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## Age-related macular degeneration and long-term risk of stroke subtypes

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### Abstract

**Background and Purpose**—We examined the relationship of age-related macular degeneration (AMD) with incident stroke, including stroke subtypes of cerebral infarction and intracerebral haemorrhage (ICH).

**Methods**—We included 12,216 participants with retinal photographs taken at the third examination visit (1993–1995) from the Atherosclerosis Risk in Communities Study (ARIC), a population-based cohort study in middle-aged persons. Images were evaluated for AMD signs according to a standardized protocol. Incident events of stroke and its subtypes were identified and validated via case record review over time.

**Results**—AMD was diagnosed in 591 participants, of whom 576 had early and 15 late AMD. After a mean follow-up of 13.0 years (standard deviation: 3.3), 619 persons developed an incident stroke, including 548 cerebral infarction and 57 ICH. Participants with any AMD were at an increased risk of stroke (multi-variable adjusted hazard ratio [HR]: 1.51; 95% confidence interval [CI]: 1.11–2.06), with a stronger association for ICH (HR: 2.64; 95% CI: 1.18–5.87) than cerebral infarction (HR: 1.42; 95% CI: 1.01–1.99).

**Conclusions**—Persons with AMD are at an increased risk of both cerebral infarction and ICH. These data provide further insights into common pathophysiological processes between AMD and stroke subtypes.

### Keywords

retinal imaging; age-related macular degeneration; cerebral infarction; intra-cerebral hemorrhage

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### DISCLOSURES

None

## INTRODUCTION

Age-related macular degeneration (AMD) and stroke share common pathogenic mechanisms.<sup>1,2</sup> Apart from classic cardiovascular risk factors (e.g. smoking, hypertension), evidence is accumulating that novel pathogenic mechanisms (e.g. inflammation) may also be linked to both AMD and stroke.<sup>1,2</sup> Nevertheless, there are few studies that have directly examined whether persons with AMD are at an increased risk of stroke.

In the Atherosclerosis Risk in Communities (ARIC) Study, we previously reported an association between AMD and incident stroke.<sup>3</sup> However, due to small numbers we could not examine the association with stroke subtypes. Therefore, our aim was to investigate whether AMD was associated with long-term risk of cerebral infarction and ICH.

## METHODS

### Study Population

The ARIC Study is a population-based cohort study that included 15,792 participants aged 45–64 years at recruitment (1987–1989).<sup>3</sup> Our study cohort consisted of individuals who participated at the third examination (1993–1995), when retinal photography was performed.<sup>3</sup> Of the 12,887 who returned for this examination, 320 persons with prevalent stroke and 351 with no or ungradable retinal images were excluded. A total of 12,216 were included for the present study. Informed consent was obtained from all participants and the study was conducted in accordance with the Declaration of Helsinki. Institutional review board approved the study.<sup>3</sup>

### AMD Grading

Retinal photography procedures and AMD assessment have previously been reported.<sup>3</sup> Early AMD was defined as the presence of either soft drusen alone, retinal pigment epithelial (RPE) depigmentation alone, or a combination of soft drusen with increased retinal pigment and/or RPE depigmentation. Late AMD was defined as the presence of exudative AMD or pure geographic atrophy.<sup>3</sup>

### Stroke Assessment

Information concerning stroke events was obtained during annual follow-up telephone interviews, by reviewing local hospital discharge lists, and by checking death certificates.<sup>3</sup> Incident stroke was defined to include first stroke events occurring between 1993–1995 and December 31, 2008. These were further sub-classified as cerebral infarction, ICH and subarachnoid hemorrhage.<sup>3</sup>

### Confounders

Measurements of arterial blood pressure, diabetes mellitus, fasting glucose, total cholesterol, HDL-cholesterol and triglyceride levels, body mass index, atrial fibrillation, white blood cell count, cigarette smoking and alcohol consumption status have been described elsewhere.<sup>3</sup>

### Statistical Analysis

Cox proportional models were used to calculate hazard ratio (HR) for stroke by AMD status. Participants were followed from the time of retinal photography to the stroke event, death, last contact or December 31, 2008, whichever came first.

## RESULTS

There were 591 (4.9%) individuals with AMD, including 576 early AMD and 15 late AMD. During a mean follow-up of 13.0 years (standard deviation: 3.3), 619 persons (13-year cumulative incidence of 5.1%) developed an incident stroke event, including 548 (4.5%) with cerebral infarction, 57 (0.5%) with ICH. There were 14 incident cases of subarachnoid hemorrhage. Table 1 shows participant characteristics according to AMD status. Persons with AMD had higher 13-year cumulative incidence of all stroke (7.6% versus 4.9%), cerebral infarction (6.4% versus 4.4%) and ICH (1.2% versus 0.4%) than those without AMD. In regression models, AMD was associated with an increased risk of stroke, with multivariable adjusted HR of 1.51 (95% confidence interval [CI]: 1.11–2.06) for all stroke, HR 2.64 (95% CI: 1.18–5.87) for ICH and HR 1.42 (95% CI: 1.01–1.99) for cerebral infarction (Table 2).

