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Retina

Investigations of Renal Function and Age-Related Macular Degeneration Phenotypes

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Purpose: To investigate potential associations between renal function and age-related macular degeneration (AMD) features as assessed with multimodal retinal imaging.

Methods: A subset of participants included in a dark adaptation study with varying AMD severities had estimated glomerular filtration rate (eGFR) values (mL/min/1.73 m^2) obtained from renal function laboratory testing of serum creatinine and cystatin C. Multimodal imaging from visit dates associated with serum samples was graded by the Wisconsin Reading Center for AMD features. Associations of eGFR with AMD features and severity grades, age, smoker status and rod–intercept time were investigated. Simple univariate analyses, age-corrected multivariate analyses, and a feature-selecting least absolute shrinkage and selection operator regression were performed for eGFR as a continuous dependent variable.

Results: A total of 110 patients (mean age, 75.1 ± 9.4 years; mean eGFR, 70.7 ± 18.2 mL/min/1.73 m^2) were included. In univariate analyses age (estimate, −1.16 units/year; 95% confidence interval [CI], −1.46 to −0.87; $P < 0.0001$), rod–intercept time (estimate, −0.54 units/minute; 95% CI, −0.81 to −0.27; $P < 0.001$) and subretinal drusenoid deposits (−11.12 units for subretinal drusenoid deposit presence in either eye; 95% CI, −20.23 to −2.01; $P = 0.017$) were associated with decreased renal function. However, in age-corrected multivariate models, age was the only significant variable associated with renal function, confirmed by least absolute shrinkage and selection operator regression.

Conclusions: Accounting for age, renal function parameters did not show an association with AMD features.

Translational Relevance: Bruch's membrane of the eye and the glomerular basement membrane of the kidney share physiologic similarities such that decreased renal function may demonstrate associations with AMD phenotypes.

Introduction

Age-related macular degeneration (AMD), one of the leading causes of blindness in developed countries and worldwide, is projected to affect as many as 196 million people by 2020 and 288 million people by 2040.[1] Chronic kidney disease (CKD) is another common condition that shows increasing prevalence with age and is estimated to affect more than 50% of the elderly in the United States.[2] Several recent studies have suggested an association between these two conditions.[3–8] Not only do they have common risk factors including age, hypertension, obesity, and smoking,[9,10] but there are also commonalities in the pathophysiology of both diseases.[11–14]

One of the first studies to examine this potential association was a substudy of the Blue Mountains Eye Study, in which a sample of 1183 participants were examined in a population-based prospective cohort; this work showed that participants with moderate CKD had three times the risk of developing AMD.[3] Subsequent studies showed a significant association between early AMD and CKD, as estimated from serum creatinine, in a cross-sectional study of 3008 participants,[6] and between late AMD and reduced

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kidney function in a cross-sectional nested case-control study using the Third National Health and Nutrition Examination Survey data.[5]

Vascular pathophysiology is a common mechanism thought to play a role in both CKD and AMD. The glomerular basement membrane and Bruch's membrane are the only two places in the body where an extracellular matrix is in direct apposition to a bed of fenestrated capillaries. This configuration has important implications for complement activation and inflammation. The kidney is often damaged by systemic atherosclerosis, hypertension, and cigarette smoking.[15,16] Likewise, atherosclerosis is also thought to play a role in the AMD disease process,[15–19] and the similar vascular anatomies found in the choroid and the capillary networks in the kidney also support this hypothesis.[11] As choroidal thinning has been shown to have an association with both geographic atrophy (GA)[20] as well as subretinal drusenoid deposits (SDD),[21] studies have looked at these two features of AMD in relation to renal dysfunction.

The purpose of this study was to characterize the phenotype of participants with AMD by multimodal imaging and functional dark adaptation testing, and determine whether these phenotypes were associated with decreased renal function.

