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Kidney function, albuminuria and age-related macular degeneration in NHANES III

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Abstract

Background. Age-related macular degeneration (AMD) and kidney disease may have shared risk factors, including cardiovascular disease risk factors; additionally AMD and dense deposit disease share a common causal link, with both associated with polymorphisms in the complement pathway. Accordingly, we explored a population-based cohort of US adults to examine if markers of kidney disease identify a higher risk population for prevalent AMD.

Methods. A cross-sectional nested case–control study matching on age, sex and race was performed using data on adult participants in the Third National Health and Nutrition Examination Survey. Predictor variables included urine albumin-to-creatinine ratio and estimated glomerular filtration rate (eGFR). Study outcomes included late AMD, defined as neovascular disease or geographic atrophy (5:1 matching), and a composite of both early AMD, defined as soft drusen or pigment irregularities with or without any drusen, and late AMD (1:1 matching).

Results. There were 51 participants with late AMD and 865 with any AMD. In conditional logistic regression adjusting for diabetes, hypertension and total cholesterol, lower eGFR was independently associated with late AMD [odds ratio (OR) = 3.05, 95% confidence interval (CI): 1.51–6.13], while albuminuria was not significant. For any AMD, neither albuminuria nor eGFR were significant in adjusted models. In sensitivity analyses excluding diabetics, albuminuria was associated with any AMD (OR = 1.56, 95% CI: 1.11–1.29 and 1.57, 95% CI: 0.61–3.69 for micro- and macroalbuminuria, respectively, P = 0.03).

Conclusions. Late AMD is more common among individuals with reduced kidney function. Whether this association reflects a common causal pathway or shared risk factors such as hypertension requires additional investigation.

Keywords: age-related macular degeneration; albuminuria; chronic kidney disease; dense deposit disease; glomerular filtration rate

Introduction

Age-related macular degeneration (AMD) is a common disease in older adults and may have shared risk factors with chronic kidney disease (CKD), including associations

with cardiovascular disease. It also has shared causal pathways with several diseases affecting the kidney, including dense deposit disease (also referred to as Type II membranoproliferative glomerulonephritis) and atypical hemolytic uremic syndrome (aHUS) [1–3]. AMD is a degenerative disease of the macula marked by drusen deposition; these are similar to the deposits seen in dense deposit disease. Many polymorphisms in the Factor H gene are associated with AMD and its progression [4, 5], and several of these polymorphisms have been noted in cases of dense deposit disease, often in conjunction with other polymorphisms affecting the alternative pathway of complement activation [1, 6–8]. Despite similar genetics, these conditions are distinct pathological entities, indicating the existence of a peculiar genotype–phenotype relationship. Notably, AMD and dense deposit disease have pathological similarities, namely accumulation of complement-containing debris within the eye and kidney, respectively. Not surprisingly, AMD-like pathology is often present in individuals with dense deposit disease [9].

AMD can be classified as early or late, with these strata often representing disparate disease states. Early AMD consists of drusen and pigment irregularities, but many early cases do not progress to the advanced form. Late AMD is far less frequent but most visually significant. Previously identified risk factors including smoking, obesity and genetic factors, are more strongly associated with late AMD [10], although there is also substantial overlap between cardiovascular disease risk factors and both early and late AMD, potentially implying that impairment of the choroidal circulation may be involved in the pathogenesis of the disease [11].

Perhaps reflecting either a shared genetic predisposition or an association with cardiovascular disease risk factors, recent literature has identified an association between AMD and reduced kidney function in large cohort studies [12, 13], while a large case–control study using administrative data describes an association between diabetic nephropathy (independent of diabetes) and a chart-based study of British elders reported an association between dipstick proteinuria and AMD in men but not in women [14, 15]. Given that most chronic kidney diseases initially manifest with small amounts of albumin in the urine, we explored the relationship of albuminuria and glomerular filtration rate (GFR) with AMD in a generalizable cohort of US adults.

