

CKD Increases the Risk of Age-Related Macular Degeneration

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ABSTRACT

Age-related macular degeneration is the leading cause of irreversible blindness in the United States and often coexists with chronic kidney disease. Both conditions share common genetic and environmental risk factors. A total of 1183 participants aged 54+ were examined in the population-based, prospective cohort Blue Mountains Eye Study (Australia) to determine if chronic kidney disease increases the risk of age-related macular degeneration. Moderate chronic kidney disease (estimated glomerular filtration rate < 60 ml/min per 1.73 m² based on the Cockcroft-Gault equation) was present in 24% of the population (286 of 1183). The 5-yr incidence of early age-related macular degeneration was 3.9% in participants with no/mild chronic kidney disease (35 of 897) and 17.5% in those with moderate chronic kidney disease (50 of 286). After adjusting for age, sex, cigarette smoking, hypertension, complement factor H polymorphism, and other risk factors, persons with moderate chronic kidney disease were 3 times more likely to develop early age-related macular degeneration than persons with no/mild chronic kidney disease (odds ratio = 3.2; 95% confidence interval, 1.8 to 5.7, *P* < 0.0001). Each SD (14.8 ml/min per 1.73 m²) decrease in Cockcroft-Gault estimated glomerular filtration rate was associated with a doubling of the adjusted risk for early age-related macular degeneration (odds ratio = 2.0; 95% confidence interval, 1.5 to 2.8, *P* < 0.0001). In conclusion, persons with chronic kidney disease have a higher risk of early age-related macular degeneration, suggesting the possibility of shared pathophysiologic mechanisms between the two conditions.

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Chronic kidney disease (CKD) is a relatively common condition whose prevalence rises rapidly with age. CKD is estimated to affect over 50% of older persons in the United States¹ and has important extrarenal systemic consequences, such as cardiovascular, metabolic, and hematologic abnormalities. However, the effects of CKD on the sensory organs, such as the eye, are not well understood.

Age-related macular degeneration (AMD) is another relatively common condition in older persons and is the leading cause of blindness and low vision in the United States.² CKD and AMD may share common risk factors and pathophysiologic mechanisms.³ For example, vascular risk factors, such as

hypertension and cigarette smoking, may increase risk of both conditions.^{4–7} CKD is known to accelerate the progression of atherosclerosis and increase propensity to oxidative stress,⁶ both of which are implicated in AMD pathogenesis.^{8,9} Systemic in-

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flammatory processes may accelerate the course of CKD¹⁰ and contribute to the development of AMD.¹¹ More recent evidence suggests that the two conditions have common susceptibility genes, such as complement factor H (*CFH*),^{12–14} complement C3,^{15,16} and apolipoprotein E (*APOE*).^{17,18} Finally, there are a number of rare inherited syndromes that involve both renal and ocular abnormalities.¹⁹

There have been no studies, however, that have examined if the two conditions are associated independently of age and common risk factors. In particular, there are no prospective studies addressing the clinically relevant question of whether persons with CKD are more likely to develop AMD. The purpose of this report is to describe prospectively the relationship of CKD with incident AMD.

RESULTS

The 1152 participants excluded from analyses did not differ from those included ($n = 1183$) on sex but were older (mean age 67.1 yr *versus* 62.0 yr), more likely to be current smokers (14.9% *versus* 10.8%), have hypertension (68.3% *versus* 57.2%), and higher serum creatinine (1.10 mg/dl *versus* 1.01 mg/dl). The rate of incident early AMD among included (7.2%) and excluded (7.0%) participants was similar.

Persons with moderate CKD were older, less likely to be current smokers, and more likely to have raised blood pressure and fibrinogen levels (Table 1). There were 102 participants with stage I (No CKD, $eGFR_{CG} \geq 90$ ml/min per 1.73 m²), 795 with stage II (mild CKD, $eGFR_{CG}$ 60 to 89 ml/min per 1.73 m²), 280 with stage III (moderate CKD, $eGFR_{CG}$ 30 to 59 ml/min per 1.73 m²), and 6 with stage IV (severe CKD, $eGFR_{CG} < 30$ ml/min per 1.73 m²).