Methods

Study Population

A total of 110 participants who had serum studies for both creatinine and cystatin C and multimodal imaging were included in this cross-sectional study Participants 50 years of age and older with and without AMD were recruited from the eye clinic at the National Eye Institute, National Institutes of Health, Bethesda, Maryland and were enrolled in a longitudinal study of dark adaptation (NCT01352975). The study was approved by the Institutional Review Board of the National Institutes of Health, and the tenets of the Declaration of Helsinki were followed. All participants provided informed consent after the nature and possible consequences of the study were explained.

Participants were excluded from the dark adaptation study for (1) advanced AMD in both eyes, (2) any other active ocular or macular disease (i.e., glaucoma, diabetic retinopathy, or Stargardt disease), (3) a history of vitamin A deficiency, (4) high oral intake of vitamin A palmitate supplement (≥10,000 international units per day), and (5) active liver disease or history of liver disease. At least one eye was required to have a best-corrected visual acuity of 20/100 or better.

Participants and Clinical Evaluation

All participants underwent a complete ophthalmoscopic examination, including measurement of best-corrected visual acuity with the Early Treatment Diabetic Retinopathy Study chart, measurement of intraocular pressure, slit-lamp examination, and dilated fundus examination. Presence of AMD features and other ocular findings (e.g., phakic status) were documented in each eye. Color fundus photographs were acquired with the TRC-50DX retinal camera (Topcon Medical Systems, Tokyo, Japan). Fundus autofluorescence imaging, infrared reflectance images and spectral domain ocular coherence tomography (OCT) scans were acquired with the Heidelberg Spectralis (Heidelberg Engineering, Heidelberg, Germany). Spectral domain OCT volume scans consisted of 121 B-scans obtained within a 30° × 25° rectangle centered on the fovea collected in both eyes. Enhanced depth imaging OCT scans were also acquired as a single horizontal scan centered at the fovea obtained over a distance of 30° consisting of 100 averaged scans.

Image Assessments

Multimodal imaging from both eyes at visit dates associated with laboratory renal testing of serum samples were graded by the Wisconsin Reading Center. The reading center consists of evaluators who are academic staff and employees of the University of Wisconsin School of Medicine and Public Health. Evaluators are trained and certified using established curricula for the indication and the image type. All reviewers completed training and were actively certified for Good Clinical Practice and compliance with the Health Insurance Portability and Accountability Act. Study-specific training of the evaluators was conducted before the start of evaluations for the study. Images were graded by a single evaluator at each visit. Color fundus photos were evaluated per AREDS report #17 and assigned a AMD severity score (AMDSC)[22] as well as for the presence or absence of large drusen (≥125 µm), and pigmentary abnormalities, defined as an area of increased pigmentation on color fundus photographs of at least 0.07 mm^2.[23] Reticular pseudodrusen, referred to hereafter as SDD, were assessed using a multimodal approach.[24] First, OCT volumes were inspected for the presence of SDD on more than one consecutive B scan. Next, a two-dimensional imaging modality (color, fundus autofluorescence, or infrared) was assessed for presence of a reticular pattern of at least one-half disc diameter to confirm the presence of SDD. GA was assessed on fundus autofluorescence images and graded as present

if a hypoautofluorescent area of at least 433 µm in diameter was present. OCT imaging was assessed for the presence of complete retinal pigment epithelium and outer retinal atrophy[25] and hyper-reflective foci (HRF). Because only annual visits were evaluated by the reading center, the presence of choroidal neovascularization was documented using OCT imaging and often fluorescein angiography imaging at the intervening visits, with evidence supporting the treatment of or presence of continued exudative disease. The reading center also evaluated OCT scans for both eyes for the following measurements: choroidal thickness (from enhanced depth imaging foveal scans measured at the fovea center), mean central retinal pigment epithelium–drusen complex (RPEDC) thickness, total RPEDC volume, mean central neurosensory retina (NSR) thickness, and total NSR volume obtained from the Heidelberg segmentation software after manual review and correction by the Wisconsin reading center graders. Data from each eye were integrated in a participant-based assessment and the presence of a given feature in either eye conferred the feature in the participant. For numerical values (e.g., retinal layer thicknesses), the mean of the two individual eye measurements was used for analysis.