Materials and methods

Study population

The Third National Health and Nutrition Examination Survey (NHANES III) is a national survey of non-institutionalized US residents using a complex, multistage clustered sampling design to achieve generalizability to the US population. NHANES III was conducted between 1988 and 1994. Fundus photography was limited to NHANES III participants aged 40 years and older ($n = 14\,464$). Of these, 8603 (59.5%) had bilateral fundus photography at the time of the complete examination [16].

Demographic and clinical characteristics

Standardized questionnaires were administered in the home, followed by a detailed physical examination and serum collection at an NHANES mobile examination center. Participants self-selected the racial category that best described them from non-Hispanic white, non-Hispanic black, Mexican American or other. Race for these analyses is dichotomized as black or non-black. Participants were considered to have diabetes mellitus if they reported ever having been told by a doctor that they had diabetes or 'sugar diabetes' other than during pregnancy or they reported taking insulin or a 'diabetes pill' at the time of the questionnaire. Participants were classified as hypertensive if their mean (of up to six readings on two separate occasions) blood pressure was $\geq$140 mmHg systolic, $\geq$90 mmHg diastolic or were prescribed antihypertensive medications. History of cardiovascular disease was defined by participant-identified history of stroke, myocardial infarction or heart failure. C-reactive protein (CRP) in NHANES was not measured using a high-sensitivity assay; accordingly, the lower level of detection was 0.3 mg/L and values below this threshold are coded as having a CRP level of 0.21 mg/dL.

Kidney data

Serum creatinine measurements were performed at a central laboratory using a modified kinetic Jaffe assay on a Hitachi 737 analyzer (Boehringer Mannheim Corp., Indianapolis, IN). In a sample of 1921 participants who had a repeated creatinine measurement at a mean of 17 days apart, the percentage of difference between the two measurements was $0.2 \pm 9.7\%$. GFR was estimated with the CKD-epidemiology collaboration equation using serum creatinine measurements recalibrated to the Cleveland Clinic laboratory [17–19].

A random spot urine sample was obtained from each participant using a clean-catch technique and sterile containers, and the sample was analyzed on frozen non-hematuric specimens. Urine albumin concentration was measured by solid-phase fluorescent immunoassay. Interassay coefficients of variation for low (1.0 mg/L) and medium (15 mg/L) urine albumin quality control standards were 16 and 10%, respectively. Urine creatinine concentration was measured by means of the modified kinetic rate Jaffe method using a Beckman Synchron AS/ASTRA analyzer (Beckman Instruments Inc., Brea, CA). Microalbuminuria was defined by a urine albumin-to-urine creatinine ratio (ACR) of 30–300 mg/g and macroalbuminuria by ACR >300 mg/g.

Fundus evaluation

Procedures for fundus evaluation have been described previously [16]. Briefly, the retina of a non-pharmacologically dilated eye was photographed, with the field centered horizontally and vertically on a point midway between the temporal edge of the optic disc and the fovea. Images were evaluated at the University of Wisconsin by two experienced graders, masked to subject information. The presence of any drusen, soft drusen, retinal pigment epithelial (RPE) depigmentation, increased retinal pigment, geographic atrophy and signs of exudative macular degeneration were assessed. Early AMD was defined as the presence of either soft drusen ($\geq$63 μm, consistent with Grade 3 drusen in the Wisconsin Age-related Maculopathy Grading System [20]) or any drusen type with areas of depigmentation or hypopigmentation of the retinal pigment epithelium without any visibility of choroidal vessels or with increased retinal pigment in the macular area. Late AMD was defined as the presence of signs of exudative macular degeneration or geographic atrophy (sharply delineated roughly round or oval area of apparent absence of the RPE in which choroidal vessels are more visible than in surrounding areas). Kappa scores for intergrader and intragrader reliability ranged from 0.62 to 0.83 for AMD [16].