Of the 1183 persons at risk, 85 (7.2%) developed incident early AMD over 5 yr. The 5-yr incidence of early AMD was 1.0%, 4.3%, and 17.5% among participants with no ($n = 102$, 1 case), mild ($n = 795$, 34 cases), and moderate ($n = 286$, 50 cases) CKD, respectively. In further analyses, we combined the categories of no CKD and mild CKD because of the low number of incident AMD cases in those with no CKD.

Table 2 shows that the incidence of early AMD was 3.9% in participants with no/mild CKD *versus* 17.5% in those with moderate CKD. After adjusting for age, sex, and *CFH* Y402H polymorphism, persons with moderate CKD had a 3-fold higher odds of incident early AMD than persons with no/mild CKD (odds ratio [OR] = 3.2; 95% confidence interval [CI], 1.8 to 5.7, $P < 0.0001$). Additional multivariable adjustment in Model 2 did not change these results.

Each SD decrease in $eGFR_{CG}$ was associated with 2-fold (OR = 2.0; CI, 1.5 to 2.8, $P < 0.0001$) higher odds of incident early AMD, with similar associations in noncarriers/heterozygous and homozygous carriers of *CFHY402H* (Table 3). We observed the same association of decreasing kidney function with increasing risk of incident early AMD with $eGFR_{MDRD}$ or serum creatinine (Table 3). After adjustment in Model 2, each SD decrease in $eGFR_{CG}$ was associated with incident pigmentary abnormalities ($n = 160$, OR = 1.4; CI, 1.1 to 1.8), incident indistinct soft or reticular drusen ($n = 69$, OR = 2.4; CI, 1.6 to 3.4) but not with incident distinct soft drusen ($n = 47$, OR = 1.2; CI, 0.8 to 1.7). The adjusted relative risk was 2.7, and the population attributable risk percent of early AMD for moderate CKD was 29%.

Table 4 shows the results of analyses stratified by age. The association of worsening $eGFR_{CG}$ with incident early AMD was present in participants 66 to 75 yr of age and in those 76 to

Table 1. Characteristics of persons with and without moderate chronic kidney disease (CKD)

	Moderate CKD ($eGFR_{CG} < 60$ ml/min/1.73m ²) ($n = 286$)	No or Mild CKD ($eGFR_{CG} \geq 60$ ml/min/1.73m ²) ($n = 897$)	<i>P</i>
Age, yr (SD; range)	69.6 (5.7; 58–94)	59.6 (6.2; 54–84)	<0.0001
Male, %	115 (40.2)	382 (42.6)	0.48
Current smoker, %	22 (7.7)	106 (11.8)	0.04
Hypertension, %	196 (68.5)	480 (53.5)	<0.0001
Diabetes, %	27 (9.4)	91 (10.1)	0.87
Systolic blood pressure, mmHg (SD)	153.2 (20.9)	146.1 (20.1)	<0.0001
Diastolic blood pressure, mmHg (SD)	83.3 (9.5)	85.1 (9.1)	0.005
Fibrinogen, mg/dl (SD)	372 (89)	348 (81)	<0.0001
White cell count, $\times 10^9$ (SD)	6.4 (1.9)	6.3 (1.6)	0.27
Serum total cholesterol, mmol/L (SD)	6.0 (1.1)	6.0 (1.1)	0.72
Serum triglycerides, mmol/L (SD)	1.5 (0.8)	1.6 (0.8)	0.26
<i>CFH</i> Y402H polymorphism status			
YY	36 (12.6)	118 (13.2)	
YH	133 (46.5)	409 (45.6)	
HH	117 (40.9)	370 (41.3)	0.87 ^b
Creatinine, mg/dl (SD)	1.17 (0.37)	0.96 (0.14)	<0.0001
$eGFR_{CG}$, ml/min/1.73m ² (SD) ^a	52.5 (9.9)	82.7 (18.4)	<0.0001

^aEstimated using Cockcroft-Gault equation.

^b*P* trend in category.