Dark Adaptation Assessments

In-house dark adaptation function (rod–intercept time [RIT]) testing measurements were recorded using the AdaptRx dark adaptometer (MacuLogix, Hummelstown, PA) in one eye (nonadvanced eye) in each participant as previously described.[24,26] The maximum test duration was 40 minutes and participants that did not reach RIT within the testing time were assigned conservatively a time of 40 minutes.[24]

Assessment of Kidney Function

Kidney function was measured once by creatinine and cystatin C from serum samples collected from each participant at a single timepoint (between July 2016 and July 2017) Our analyses used a combined creatinine–cystatin C equation ("estimated glomerular filtration rate [eGFR] creatinine–cystatin C") using serum creatinine and standardized cystatin C to calculate glomerular filtration rate.[27,28]

Statistical Analyses

Data were analyzed using nonparametric statistics computed using R-Studio (Version 1.2.5033). We performed univariate analyses considering GFR as either a continuous or categorical variable. As CKD is defined as kidney damage or eGFR less than 60 mL/min/1.73 m^2 for at least 3 months, we used the following categorical values to define varying levels of renal dysfunction, based on eGFR: less than 60 mL/min/1.73 m^2, 60–90 mL/min/1.73 m^2, and more than 90 mL/min/1.73 m^2. Of note, eGFR measurements in this study were conducted at a single timepoint.

We also created an age-adjusted multivariable model using eGFR as a continuous variable, because age had the strongest association with eGFR in the univariate analysis. The age-adjusted model was then used to determine if associations existed between eGFR and each of the AMD features.

Simple univariate analyses, age-corrected multivariable analyses, and a least absolute shrinkage and selection operator regression were performed for eGFR as a continuous, dependent variable and age, gender, smoking status, and retinal characteristics obtained at dates of corresponding imaging visits, as independent variables. Random forest regression was also conducted. For all tests, a P value of less than 0.05 was considered statistically significant.

Results

Participant Demographics

The study population comprised 110 participants, with a mean age of 75.1 ± 9.4 years (range, 53–95 years). Eight participants were found to have an AMDSC of 0 for both eyes. It was predominantly Caucasian (n = 98 [89.1%]), 55 participants were female, and 56 participants were current or former smokers. The mean eGFR creatinine–cystatin C (eGFR–CrCys) was 70.7 ± 18.2 mL/min/1.73 m^2 (median, 73.6 mL/min/1.73 m^2; range, 19.3–109.8 mL/min/1.73 m^2). Ninety-five participants had an eGFR–CrCys of less than 90 mL/min/1.73 m^2 and 36 participants had an eGFR–CrCys of less than 60 mL/min/1.73 m^2. The demographics of participants with varying AMD characteristics can be found in Table 1. The AMDSCs in this group of participants ranged from 0 to 11.

In this study population, creatinine-based eGFR values were on average higher (mean, 74.25 ± 16.85 mL/min/1.73 m^2) and had a higher median (76.50 mL/min/1.73 m^2) than those estimated from the other two equations (Fig. 1). Estimating eGFR using only serum cystatin C values resulted in, on average, the lowest eGFR values (mean, 66.04 ± 19.84 mL/min/1.73 m^2; median, 67.00 mL/min/1.73 m^2). The values obtained from eGFR as determined by a combination of a participant's creatinine and cystatin C values (mean, 74.25 ± 16.85 mL/min/1.73 m^2; median,

Table 1. Number, Age, and eGFR in Participants Exhibiting Different AMD Characteristics

