary dilation, the presence of an artificial eye, or an out-of-focus image. Participants with missing retinal vessel caliber measurements (*n* = 111) were significantly older and more likely to have moderate to severe cataract than those with retinal images captured (*P* < 0.001; 84.8 vs. 76.3 years; Table 1); 11 had no retinal images captured, and 60 had macula-centered images only, which were not amenable to measurement using the IVAN software. The mean age of the 1122 participants included was 76.3 years (range, 56–100 years).

Iris Color and Retinal Vessel Caliber

Iris color was characterized as blue (59.0%), brown (20.2%), hazel (14.4%), or green (6.5%). Central retinal arteriolar equivalent and CRVE were normally distributed, with means and standard deviations (SD) of 120.4 (12.6) and 169.0 (18.3)

TABLE 2. Summary Retinal Vessel Caliber Measurements: CRAE and CRVE by Iris Color

Color	<i>N</i>	Mean, $\mu$ m	SD
Central retinal arteriolar caliber (CRAE)			
Blue	662	120.0	12.5
Brown	227	121.6	12.7
Hazel	161	119.6	12.8
Green	72	121.1	12.4
Central retinal venular caliber (CRVE)			
Blue	662	168.0	18.3
Brown	227	170.8	18.1
Hazel	161	169.3	18.2
Green	72	171.3	19.1

$\mu$ m, respectively. Table 2 shows the diameters ( $\mu$ m) for retinal vessel caliber categorized by iris color. Initial one-way analysis of variance showed no significant differences in mean CRAE (*P* = 0.34) and CRVE (*P* = 0.15) between the iris color groups.

Although an unadjusted analysis suggested that individuals with brown iris color had significantly broader retinal venules (*P* = 0.05) compared to those with blue iris color (Table 3), this finding was not corrected for multiple comparisons. Iris color was no longer significantly associated with vascular caliber following adjustment for refraction, age, BMI, and MABP (model 2), and additional covariates diabetes mellitus, hypertension, ever smoker, IHD, CVA, alcohol consumption (yes/no), and fellow vessel (models 3 and 4). All comparisons for arterioles were nonsignificant.

AMD Status and Retinal Vessel Caliber

Age-related macular degeneration status was categorized as no AMD (*n* = 975), early AMD (*n* = 99), and late AMD (*n* = 27). The summary statistics for those with any AMD and those without AMD are displayed in Table 4. In an unadjusted analysis, individuals with any AMD had significantly narrower CRAE (*P* < 0.05) and CRVE (*P* = 0.03) compared to those without AMD. Following adjustment for refraction, age, BMI, MABP (minimally adjusted, model 2), and also for additional covariates (models 3 and 4), AMD status was no longer significantly associated with vessel caliber (Table 5).

AMD Status and Iris Color

Although a decrease in risk for any AMD was observed in association with brown compared to blue iris color, this was not significant in both an unadjusted analysis (odds ratio [OR] = 0.73; confidence interval [CI]: 0.44–1.20; *P* = 0.22) and an analysis adjusted for age, BMI, MABP, and refraction (OR = 0.74; CI: 0.44–1.24; *P* = 0.25). Similarly, a decrease in risk for late AMD only was observed in association with brown compared to blue iris color, but again this was not significant in both an unadjusted analysis (OR = 0.35; CI: 0.20–1.77; *P* = 0.35) and an

**TABLE 3.** Difference in Mean Retinal Vessel Caliber (µm) for Each Iris Color Compared to Blue (Reference Group) in Unadjusted (Model 1), Minimally Adjusted (Model 2), and Fully Adjusted (Models 3 and 4) Analyses

	Model 1 (95% CI)	P	Model 2 (95% CI)	P	Model 3 (95% CI)	P	Model 4 (95% CI)	P
<b>CRAE</b>								
Brown	1.6 (−0.4, 3.5)	0.11	1.2 (−0.6, 3.0)	0.19	0.8 (−1.2, 2.8)	0.46	−0.1 (−1.6, 1.5)	0.92
Hazel	−0.4 (−2.6, 1.8)	0.72	0.2 (−1.9, 2.3)	0.84	−0.9 (−3.2, 1.4)	0.44	−1.0 (−2.8, 0.7)	0.25
Green	1.1 (−2.0, 4.1)	0.49	−0.3 (−3.2, 2.6)	0.83	−1.1 (−4.2, 2.1)	0.50	−1.4 (−3.8, 1.0)	0.26
<b>CRVE</b>								
Brown	2.8 (0.1, 5.6)	0.05	2.3 (−0.3, 4.9)	0.09	2.0 (−1.0, 4.9)	0.19	1.3 (−1.0, 3.5)	0.28
Hazel	1.3 (−1.8, 4.5)	0.41	1.8 (−1.2, 4.8)	0.25	0.3 (−3.0, 3.7)	0.85	1.2 (−1.4, 3.8)	0.39
Green	3.3 (−1.1, 7.8)	0.14	1.4 (−2.8, 5.6)	0.53	0.8 (−3.8, 5.3)	0.75	1.7 (−1.8, 5.3)	0.34