Statistical analysis

Albuminuria is highly prevalent in the general population and has multiple common associates, including older age, diabetes and hypertension. Reflecting the competing causes of microalbuminuria whereby these medical comorbid conditions are more likely to be associated with microalbuminuria than AMD, we elected to use nested case–control methodology with variable control optimal matching [21]. Prior to matching, individuals with and without AMD were compared using analysis of variance and Wald chi-square tests. To obtain a matched cohort for individuals with late AMD, we performed variable control optimal matching with exact matching on sex, race and age (within 1 year) to obtain five controls without AMD for each case. To obtain a matched cohort for individuals with either early or late AMD, we again performed variable control optimal matching with exact matching on sex, race and age (within 2 years) in order to obtain one control for each case. We performed univariate conditional logistic regression on the matched case–control data to assess differences.

Table 1. Baseline characteristics of participants in NHANES III who underwent fundoscopy[a]

	No AMD, $N = 6802$	Early AMD, $N = 814$	Late AMD, $N = 51$	Total, $N = 7667$	P-value
Demographics					
Age	58.1 ± 12.7	68.2 ± 12.7	79.4 ± 7.6	59.3 ± 13.1	<0.0001
Female sex	51.2	57.5	47.1	51.8	0.002
African American	24.9	19.0	5.9	24.1	<0.0001
Medical history					
Diabetes	13.6	12.3	11.8	13.5	0.53
CVD	11.2	16.9	29.4	11.9	<0.0001
Hypertension	43.5	58.7	78.0	45.4	<0.0001
Smoking					
Current	23.3	18.4	9.8	22.7	<0.0001
Past	33.3	31.6	39.2	33.2	
Never	43.4	50.0	51.0	44.1	
Clinical variables					
Systolic BP	132.2 ± 19.9	139.6 ± 20.4	143.1 18.6	133.0 ± 20.1	<0.0001
Diastolic BP	76.7 ± 10.3	75.0 ± 10.9	74.0 ± 7.7	76.5 ± 10.3	<0.0001
BMI	27.8 ± 5.6	27.2 ± 5.5	26.4 ± 4.7	27.7 ± 5.6	0.004
BMI category					
<18.5	1.5	2.0	2.0	1.6	0.54
18.5–24.9	30.7	33.8	33.3	31.0	
25–29.9	39.0	37.0	43.1	38.8	
≥30	28.8	27.3	21.6	28.6	
Laboratory results					
ACR, mg/g	6.9 (3.9–15.0)	9.3 (4.9–23.1)	12.6 (5.7–35.4)	7.1 (4.0–15.90)	<0.0001
ACR category, mg/g					<0.0001
<30	86.1	80.8	72.6	85.4	
30–300	11.4	15.6	25.5	11.9	
>300	2.5	3.6	2.0	2.7	
eGFR, mL/min/1.73m^2	89.1 ± 20.1	79.8 ± 19.9	62.8 ± 17.8	87.9 ± 20.3	<0.0001
eGFR <60, mL/min/1.73m^2	8.5	17.9	52.9	9.8	<0.0001
Total cholesterol	217.6 ± 43.8	219.1 ± 45.4	224.7 ± 39.2	217.8 ± 43.9	0.34
Triglycerides	164.0 ± 135.2	154.1 ± 104.2	164.3 ± 78.0	162.9 ± 131.9	0.13
LDL cholesterol	135.8 ± 38.3	137.1 ± 40.4	139.1 ± 39.4	135.9 ± 38.5	0.57
HDL cholesterol	50.7 ± 16.0	52.6 ± 17.9	53.0 ± 20.2	50.9 ± 16.2	0.005
WBC count	7.1 ± 0.9	7.4 ± 3.6	7.2 ± 2.4	7.1 ± 2.4	0.02
CRP <0.3 mg/dL	61.5	57.4	56.9	61.0	0.16
Median CRP	0.7 (0.4–1.1)	0.7 (0.4–1.1)	0.6 (0.4–0.8)	0.7 (0.4–1.1)	0.08