	N (Count)	Mean Age (Years)	Median eGFR Creatinine–Cystatin C [25th Percentile, 75th Percentile] (mL/min/1.73 m^2)	No. of eGFR Creatinine–Cystatin C < 60 (mL/min/1.73 m^2)		Median eGFR Creatinine–Cystatin C [25th Percentile, 75th Percentile] < 60 (mL/min/1.73 m^2)
				N	%	
SDD	18	81.1	60.02 [48.25, 68.99]	9	50.0	46.62 [44.71, 53.77]
GA	14	76.3	68.45 [55.89, 76.40]	4	28.6	49.53 [44.81, 53.24]
cRORA	18	75.6	70.20 [60.79, 76.74]	4	22.2	49.53 [44.81, 53.24]
CNV	20	78.2	62.08 [53.26, 75.75]	9	45.0	53.14 [44.74, 54.43]
Large drusen	89	74.9	73.44 [58.82, 84.35]	24	27.0	51.98 [46.42, 54.31]
HRF	32	76.7	64.81 [54.39, 74.29]	11	34.4	50.61 [46.57, 54.35]
Pigment	58	74.9	71.48 [54.93, 81.87]	17	29.3	50.03 [44.71, 53.30]
No features	14	75.3	75.28 [57.93, 81.70]	5	35.7	53.71 [39.29, 57.53]

cRORA, complete retinal pigment epithelium and outer retinal atrophy.

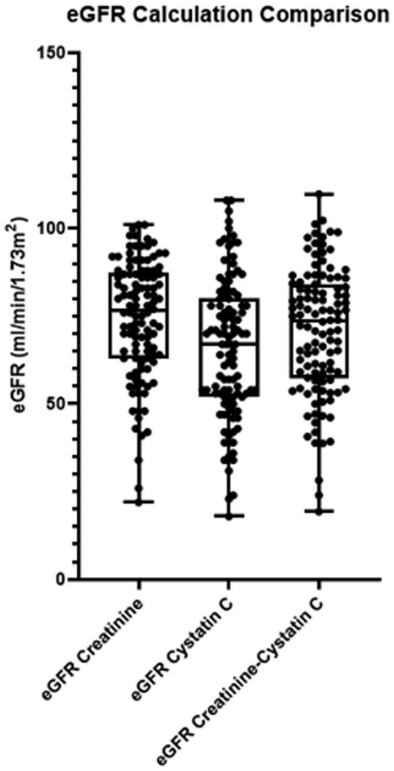

Figure 1. eGFR calculation comparison.

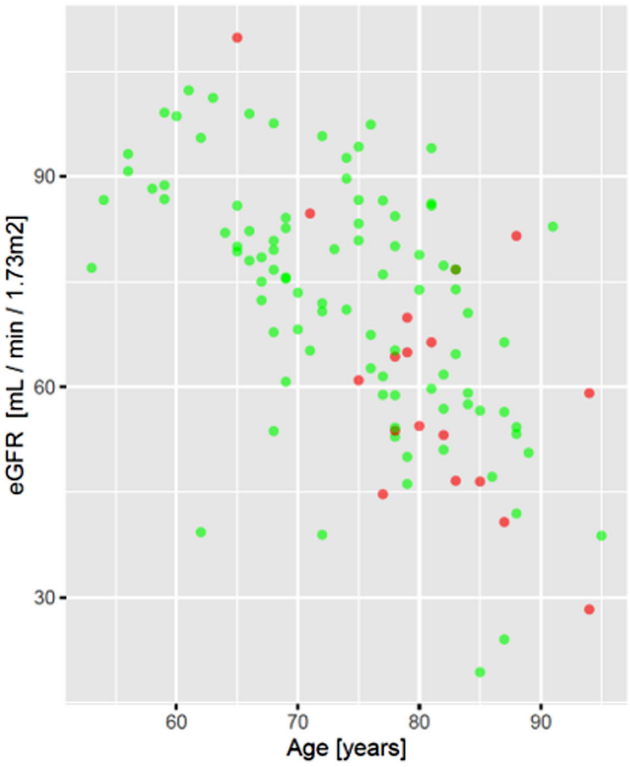

Figure 2. Association of eGFR–CrCys and age. One circle represents one eye, red circles represent eyes with SDD. R^2/R^2 adjusted: 0.359/0.353. $P < 0.001$.