Table 2. Chronic kidney disease and incident early AMD

Chronic Kidney Disease Stage	Incident Early AMD		Odds Ratio (95% confidence interval)			
	No. at Risk	No. (%) Affected	Age-, Sex-, <i>CFH</i> Y402H Polymorphism-Adjusted	P	Multivariable Adjusted ^a	P
No/mild (eGFR _{CG} ≥ 60)	897	35 (3.9)	1.0	—	1.0	—
Moderate (eGFR _{CG} < 60)	286	50 (17.5)	3.2 (1.8–5.7)	<0.0001	3.0 (1.6–5.4)	0.0004
P		<0.0001				

AMD, age-related macular degeneration; eGFR_{CG}, estimated glomerular filtration rate (in ml/min/1.73m²) using the Cockcroft-Gault formula.

^aAdjusted for age (continuous), sex, hypertension (present, absent), systolic blood pressure, diastolic blood pressure (both continuous), diabetes (present, absent), cigarette smoking (current, ex), pack-yr of cigarette smoking, white cell count, plasma fibrinogen, fasting plasma cholesterol, fasting plasma triglycerides (all continuous), *CFH* Y402H genotype (homozygous, heterozygous, noncarrier), and body mass index (continuous).

Table 3. Estimated glomerular filtration rate and incident early AMD

	Incident Early AMD		Odds Ratio (95% confidence interval)			
	No. at Risk	No. (%) Affected	Age-, Sex-, <i>CFH</i> Y402H Genotype-Adjusted	P	Multivariable Adjusted ^a	P
Per SD decrease eGFR _{CG}	1183	85 (7.2)	2.0 (1.4–2.8)	<0.0001	2.0 (1.5–2.8)	<0.0001
By <i>CFH</i> Y402H genotype						
in noncarriers/heterozygotes (YY/YH)	696	59 (8.5)	1.8 (1.2–2.6)	0.003	1.7 (1.2–2.6)	0.008
in homozygotes (HH)	487	26 (5.3)	2.5 (1.3–4.8)	0.006	2.6 (1.3–5.3)	0.009
Per SD decrease eGFR _{MDRD}	1183	85 (7.2)	1.6 (1.3–2.1)	0.0002	1.6 (1.3–2.1)	0.0001
Per SD increase serum creatinine			1.3 (1.1–1.5)	0.008	1.3 (1.1–1.5)	0.008

Units in either ml/min/1.73m² (eGFR) or mg/dl (creatinine). AMD, age-related macular degeneration; eGFR_{CG} and eGFR_{MDRD}, estimated glomerular filtration rate (in ml/min/1.73m²) using the Cockcroft-Gault and MDRD formulae, respectively; SD, standard deviation (14.8 ml/min/1.73m² for eGFR_{CG}; 12.5 ml/min/1.73m² for eGFR_{MDRD}; 0.24 mg/dl for creatinine).

^aAdjusted for age (continuous), sex, hypertension (present, absent), systolic blood pressure, diastolic blood pressure (both continuous), diabetes (present, absent), cigarette smoking (current, ex), pack-yr of cigarette smoking, white cell count, plasma fibrinogen, fasting plasma cholesterol, fasting plasma triglycerides (all continuous), *CFH* Y402H genotype (homozygous, heterozygous, noncarrier), and body mass index (continuous).

Table 4. Chronic kidney disease and incident early AMD, stratified by age

Age category	Incident Early AMD		Odds Ratio (95% confidence interval)	
	No. at Risk	No. (%) Affected	Age-, Sex-, <i>CFH</i> Y402H Polymorphism-Adjusted	P
54–65 yr				
per SD decrease eGFR _{CG}	524	13 (2.5)	1.0 (0.6–1.8)	0.98
66–75 yr				
per SD decrease eGFR _{CG}	503	51 (10.1)	1.9 (1.3–2.8)	0.0004
76–94 yr				
per SD decrease eGFR _{CG}	156	21 (13.5)	1.9 (1.2–3.2)	0.008

AMD, age-related macular degeneration; eGFR_{CG}, estimated glomerular filtration rate (in ml/min/1.73m²), using the Cockcroft-Gault formula.