[a]All values are mean ± SD or %. BMI, body mass index in kg/m^2 BP, blood pressure in mmHg; CVD, cardiovascular disease; HDL, high-density lipoprotein cholesterol; LDL, low-density cholesterol. Cholesterol and CRP levels are in mg/dL. Median CRP levels are reported for ≥0.3 mg/dL only. Median and 25th–75th percentile are reported for ACR and CRP, with P-values calculated using a Wilcoxon sum-rank test.

Multivariable analyses further adjusted for variables with $P < 0.10$ in univariate models. Candidate variables included those described in Table 1. Due to the strong association with microalbuminuria and kidney disease, diabetes was included in all multivariable models. Sensitivity analyses were performed that excluded individuals with diabetes; these analyses were otherwise identical to those described above with the exception that we obtained only four controls for each late AMD case. All analyses were performed using SAS version 9.2 (Cary, NC).

Results

Among 8603 NHANES III participants with fundus photography, 8208 were gradable as none, early or late AMD. After excluding participants missing data on serum creatinine or urine albumin, there were 7667 participants: 6802 (88.7%) had no evidence of AMD, 814 (10.6%) were classified as early AMD and 51 (0.7%) as late AMD (Table 1).

Late AMD

As the youngest NHANES participant diagnosed with late AMD was 59 years old, we limited the control population to NHANES III participants aged 59 years or older, resulting in 3227 available controls. Table 2 presents the results of 5:1 matching. Cases and controls were similar in baseline characteristics, although individuals with late AMD were more likely to have a history of hypertension (78.0 versus 60.0%, $P = 0.02$) and lower estimated glomerular filtration rate (eGFR) (62.8 ± 17.8 versus 68.7 ± 17.6 mL/min/1.73m^2, $P = 0.03$). The ACR did not differ between groups [median (interquartile range) 12.6 (5.7–35.4) versus 12.1 (6.8–27.6) mg/g, $P = 0.90$]. In univariate conditional logistic regression models, history of hypertension [odds ratio (OR) = 2.24, 95% confidence interval (CI): 1.11–4.51, $P = 0.02$] and eGFR below 60 mL/min/1.73m^2 (OR = 3.22, 95% CI: 1.63–6.40, $P = 0.001$) were associated with the presence of late AMD, while there was no association of microalbuminuria ($P = 0.60$) or log-transformed ACR ($P = 0.93$) with late AMD. There was a borderline association between higher total cholesterol level and late AMD [OR = 1.31, 95% CI: 0.97–1.77, $P = 0.08$ for each SD (41.8 mg/dL) increase]. In multivariable analyses, the association between eGFR and late AMD remained significant after adjusting for history of diabetes, history of hypertension and cholesterol level

Table 2. Baseline characteristics of individuals with late AMD and matched controls (sex, race and age) with no evidence of AMD[a]