73.65 mL/min/1.73 m^2) fell in between the eGFR values determined from either serum marker alone.

Univariate and Multivariate Analyses of AMD Features and Renal Function

It has been well-established that age has a significant impact on kidney function. In our participants, age exhibited a negative, strong association with eGFR–CrCys calculations (estimate, −1.16 units/year; 95% CI, −1.46 to −0.87; $P < 0.001$) (Fig. 2, Table 2).

The association of individual AMD characteristics (large drusen, SDD, pigment, HRF, choroidal neovascularization (CNV), GA, AMDSC) with renal function is shown in Table 2. In these univariate analyses, statistical significance was found for the association between

Table 2. Univariate Analyses of AMD Features for eGFR–CrCys as a Continuous Variable

	eGFR Creatinine–Cystatin C	
AMD Characteristic	Parameter Estimate (95% CI)	*P* Value
Age (n = 110)	−1.16 (−1.46 to −0.87)	<0.001
Male sex (n = 110)	−3.90 (−10.78 to 2.98)	0.264
Large drusen (n = 89)	3.28 (−5.50 to 12.06)	0.460
SDD (n = 18)	−11.12 (−20.23 to −2.01)	0.017
Pigment (n = 58)	−2.09 (−9.01 to 4.83)	0.551
HRF (n = 32)	−7.97 (−15.44 to −0.51)	0.037
CNV (n = 20)	−6.79 (−15.66 to 2.09)	0.133
GA (n = 14)	−4.91 (−15.25 to 5.43)	0.349
AMDSC (n = 110)	−0.83 (−1.81 to 0.15)	0.095
Mean central RPEDC thickness (n = 110)	−0.04 (−0.22 to 0.14)	0.660
Total RPEDC volume (n = 110)	6.77 (−17.45 to 30.98)	0.581
Mean central NSR thickness (n = 110)	0.02 (−0.07 to 0.12)	0.655
Total NSR volume (n = 110)	9.58 (2.85 to 16.30)	0.006
Choroidal thickness (n = 110)	0.03 (−0.01 to 0.07)	0.149
Rod intercept time (n = 110)	−0.54 (−0.81 to −0.27)	<0.001

Table 3. Age-Corrected Analyses of AMD Features With eGFR–CrCys as a Continuous Variable

	eGFR Creatinine–Cystatin C	
AMD Characteristic	Parameter Estimate (95% CI)	*P* Value
Age (n = 110)	−1.16 (−1.46 to −0.87)	<0.001
Large drusen (n = 89)	2.15 (−4.93 to 9.22)	0.549
SDD (n = 18)	−3.04 (−10.87 to 4.78)	0.442
Pigment (n = 58)	−2.42 (−7.97 to 3.14)	0.391
HRF (n = 32)	−5.38 (−11.46 to 0.70)	0.082
CNV (n = 20)	−2.39 (−9.69 to 4.90)	0.517
GA (n = 14)	−3.29 (−11.63 to 5.05)	0.436
AMDSC (n = 110)	−0.77 (−1.56 to 0.01)	0.054
Mean central RPEDC thickness (n = 110)	−0.02 (−0.16 to 0.12)	0.762
Total RPEDC volume (n = 110)	10.02 (−8.69 to 28.72)	0.291
Mean central NSR thickness (n = 110)	0.01 (−0.06 to 0.08)	0.788
Total NSR volume (n = 110)	3.00 (−2.62 to 8.63)	0.292
Choroidal thickness (n = 110)	−0.02 (−0.05 to 0.01)	0.231
Rod intercept time (n = 110)	−0.22 (−0.47 to 0.03)	0.079