94 yr of age, but not in those 54 to 65 yr of age. There were only 13 incident early AMD cases in the age group of 54 to 65 yr.

None of the prespecified interaction terms tested was significant ($P > 0.10$). We additionally adjusted for nuclear cataract as a biologic aging marker in Model 2 and found the results remained essentially unchanged. In unadjusted analyses, moderate CKD was associated with increased risk of incident late AMD (OR = 3.8; CI, 1.8 to 8.0, $P = 0.0002$). There were too few incident late AMD cases ($n = 27$) to perform further multivariable adjusted analyses.

DISCUSSION

CKD and AMD often coexist in the elderly, but it is not clear if they are linked in ways independent of age and common risk factors, such as hypertension. In this community-based cohort

study, we demonstrate a strong, graded and consistent association of CKD and risk of early AMD that was independent of age and other known measured risk factors. In our study population, CKD accounted for a substantial portion of the population attributable risk of early AMD.

Although there are few data with which to compare our findings, our results are consistent with existing knowledge and supported by plausible biologic mechanisms. First, CKD and AMD share vascular risk factors, such as hypertension and cigarette smoking.^{4–7} Atherosclerosis of the choroidal circulation has been hypothesized as a pathogenic factor for AMD development, and atheroma-like deposits of lipid in Bruch’s membrane have been found in eyes with AMD.⁸ Oxidative stress has also been implicated in AMD pathogenesis.⁷ As CKD accelerates, the progression of atherosclerosis and increases propensity to oxidative stress⁶; these processes may potentially

explain the increased risk of AMD. Additionally, microvascular disease involving smaller vessels in both the renal and retinal circulations may also potentially play a role in explaining our findings, particularly as the microstructure at the interface of the capillary tuft, glomerular basement membrane, and the glomerular epithelial cells in the kidney is similar to the interface involving choriocapillaris, Bruch's membrane, and retinal pigment epithelium in the eye (the sites where AMD pathology occurs).¹⁵ Second, recent studies suggest that CKD and AMD share several common genetic susceptibility loci, in particular, those related to key complement pathway proteins.^{12–18,20,21} Genetic variants in complement factor H are associated with some forms of kidney disease, such as atypical hemolytic uremic syndrome,^{12,14} whereas C3 variants are associated with IgA nephropathy.¹⁶ Both complement factor H and C3 deficiency are associated with type II membranoproliferative glomerulonephritis,^{14,20,21} a disease characterized by kidney failure and early onset retinal drusen, which are structurally and compositionally identical to those that occur in AMD. Variants in these two key complement protein genes are thought to account for a significant proportion of AMD risk.^{13,15} Another non—complement-related gene, the *APOE* ϵ 2 allele, has been linked to increased risk of both CKD and AMD, and part of this association may be mediated by its effects on lipid metabolism.^{17,18} However, in our study, adjusting for *CFHY402H* polymorphism, serum lipids, systemic inflammatory markers, hypertension, and diabetes did not attenuate the association between CKD and AMD, suggesting links between the two diseases that are not entirely explained by these factors. We did not adjust for other inflammatory markers, such as C-reactive protein or other complement protein variants associated with CKD.

Our study has several strengths: prospective follow-up of a population-based sample, masked and standard methods to ascertain AMD, which have been used successfully to detect associations with other AMD risk factors,^{22,23} and well-documented data on potential confounders of CKD and incident AMD. Study limitations are potentially important. First, we estimated GFR from formulas, which could result in misclassification, although such misclassification is likely random with respect to AMD. Additionally, we found consistently strong associations with the Cockcroft-Gault, Modified Diet Renal Disease (MDRD) equations, and serum creatinine, suggesting little, if any, bias from misclassification. Second, a proportion of participants from our study were excluded because of missing data; this may have introduced selection bias because they differed from included participants on several characteristics. Nonetheless, excluded participants had a similar incidence of early AMD, suggesting that such potential selection bias is unlikely to completely explain our findings. Third, although we adjusted for age continuously and in stratified analyses, residual confounding from age and other unmeasured factors may remain. The results remained unchanged after additionally adjusting for a biologic aging marker (nuclear cataract), arguing against inadequate age adjustment. Fi-

nally, the number of participants who developed incident late AMD was too few for multivariable adjusted analyses, although in unadjusted analyses the same association was present. This limitation does not materially change our conclusions, as early AMD is the main precursor of progression to late AMD.