Model 1: unadjusted; model 2: adjusted for refraction, age, BMI, and MABP; model 3: adjusted for refraction, age, BMI, MABP, diabetes mellitus, hypertension, ever smoker, IHD, CVA, alcohol consumption (yes/no); model 4: adjusted for refraction, age, BMI, MABP, diabetes mellitus, hypertension, ever smoker, IHD, CVA, alcohol consumption (yes/no), and fellow vessel caliber.

analysis adjusted for age, BMI, MABP, and refraction (OR = 0.61; CI: 0.20–1.86; P = 0.39).

**DISCUSSION**

In this study, we did not find a significant association between retinal vessel caliber and iris color in our study population of white Irish nuns. The Sydney Childhood Eye Study<sup>10</sup> (SCES) reported that both CRAE and CRVE were significantly wider in children of East Asian ethnicity compared with white children and that white children with darker iris color had both wider CRAE and CRVE. Rochtchina and colleagues<sup>10</sup> hypothesized that the ethnic variability observed in association with retinal vessel caliber may have contributed to measurement error as a consequence of contrast sensitivity associated with the software’s ability to delineate the vessel edges against the background retinal pigment epithelium and its associated level of pigmentation (iris color as a proxy for skin pigmentation). If true, this could result in an overestimation of vessel caliber as the software finds it more difficult to delineate the true blood vessel edges.

The association between RVC and ethnicity was well established with the Multi-ethnic Study of Atherosclerosis<sup>12</sup> (MESA) concluding that blacks and Hispanics had wider CRAE and CRVE than whites and Chinese. Similarly, the Singapore Childhood Study of Risk Factors for Myopia<sup>11</sup> (SCORM) demonstrated that CRAE and CRVE were both significantly narrower in Chinese children compared to Malay and Indian children. The findings from SCORM suggested that the underlying reasons for the variations between ethnic and racial groups observed were unclear but perhaps reflected differences and varying susceptibility to vascular risk factors such as blood pressure, anthropometric and ocular measures,

and/or genetics. More recently, the Multi-ethnic study of Healthy Asians<sup>9</sup> reported that Indians had the widest CRAE and CRVE measurements, followed by the Malay and then the Chinese.

Our study was limited to white Irish nuns (females only), minimizing ethnicity as a potential confounder. Our findings do not indicate any significant association between RVC and iris color, which in part adds support to previous suggestions that variation observed in RVC may be influenced by underlying ethnic differences, as opposed to iris color per se. Nevertheless, the possibility that iris color and/or retinal pigmentation levels may influence contrast sensitivity and the ability of the analysis software to delineate blood vessel edge cannot be excluded.

We failed to find an association with AMD following adjustment for potential confounders; and our findings support those from previous studies<sup>19–21,24,25</sup> but contrast with those from the Singapore Malay Eye Study<sup>22</sup> and the Handan Eye Study.<sup>23</sup> The Handan Eye Study consisted of 199 individuals with early AMD and 400 age-matched controls (mean age 58.6), and reported a significant association between wider retinal arteriolar caliber and early AMD and soft distinct drusen. The Singapore Malay Eye Study comprised 3280 participants aged between 40 and 80 years (mean age 58.7 years), and reported a wider venular caliber associated with an increased prevalence of early AMD.