	Late AMD, $N = 51$	Controls, $N = 255$	P-value
Demographics			
Age	79.4 ± 7.6	79.3 ± 7.6	0.97
Female sex	47.1	47.1	1.0
African American	5.9	5.9	1.0
Medical history			
Diabetes	11.8	16.1	0.44
CVD	29.4	23.2	0.35
Hypertension	78.0	60.0	0.02
Smoking			
Current	9.8	9.0	0.85
Past	39.2	43.5	
Never	51.0	47.5	
Clinical variables			
Systolic BP	143.1 ± 18.6	142.1 ± 22.6	0.77
Diastolic BP	74.0 ± 7.7	72.2 ± 10.4	0.25
BMI	26.4 ± 4.7	25.7 ± 4.2	0.31
BMI category			
<18.5	2.0	3.9	0.41
18.5–24.9	33.3	41.2	
25–29.9	43.1	39.2	
BMI ≥30	21.6	15.7	
Laboratory results			
ACR, mg/g	12.6 (5.7–35.4)	12.1 (6.8–27.6)	0.90
ACR category, mg/g			
<30	72.6	76.1	0.77
30–300	25.5	21.2	
>300	2.0	2.8	
eGFR, mL/min/1.73m^2	62.8 ± 17.8	68.7 ± 17.6	0. 03
eGFR <60, mL/min/1.73m^2	52.9	29.4	0.001
Total cholesterol	224.7 ± 39.2	213.8 ± 42.2	0.09
Triglycerides	164.3 ± 78.0	147.3 ± 86.9	0.20
LDL cholesterol	139.1 ± 39.4	134.5 ± 37.4	0.44
HDL cholesterol	53.0 ± 20.2	50.8 ± 15.7	0.38
WBC count	7.2 ± 2.4	7.3 ± 2.2	0.89
CRP <0.3 mg/dL	56.9	63.9	0.43
Median CRP	0.6 (0.4–0.8)	0.7 (0.4–1.2)	0.74

[a]All variables as mean ± SD or %, except ACR and CRP which are reported as median (25th–75th percentile). BMI, body mass index in kg/m^2; BP, blood pressure (in mmHg); CVD, cardiovascular disease; LDL, low-density cholesterol; HDL, high-density lipoprotein cholesterol, lipids as mg/dL and CRP as mg/dL. Median CRP levels are reported for ≥0.3 mg/dL only. Median and 25th–75th percentile are reported for ACR and CRP, with P-values calculated using a Wilcoxon sum-rank test.

(Table 3). ACR remained non-significant in multivariable models and is not presented in Table 3.

Composite of early and late AMD

From 6802 individuals without AMD, 865 controls were selected for the matched cohort (Table 4). Similar to late AMD analyses, individuals with any AMD were more likely to have hypertension than controls (59.8 versus 53.7%, P = 0.01). Of controls, 16.0% had micro- or macroalbuminuria, while 19.7% of cases had micro- or macroalbuminuria (P = 0.05). Median ACR did not significantly differ between individuals with any AMD versus controls [9.5 (4.9–23.4) versus 8.7 (5.0–18.3) mg/g, P = 0.16]. There was no difference in eGFR or the proportion of individuals with eGFR below 60 mL/min/1.73m^2 between groups. In univariate conditional logistic regression models, history of hypertension (OR = 1.32, 95% CI: 1.08–1.62, P = 0.007), presence of micro- or macroalbuminuria (OR = 1.21, 95% CI: 0.93–1.58 and OR = 2.10, 95% CI: 1.10–4.00, respectively, overall P = 0.02) and higher systolic and diastolic blood pressure levels were all associated with the presence of AMD (OR = 1.14, 95% CI: 1.03–1.27 and OR = 1.13, 95% CI: 1.03–1.25 per SD rise, respectively). Diabetes was associated with a 35% decrease in the likelihood of AMD (OR = 0.65, 95% CI: 0.49–0.86), while the relationship between eGFR below 60 mL/min/1.73m^2 and AMD was non-significant (OR = 1.18, 95% CI: 0.90–1.54). BMI of 30 kg/m^2 or higher was also associated with AMD (OR = 1.36, 95% CI: 1.05–1.75 versus a reference group of 18.5–24.9 kg/m^2). Inflammatory markers were also associated with the presence of AMD, with an 11% increased risk of AMD with each doubling of CRP (OR = 1.11, 95% CI: 1.02–1.21) and an 18% increase with each SD rise in the white blood cell (WBC) count (OR = 1.18, 95% CI: 1.05–1.34). In multivariable analyses, the association between ACR and AMD was in the positive direction but was not significant. Hypertension, obesity and higher WBC count were associated with a higher prevalence of AMD (Table 5). As WBC count and CRP were collinear and WBC count was a more powerful predictor, and CRP was not included in the multivariable model. There was no significant association between eGFR and composite AMD. Univariate and multivariable models examining the 814 individuals with early AMD in a 1:1 match are similar to those evaluating the composite of early and late AMD discussed above.