## DISCUSSION

In this study, we establish that persons with AMD were at an increased risk of developing an incident stroke over 13-years of follow-up period. The relationship was somewhat stronger for ICH than for cerebral infarction.

Previous population-based studies examining the association between AMD and stroke or subclinical cerebrovascular disease provided inconsistent results.<sup>4–7</sup> In the Cardiovascular Health Study, early AMD signs were associated with white matter lesions on neuroimaging,<sup>8</sup> but not related to incident stroke.<sup>5</sup> The Blue Mountains Eye Study reported that neither early nor late AMD was associated with stroke mortality,<sup>6</sup> whereas a study from Taiwan found that neovascular AMD increased the risk of stroke-related death.<sup>4</sup> Recently, the population-based Rotterdam Study reported that late AMD was associated with an increased risk of stroke, but only due to a strong association with ICH.<sup>7</sup> Our present study further extended these findings and showed that any AMD was associated with both cerebral infarction and ICH.

Recently, anti-vascular endothelial growth factor (VEGF) agents used in the treatment of neovascular AMD, have been suggested to increase the risk of ICH.<sup>9</sup> Based on our findings, it appears that AMD patients may already be at an increased risk of ICH, and thus, anti-VEGF therapy could potentially increase this risk further. However, additional studies are needed to confirm this potential side-effect of anti-VEGF agents.

Several methodological issues need to be discussed. First, we used a 45° non-stereoscopic fundus photograph taken through non-dilated pupil on one eye, making AMD grading more variable.<sup>3</sup> Second, unilateral AMD would be missed if the involved eye was not photographed. However, this misclassification of AMD cases as controls is independent of a person developing a stroke and thus would result in bias towards the null suggesting that the true association may be stronger. Third, we did not have sufficient late AMD cases to examine whether the association between AMD and stroke subtypes was driven by early AMD only or early and late AMD both. Finally, among persons with AMD there were few ICH cases (n=7), leading to relatively large confidence intervals.

In conclusion, we demonstrated among middle-aged persons an independent association between the presence of AMD and incident stroke, including cerebral infarction and ICH.

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**Table 1**

Participant characteristics according to age-related macular degeneration (AMD) status

	Age-related macular degeneration	
	Present (n= 591)	Absent (n= 11,625)
Age, years	61.9	59.8*
Men, %	48.6	44.0*
African-Americans, %	15.9	22.6
Hypertension, %	40.6	40.1
Systolic blood pressure, mmHg	124.3	124.3
Diastolic blood pressure, mmHg	70.6	71.8*
Blood glucose, mg/dL	109.7	110.8
Diabetes mellitus, %	15.5	14.8
Body mass index, kg/m <sup>2</sup>	28.3	28.5
Total cholesterol, mg/dL	207.5	207.5
HDL-cholesterol, mg/dL	50.9	52.3
Total triglyceride, mg/dL	142.8	142.4
Cigarette smoking, ever, %	59.0	58.8
Alcohol use, ever, %	78.0	75.2

HDL = high-density lipoprotein.

\* Mean differences statistically significant at p&lt;0.05

**Table 2**  
Hazard ratios for all stroke and its subtypes associated with age-related macular degeneration (AMD)

	All stroke			Cerebral infarction			Intracerebral haemorrhage		
	Person-years	No. of cases	HR (95% CI)*	No. of cases	HR (95% CI)*	HR (95% CI) <sup>†</sup>	No. of cases	HR (95% CI)*	HR (95% CI) <sup>†</sup>
No AMD (n = 11625)	151,680.81	574	Reference	510	Reference	Reference	50	Reference	Reference
AMD (n = 591)	7,406.57	45	1.48 (1.09–2.01)	38	1.51 (1.11–2.06)	1.42 (1.01–1.99)	7	2.67 (1.20–5.92)	2.64 (1.18–5.87)
Early AMD (n = 576)	7,244.80	45	1.53 (1.13–2.07)	38	1.56 (1.15–2.13)	1.47 (1.05–2.06)	7	2.72 (1.23–6.05)	2.72 (1.22–6.06)

\* Hazard ratio (95% confidence intervals) adjusted for age, gender, race and field center

<sup>†</sup> additionally adjusted for mean arterial blood pressure, anti-hypertensive medications, fasting glucose, total cholesterol, HDL-cholesterol, triglyceride levels, body mass index, atrial fibrillation, white blood cell count, cigarette smoking and alcohol consumption status.