Much of the morbidity and mortality of CKD arises from its adverse effects on other organ systems, particularly the circulatory, endocrine, and skeletal systems.⁶ There is little knowledge of the effects of CKD on the sensory organs, such as the eye. We demonstrate that persons with CKD have a 3-fold higher risk of developing early AMD within 5 yr, and that a substantial portion of early AMD cases could be attributed to its association with CKD. This relationship suggests shared pathogenic factors and/or processes between CKD and AMD, which could have implications for the prevention and treatment of both conditions. Additional research and replication in other populations is clearly needed; but if our findings are confirmed, efforts at early detection and prevention of progression of CKD may have a potential unexpected benefit: in addition to reducing the burden of end-stage renal disease and cardiovascular disease, the burden of blindness from AMD may also be lessened.

CONCISE METHODS

Study Population

The Blue Mountains Eye Study is a population-based cohort study of predominantly white persons designed to identify risk factors for AMD and other age-related eye diseases. The detailed methodology of the Blue Mountains Eye Study has been reported elsewhere.^{24–26} In brief, participants were examined every 5 yr from 1992 to 2004: baseline in 1992 to 1994, the 2nd examination in 1997 to 1999, and the third examination in 2002 to 2004.

Our current analysis is based on participants who attended the 2nd and 3rd examinations. Of the 2335 who participated at the 2nd examination, we excluded 1152 (374 with preexisting AMD, 109 who did not have creatinine measurement, 109 with missing data on important variables such as smoking, blood pressure, and *CFHY402H* polymorphism, and 560 who did not return for the 3rd examination), leaving 1183 at risk of incident AMD over 5-yr of follow-up. The age range of the participants was 54 to 94 yr. This study was conducted according to the recommendations of the Declaration of Helsinki and approved by the Western Sydney Area Human Ethics Committee. Written, informed consent was obtained from all participants.

Assessment of CKD

Serum creatinine was measured within 4 h of fasting venous blood collection with a Hitachi 747 biochemistry analyzer (Roche reagents, modified kinetic Jaffe) at the 2nd examination concurrent with retinal photography. We used the Cockcroft-Gault (CG) equation²⁷ corrected for body surface area, to obtain estimated GFR ($eGFR_{CG}$) in ml/min per 1.73 m². This equation is reported to be more accurate in

the elderly,²⁸ and in the general healthy population with normal range of kidney function.²⁹

$$\text{Cockcroft-Gault} \frac{(140 - \text{age}) \times \text{weight}}{72 \times \text{serum creatinine}} (\times 0.85 \text{ if female})$$

In sensitivity analyses, we also used the abbreviated 4-variable MDRD equation³⁰ to obtain eGFR_{MDRD} from serum creatinine.

$$\text{Abbreviated MDRD: } 175 \times \text{serum creatinine}^{-1.154} \times \text{age}^{-0.203} \\ \times (1.212 \text{ if black}) \times (0.742 \text{ if female})$$

We defined CKD stages according to the National Kidney Foundation guidelines²⁷ (*i.e.*, no CKD: eGFR_{CG} \geq 90 ml/min per 1.73 m²; mild CKD, 60 \leq eGFR_{CG} < 90 ml/min per 1.73 m²; moderate CKD, eGFR_{CG} < 60 ml/min per 1.73 m²).

Assessment of AMD

We took two 30° stereoscopic color retinal photographs of the macula of both eyes, which were graded for presence of early and late AMD using the Wisconsin AMD Grading System.^{22,24,31} Graders were masked to participants' CKD status, and the intergrader and intragrader reliability showed good agreement in identifying individual lesions.