Table 3. Results of multivariable conditional logistic regression models for late AMD[a]

	OR	95% CI	P-value
eGFR <60, mL/min/1.73m^2	3.05	1.51–6.13	0.002
Diabetes	0.58	0.21–1.55	0.28
Hypertension	2.14	1.04–4.43	0.04
Total cholesterol	1.23	0.89–1.70	0.22

[a]Groups are matched on age, sex and race. OR associated with total cholesterol is per each SD (41.8 mg/dL) increase. The model only includes covariates listed in the table. Hypertension is defined by mean blood pressure of ≥140 mmHg systolic, ≥90 mmHg diastolic or antihypertensive medication use.

Sensitivity analyses: individuals without diabetes

There were 45 individuals with late AMD matched with 180 controls without AMD. Baseline data only differed significantly for eGFR (61.4 ± 16.6 versus 67.8 ± 16.2 mL/min/1.73m^2 for late AMD and non-AMD, respectively, P = 0.02) and the number of individuals with eGFR below 60 mL/min/1.73m^2 (55.6 versus 31.1%, respectively, P = 0.002). In models adjusting for hypertension and triglyceride level, eGFR below 60 mL/min/1.73m^2 was associated with a similar increase in the likelihood of late AMD to that seen in models including individuals with diabetes (OR = 2.80, 95% CI: 1.25–6.30, P = 0.01). There was no association between ACR and late AMD (data not shown).

There were 759 individuals without diabetes with either early or late AMD; these individuals were matched with

Table 4. Characteristics of individuals with early or late AMD and matched controls (sex, race and age) with no evidence of AMD[a]

	Any AMD, $N = 865$	Controls, $N = 865$	P-value
Demographics			
Age	68.9 ± 12.7	68.8 ± 12.6	0.92
Female sex	56.9	56.9	1.0
African American	18.3	18.3	1.0
Medical history			
Diabetes	12.3	17.3	0.003
CVD	17.6	17.3	0.86
Hypertension	59.8	53.7	0.01
Smoking			
Current	17.9	16.9	0.58
Past	32.0	34.3	
Never	50.1	48.8	
Clinical variables			
Systolic BP	139.8 ± 20.3	137.6 ± 21.0	0.03
Diastolic BP	75.0 ± 10.7	73.8 ± 10.0	0.02
BMI	27.2 ± 5.5	26.8 ± 5.0	0.17
BMI category			
<18.5	2.0	2.4	0.01
18.5–24.9	33.8	34.7	
25–29.9	37.3	42.4	
≥30	26.9	20.5	
Laboratory results			
ACR, mg/g	9.5 (4.9–23.4)	8.7 (5.0–18.3)	0.16
ACR category, mg/g			
<30	80.4	84.1	0.05
30–300	16.2	14.1	
>300	3.5	1.9	
eGFR, mL/min/1.73m^2	78.8 ± 20.2	78.9 ± 20.7	0.90
eGFR <60, mL/min/1.73m^2	20.0	17.9	0.27
Total cholesterol	219.4 ± 45.1	221.3 ± 48.1	0.41
Triglycerides	154.7 ± 102.8	160.5 ± 131.2	0.30
LDL cholesterol	137.2 ± 40.3	138.5 ± 39.6	0.51
HDL cholesterol	52.6 ± 17.9	51.6 ± 15.7	0.005
WBC count	7.4 ± 3.5	7.0 ± 2.1	0.005
CRP <0.3 mg/dL	57.3	64.6	0.02
Median CRP	0.7 (0.4–1.1)	0.7 (0.4–1.0)	0.82

[a]All variables as mean ± SD or %, except ACR and CRP which are reported as median (25th–75th percentile). BMI, body mass index in kg/m^2; BP, blood pressure (in mmHg); CVD, cardiovascular disease; LDL, low-density cholesterol; HDL, high-density lipoprotein cholesterol, lipids as mg/dL and CRP as mg/dL. Median CRP levels are reported for ≥0.3 mg/dL only. Median and 25th–75th percentiles are reported for ACR and CRP, with P-values calculated using a Wilcoxon sum-rank test.