eGFR–CrCys and both the presence of SDD ($P = 0.017$) (Fig. 2) and HRF ($P = 0.037$). Figure 2 demonstrates that SDD participants are overall older than the general group of participants, but do not show a markedly decreased eGFR–CrCys compared with age-similar participants without SDD. The association between AMDSC and eGFR–CrCys as a continuous variable demonstrated borderline statistical significance toward worse renal function in significant effect of AMDSC stages (parameter estimate, −0.77; $P = 0.054$). Similarly, univariate analyses assessing RIT and OCT measurements (choroidal thickness, mean central RPEDC volume, total RPEDC volume, mean central NSR volume, and total NSR volume) as continuous variables, found RIT (estimate, −0.54 units/minute; 95% CI, −0.81 to −0.27; $P < 0.001$) and total NSR volume (estimate, 9.58 units/minute; 95% CI, 2.85–16.30; $P = 0.006$) to be significantly correlated with decreased renal function (Table 2). However, after adjustment for age, no association was found with decreased renal function for any of the AMD features (Table 3). This was also the case when eGFR–CrCys

was assessed as a categorical variable with four groups (>90, 60–90, 30–60, and <30). This finding implies a colinearity of AMD features with age, rather than a true effect of AMD parameters.

As additional evidence for this variable selection, we also conducted least absolute shrinkage and selection operator regression. This process also confirmed age as the only parameter to best model predicted eGFR–CrCys values. To detect potential complex associations, random forest regression was applied, but did not detect any interaction terms.

Discussion

In these participants aged 50 years and older, with and without AMD, we found no multivariate associations between AMD phenotypes and renal function. Univariate associations between eGFR–CrCys and various AMD phenotypes such as SDD, HRF, total NSR volume, and RIT were discovered; however, they were not found to be statistically significant with age correction, and age was the only factor strongly correlated with renal function. Although there have been several studies that have looked at potential associations between AMD and renal function using creatinine-derived and cystatin C-derived equations,[3,4,6,29] to our knowledge, this investigation is the first using an eGFR model with both creatinine and cystatin C serum values to analyze renal function in the setting of various AMD phenotypes. In addition, our statistical models adjusted for age and included several different AMD variables. Our findings highlight the main contributory factor of age in both conditions, as shown by our multivariable analysis.

There have been several reports in the literature investigating the potential increased risk of AMD in patients with CKD.[3–5,8] CKD and AMD share overlapping risk factors such as smoking status and history, hypertension, diabetes, and obesity,[30] which suggests that the causative pathogenesis of these factors may play a role in disease development. A population-based study in Taiwan investigated the association of mild to moderate CKD in patients over 18 years of age and control patients without CKD using ICD-9 codes finding an increased risk of macular degeneration in patients with CKD.[8] Other studies investigating the relationship of specific AMD phenotypes and renal function have found GA, SDD, and choroidal thickness each to be correlated with CKD.[6,31–33] In a study of 107 participants with AMD, Leisy et al.[31] investigated the association between presence of GA and GFR and found that, although a lower GFR was statistically significantly associated with presence of GA even after controlling for age, gender, smoking, and other risk factors, the area of GA as a continuous variable was not statistically significantly associated with a decreased GFR.[32] In another study of 107 participants with a range of AMD, patients with a GFR of less than 60 units were more likely to have thinner choroidal measures.[31] In addition, in a study of Korean individuals, the presence of peripheral SDD was found to be more likely in the presence of CKD.[6]

Despite previous studies suggesting an association between AMD features, such as the presence of GA and choroidal thickness, and decreased renal function,[31,32] this study did not find any association with these features. The disappearance of significant associations between renal dysfunction and all AMD characteristics, after adjustment for age, in this study highlights the key role that age plays in the development of both diseases. Some previous studies demonstrating significant univariate relationships between AMD phenotypes and CKD did not conduct multivariable analysis on their data.[4] Those that did demonstrated variable results, with some studies maintaining significance with the transition to multivariable analyses[6,31] and others experiencing loss of significance when correcting for age and other factors. For example, choroidal thinning was found to be significantly correlated with a decreased GFR, but this association did not hold after age correction.[32] Another study focusing on visual impairment in patients with CKD found that there was no significance between CKD and AMD when multiple factor-corrected multivariable analyses were performed.[34] However, some other studies reported maintained significance even after correcting for multiple confounders including age, hypertension, and diabetes. The variable results can also depend on the population being studied and the definitions and rigor by which the AMD diagnosis and phenotypes were assessed, as well as the sample size of the respective study group.