The detailed methodology of AMD ascertainment in this population has been reported extensively elsewhere.^{22,24,31} Incident early AMD was defined as the absence of late AMD and presence of either: 1) large (>125- μ m diameter) indistinct soft or reticular drusen or 2) both large distinct soft drusen and retinal pigmentary abnormalities (hyperpigmentation or hypopigmentation) at the 3rd examination in either eye of persons free of early AMD in both eyes at the 2nd examination.³¹ Similarly, incident late AMD was defined as the appearance of neovascular AMD or geographic atrophy at the 3rd examination in either eye of persons without AMD lesions in both eyes at the 2nd examination.³¹ A retinal specialist (P.M.) adjudicated all uncertain retinal pathology and confirmed all late AMD cases.

Assessment of Other Variables

We measured systolic and diastolic blood pressure using a single mercury sphygmomanometer with appropriate adult cuff size, after participants were seated for at least 10 min. We followed the 2003 World Health Organization (WHO)/ International Society of Hypertension (ISH) guidelines to define hypertension as WHO/ ISH category grade 2 or 3, *i.e.*, a systolic blood pressure \geq 160 mmHg or diastolic blood pressure \geq 100 mmHg at examination or current use of antihypertensive medications. Diabetes was defined as a physician diagnosis of diabetes, or a fasting blood sugar \geq 7 mmol/L. Smoking status was determined from history as never smoked, past smoker, and current smoker (which included those who had ceased smoking within the last 12 mo). Body mass index was calculated from measured height and weight. We genotyped the *CFH* (Try402 \rightarrow His402 polymorphism (rs 1061170, *CFHY402H*) using a Taqman assay (Applied Biosystems, Foster City, CA). Measurement of other variables is described elsewhere.^{22,24,25}

Statistical Analyses

We examined the frequency of early and late AMD according to CKD categories. Because there were very few cases of AMD in those with no CKD, we classified CKD as no/mild and moderate for analyses. We used logistic regression to determine the adjusted odds of incident early and late AMD. Next we modeled eGFR_{CG} continuously and determined the adjusted odds of incident AMD per SD, SD decrease in eGFR_{CG}. On visual inspection of the distribution and quantile-quantile plot, eGFR_{CG} was normally distributed with a mean of 70.1 ml/min per 1.73 m² (SD, 14.8; range, 15.3 to 136.1 ml/min per 1.73 m²). eGFR_{MDRD} and serum creatinine were also normally distributed. We performed analyses stratified by *CFHY402H* genotype in a recessive model for H (*i.e.*, a dominant model for Y), where we combined noncarriers and heterozygotes for the risk allele (YY/YH) into one strata and homozygotes (HH) in the other. This was done because of small numbers of noncarriers. We repeated analyses with incident pigmentary abnormalities, large indistinct soft or reticular drusen, and large distinct soft drusen as outcome variables. We adjusted for age (continuous), sex, and *CFHY402H* polymorphism (YY, YH, and HH) in Model 1. We additionally adjusted for cigarette smoking (current, ex, or never), pack-yr of cigarette smoking (<20 pack-yr, \geq 20 pack-yr <40, and \geq 40 pack-yr), hypertension (yes, no), diabetes (yes, no), fibrinogen, white cell count, serum total cholesterol, triglycerides, and body mass index (all continuous) in Model 2. Model 2 fitted the data well (Hosmer-Lemeshow goodness of fit, $c = 0.78$). We tested for multiplicative interaction between eGFR_{CG}, *CFHY402H* polymorphism, age, sex, hypertension, and diabetes on risk of early AMD in Model 2 with GFR_{CG} modeled continuously. We repeated analyses with eGFR_{MDRD} and serum creatinine. We also performed analyses in groups stratified by age. We calculated population attributable risk percent as $P_{\text{CKD}} \times (\text{Relative Risk} - 1) / [P_{\text{CKD}} \times (\text{Relative Risk} - 1) + 1] \times 100\%$, where P_{CKD} refers to prevalence of moderate CKD. We estimated the adjusted relative risk from the adjusted OR from multivariable Model 2 using the method suggested by Zhang and Yu.³² SAS v9.1 (SAS Institute, Cary, NC) was used.

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DISCLOSURES

All authors have no competing conflicts of interest, financial or otherwise, to declare. The principal author, Gerald Liew, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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