759 individuals without AMD by sex, race and age (within 3 years). Individuals with AMD had a higher prevalence of hypertension (58.1 versus 51.7%, P = 0.002), higher WBC count (7.3 ± 3.7 versus 6.9 ± 2.1, P = 0.01) and were more likely to have micro- or macroalbuminuria (15.3 versus 10.1% and 2.2 versus 1.2%, respectively, P = 0.002). There was no difference in the number of individuals with eGFR below 60 mL/min/1.73m^2 or in eGFR level between groups. In multivariable analyses adjusting for hypertension, obesity and WBC count, the presence of micro- or macroalbuminuria was independently associated with the presence of AMD (OR = 1.56, 95% CI: 1.11–1.29 and OR = 1.57, 95% CI: 0.61–3.69, respectively, P = 0.03).

Discussion

In this nested case–control study of participants in the NHANES III population sample of non-institutionalized US adults, we evaluated the association of albuminuria (an early marker of kidney damage) and eGFR with AMD. Major findings in the current study include (i) individuals with eGFR <60 mL/min/1.73m^2 had a 2.5 times increased risk of late AMD compared to no AMD; (ii) albuminuria was not significantly associated with late AMD; (iii) albuminuria had a borderline association with any AMD that was statistically significant in a sensitivity analysis evaluating individuals without diabetes and (iv) eGFR was not significantly associated with the presence of any AMD, although, in most analyses, hypertension was associated with AMD. Of note, analyses evaluating late AMD were limited by the relatively small number of NHANES III participants with this condition.

Table 5. Results of multivariable conditional logistic regression models for the composite of early and late AMD[a]

	OR	95% CI	P-value
ACR, mg/g			0.12
<30	Reference	—	
30–299	1.17	0.87–1.55	
300+	1.96	0.99–3.90	
Diabetes	0.57	0.42–0.78	0.001
Hypertension	1.29	1.04–1.61	0.02
BMI			
<18.5	0.86	0.44–1.68	
18.5–24.9	Reference	—	0.05
25–29.9	0.92	0.73–1.15	
>30	1.31	1.00–1.73	
WBC count	1.15	1.02–1.30	0.02

[a]Groups are matched on age, sex and race. The model only includes covariates listed in the table. BMI, body mass index in kg/m^2. Hypertension is defined by mean blood pressure of ≥140 mmHg systolic, ≥90 mmHg diastolic or antihypertensive medication use. The OR associated with the WBC count is per SD rise (2.9 K/μL).

Why might kidney disease and AMD be associated with each other? Firstly, CKD and AMD share cardiovascular risk factors, most notably hypertension [22, 23]. Potentially underlying this association is the hypothesis that atherosclerosis of the choroidal circulation may contribute to the development of AMD [11, 24]. Secondly, albuminuria, the most common indicator of kidney damage, is a powerful marker for systemic epithelial burden in the microvasculature of the kidney; critically, microvascular disease involving smaller vessels in retinal circulation, specifically the retinal pigment epithelium in the eye, may be an important contributor [11, 24–26]. Thirdly, recent data suggest a potential shared genetic predisposition for dense deposit diseases of the eyes and of the kidneys that are related to key pathways for complement activation, with variants in complement factor H, complement factor I and complement three genes accounting for a significant proportion of AMD risk [5, 27–30].