Most commonly, the GFR is estimated using only serum creatinine values. However, such estimates are highly variable, depending on a person's state of illness, as well as muscle mass and diet.[27] Cystatin C, a nonglycosylated protein filtered from the blood through the glomerulus, has been used as an alternative to serum creatinine for estimating the GFR. Levels of cystatin C do not change with inflammatory conditions or metabolic disorders, and cystatin C has less dependency on diet and muscle mass.[35] In addition, it is more strongly associated with all-cause mortality and cardiovascular events.[35] However, there seem to be some unknown determinants that influence cystatin C,

such that the estimate remains imperfect.[27,28] There is some evidence that a combined creatinine–cystatin C estimating equation allows for the most precise and accurate estimate of the GFR.[27,28]

It is important to note that most other studies measured the eGFR using serum creatinine, whereas our study investigated renal function using eGFR calculations based on serum creatinine and serum cystatin C. Although there have been studies investigating which eGFR estimating equation (serum creatinine only, serum cystatin C only, and creatinine and cystatin C combined) is the most accurate measure of renal function, there is no consensus in the literature with regard to which eGFR estimating equation should be used in a given population. The combined creatinine–cystatin C equation has been found to have better accuracy in measuring GFR in the elderly than either biomarker's equation alone and has the best performance in confirming CKD[28,36] and the most consistent.[37] We, therefore, compared measurements from each of the three eGFR calculation in our population to better understand how they compare with one another in our participants (Fig. 1).

Upon examining the different estimating equations of eGFR, we found that eGFR–CrCys values fell largely between the eGFR estimates obtained with creatinine or cystatin C alone (Fig. 1). Our results suggest that we could identify fewer participants with decreased renal function when using the creatinine-based eGFR values and a higher number of participants with reduced renal function when using the eGFR using only serum cystatin C values equation (Fig. 1). We find this to be true in our study population, as the percentage that met the criteria for decreased renal dysfunction, defined as an eGFR of less than 60 mL/min/1.73 m^2, varied widely depending on which eGFR estimating equations was used (creatinine-based eGFR values 19.1%, eGFR using only serum cystatin C values 40.9%, eGFR–CrCys 30.0%). Because creatinine as a serum marker is highly influenced by the person's muscle mass, diet, and chronic illnesses, it is not surprising that, in our population, the eGFR measured by creatinine alone would estimate a higher eGFR than a measure that does not depend on a factor influenced by age and muscle mass. Previous studies have demonstrated the overestimation of eGFR using creatinine-only estimating equations, and the underestimation of cystatin-only equations, similar to what we find in our participants.[38] More recently, new equations have been developed that can be used across the full age spectrum using the different serum markers,[39,40] and further evaluation using these equations may prove to be useful in future risk assessments for renal dysfunction and CKD.

The strength of this study is the well-phenotyped AMD cohort that included rigorous reading center gradings. However, it is also limited by its cross-sectional approach, reliance on human grading of retinal features, and binary evaluation of some AMD features. This cross-sectional study allowed for the investigation of AMD features with measurements of eGFR at the same timepoint. Future longitudinal studies of renal function measurements with retina imaging may allow for insight into the progression of both conditions and their associations with each other over time. A high number of phenotypic characteristics were tested in the multivariable models, which might be a putative limitation in finding weak associations. Also, univariate analyses did not have a Bonferroni-adjusted *P* value. Additionally, although smoking status was assessed for our participants, other risk factors such as hypertension, hyperlipidemia, diabetes, and other etiologies of renal disease can expound upon the above analysis. Future interdisciplinary studies should focus on the longitudinal collection of renal data alongside quantifiable AMD phenotype variables while also accounting for all known participant specific risk factors. Overall, this cross-sectional study finds no association between AMD features and renal function after correction for age.

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