Within our study, it is important to consider the pathological pathways involved in AMD etiology, such as inflammation, which may influence the retinal microvasculature, although whether the retinal or choroidal circulation is more likely to influence the disease processes requires further investigation.<sup>25</sup> Previous studies have implicated common mechanistic processes and risk factors shared between AMD and CVD, with subsequent risk modification for both conditions by smoking, hypertension, inflammatory markers, and common genetic variants, although consistent supporting evidence from cross-sectional studies has proved elusive, possibly as a consequence of potential confounding.<sup>30,31</sup> Studies examining the relationship between AMD and CVD risk factors have identified associations between higher pulse pressure, higher SBP, and increased carotid wall thickness and incident AMD, implicating a vascular remodeling process.<sup>32,33</sup> Previous studies have also suggested that lighter iris color increases associated AMD risk; that is, individuals with blue iris color were more inclined to have a higher prevalence and a stronger likelihood of progression to late AMD than those with a darker iris color.<sup>13</sup> We were unable to corroborate these findings in our study.

The strengths of this study include the relatively large sample size and the high proportion of gradable digital

**TABLE 4.** Summary Statistics of Participants Included for Retinal Vessel Assessment by AMD Status

Characteristic	No AMD, n = 976	Any AMD, n = 126	P
Mean age, y (SD)	75.6 (8.0)	81.3 (6.7)	<0.001
Mean BMI, kg/m <sup>2</sup> (SD)	24.7 (5.1)	24.5 (4.8)	0.70
Mean MABP, mm Hg (SD)	92.1 (10.3)	94.5 (10.9)	0.02
IHD, n (%)	99 (10)	14 (11)	0.74
CVA, n (%)	28 (3)	7 (6)	0.11
Ever smoked, n (%)	42 (4)	7 (6)	0.53
Diabetes, n (%)	28 (3)	6 (5)	0.27
Hypertension, n (%)	390 (40)	57 (45)	0.26

Any AMD is composed of early and late AMD.

**TABLE 5.** Unadjusted (Model 1), Minimally Adjusted (Model 2), and Fully Adjusted (Models 3 and 4) Analysis of Retinal Vessel Caliber by AMD Status (Any AMD Versus No AMD)

	Model 1 (95% CI)	P	Model 2 (95% CI)	P	Model 3 (95% CI)	P	Model 4 (95% CI)	P
CRAE	-3.8 (-6.8, -1.5)	0.001	-1.3 (-3.6, 1.0)	0.27	-2.0 (-4.5, 0.6)	0.13	-1.9 (-3.9, 0.1)	0.06
CRVE	-3.7 (-7.0, -0.3)	0.03	0.1 (-3.3, 3.4)	0.98	-0.3 (-3.9, 3.4)	0.88	1.5 (-1.4, 4.4)	0.30

Model 1: unadjusted; model 2: adjusted for refraction, age, BMI, MABP, and iris color; model 3: adjusted for refraction, age, BMI, MABP, iris color, diabetes mellitus, hypertension, ever smoker, IHD, CVA, and alcohol consumption (yes/no); model 4: adjusted for refraction, age, BMI, MABP, iris color, diabetes mellitus, hypertension, ever smoker, IHD, CVA, alcohol consumption (yes/no), and fellow vessel caliber.

retinal images. Masked evaluation of RVC was performed by a single trained grader. A semiautomated computer-based technique<sup>34</sup> was used to measure RVC. The collection of data on potential confounders including anthropometric factors was standardized, and the relative uniformity of the nuns' backgrounds meant fewer variations in lifestyle, reducing potential confounding, and provided an opportunity to examine the potential complex relationship that exists between AMD and CVD risk factors, iris color, and the resultant effect on RVC. Importantly, our study was performed on a well-characterized and aged cohort (mean age 76.3 years), free from sex- or ethnicity-related confounding, which is particularly important for the analysis of age-related conditions such as AMD. Due to the nature of their lifestyle, this novel population has lower rates of some well-recognized environmental and lifestyle-related risk factors; that is, the majority were nonsmokers and had lower rates of alcohol consumption with reduced prevalence of CVD and diabetes, providing an opportunity to better examine lifestyle and environmental factors that contribute to the etiology of complex diseases.

Limitations of our study include its cross-sectional design, which did not let us determine whether changes observed precede or are a consequence of AMD. The data available to evaluate late AMD were relatively few in number, limiting the power to evaluate RVC in the advanced form of this condition. Furthermore, certain data that may affect RVC, including intraocular pressure,<sup>35</sup> were unavailable. While convent or religious orders may not truly reflect the general population, they nevertheless offer an excellent opportunity to study a well-characterized model of "healthy aging."

In conclusion, our cross-sectional study of aged white Irish Nuns did not find a significant association between retinal vascular caliber and iris color, between retinal vascular caliber and AMD, or between iris color and AMD following adjustment for appropriate known confounders.

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