The latter relationship between kidney disease and AMD is particularly interesting, given the relationship of polymorphisms both in the complement Factor H gene and elsewhere in the complement pathway with kidney diseases like thrombotic microangiopathy (specifically aHUS) [3, 31] and dense deposit disease [6, 8]. Factor H has three primary functions: (i) it is a cofactor for the serine protease, Factor I, which cleaves C3b; (ii) it prevents amplification

of the alternative complement pathway by subsequent cleavage of additional C3 to C3b by blocking the formation of C3bBb and (iii) it competitively blocks binding of C3b to host cell surfaces and tissue matrices [32]. Relative deficiencies in complement Factor H can result in excessive alternative pathway activation, particularly in times of stress, and promote both thrombotic microangiopathy as well as debris deposition.

Reflecting interest in the genetic links as well as cardiovascular links between kidney disease and AMD, several cohort studies have explored the longitudinal relationship between kidney function and AMD. A *post hoc* analysis of the Australian Blue Mountains Eye Study cohort evaluated 1183 participants aged 54 years and older [13]. The 5-year incidence of early AMD was 3.9% in participants with creatinine clearance $\geq$60 mL/min/1.73m^2 estimated using the Cockroft Gault equation and 17.5% in those with creatinine clearance <60 mL/min/1.73m^2. In multivariable models that included a term for complement factor H *Y402H* genotype (homozygous, heterozygous and noncarrier), persons with reduced kidney function were three times more likely to develop early AMD than those with intact kidney function (OR 3.2, 95% CI, 1.8–5.7, P < 0.0001). Notably, no relationship was seen in the subgroup of individuals aged <65 years old. The other study examined the Beaver Dam cohort in Wisconsin, USA, and noted that mild elevations in serum cystatin C as well as eGFR <60 mL/min/1.73m^2 were associated with incident early AMD but were not associated with incident pure geographic atrophy or progression of AMD [12]. Higher cystatin C was also associated with incident exudative AMD in multivariable analyses in the Beaver Dam Study, although these analyses were limited by the relatively low number of cases (~60).

Our study further explores the cross-sectional relationship between kidney markers and AMD. Interestingly, we did note a relationship between low eGFR and late AMD but no significant relationship with albuminuria. There are several possible explanations for our negative findings for the effect of albuminuria: (i) using a nested case–control design, we were able to effectively match for age, sex and race, perhaps eliminating much of the confounds introduced by these demographic factors; (ii) there is a survival bias such that individuals with systemic vascular disease as indicated by albuminuria do not survive to develop AMD; (iii) the finding that diabetes is associated with a lower likelihood of AMD may obscure this relationship, although it is also possible that this represents ascertainment bias as individuals with diabetic retinopathy are less likely to have gradable fundus photography [16] and (iv) albuminuria and AMD are truly not associated. To more fully explore several of these possibilities, we performed sensitivity analyses excluding individuals with diabetes; results remained similar in these analyses, although the association between albuminuria and the composite of early and late AMD achieved statistical significance, supporting our hypothesis that an ascertainment bias may be introduced with inclusion of individuals with diabetes in the primary analyses.

The current study has several strengths. Most notable is the use of a large broadly generalizable population. Additionally, by using a nested case–control design, we are able to minimize the influence of confounding factors. There are also some weaknesses, most notably the cross-sectional design and the lack of information on specific genes that may impact both kidney function and AMD. Additionally, there are a limited number of individuals with late AMD resulting in difficulty disproving the null hypothesis for several analyses; however, we used a nested case–control design to maximize our ability to explore the association between late AMD and kidney disease in this generalizable cohort.

Conclusions

Our study revealed modest associations between reduced GFR and late AMD as well as a modest association between albuminuria and early or late AMD in individuals without diabetes. Although these results do not strongly support use of kidney markers as tools to identify a high-risk population for prevalent AMD, they do shed light on what is likely a multifactorial disease process with multiple factors affecting disease expression and organ manifestations.

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