Six-Year Incidence of Age Related Macular Degeneration in Kenya

Nakuru Eye Disease Cohort Study

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Key Points

The incidence of AMD is unknown in Africa

A population-based six-year cohort study of adult Kenyans (aged 50 and over) was conducted and the six-year weighted (for loss to follow-up) cumulative incidence of early AMD was 164.2 per 1000 people

AMD will become a greater public health concern in the future with population ageing and as other more treatable eye conditions come under control.

Abstract

Importance: The incidence of age-related macula degeneration (AMD) is unknown in Africa.

Objectives: To estimate the six-year cumulative incidence and progression of AMD in older adults (≥ 50 years) in Nakuru, Kenya.

Design, Setting and Participants: A population-based cohort with six-year follow-up of 1,626 participants seen at baseline (26-January-2007 to 11-November-2008) and follow-up (7-January-2013 to 12-March-2014) with retinal images.
Random cluster sampling with probability-proportionate-to-size procedures were used to select a representative cross-sectional sample of adults aged ≥50 years in 2007-8. A six-year follow-up was undertaken in 2013-14. On both occasions a comprehensive ophthalmic examination was performed including LogMAR visual acuity, digital retinal photography and grading of images at Moorfields Eye Hospital Reading Centre. Data were collected on general health and risk factors.

Main Outcome and Measures: Incident AMD in those with no AMD at baseline and progression from early to late AMD.

Results: 1,453 (50%) of the people at-risk of AMD were followed up after six-years (mean age (SD) 60.7 (8.2), Female 49.5%, Ethnicity: 63.2% Kikuyu, 25.3% Kalenjin, 12.4% Other); 1,282 had data on AMD status at follow-up. Of these, 202 developed early AMD and no participants developed late AMD. The six-year weighted (for loss to follow-up) cumulative incidence of early AMD was 164.2 per 1000 people (95% CI: 136.7-195.9). Two cases with baseline early AMD from the 142 at-risk had developed late AMD at follow-up, with a six-year cumulative incidence of progression from early to late AMD of 24.5 per 1000 people (95%CI: 5.0-111.7). Cumulative incidence of AMD increased with age (80+: 1.8, 95%CI (0.9,3.5) vs. 50-59) and was higher in women (Female: 1.6, 95%CI (1.2,2.1) vs. Male) and people with diabetes (Diabetes: 1.7, 95%CI (1.0,2.8) vs. No diabetes.

Conclusions and Relevance: We estimate that in Kenya, over 100,000 new cases of AMD, mainly early AMD, will develop every year in people aged >=50 years, although a 50% loss to follow-up and wide confidence intervals for progression to late AMD limit definitive conclusions from these findings.

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Introduction

Age-related macular degeneration (AMD) is a progressive degenerative disease affecting the central retina and is highly associated with age.[1] Advanced AMD including geographic atrophy (late dry) and neovasuclar AMD (wet) lead to central vision loss. In the early dry form of the disease, deposits known as drusen are layered between the retina and choroid and subtypes of drusen (based on size and morphology) form part of the more detailed classifications. AMD is a leading cause of visual impairment and blindness in populations living in high-income countries,[2] but there is a paucity of available data from low and middle-income countries (LMICs),[3] including within Sub-Saharan Africa. However, a recent systematic review found that overall posterior-segment disease is a common cause of visual impairment within Sub-Saharan Africa,[4] and a survey in Kenya showed that one in ten people aged 50 years and above had signs of AMD.[5]

Estimation of the incidence and progression of AMD and associated sight loss is important for planning of services. Treatment for neovascular AMD is currently possible within well-established health systems, but infrequently available in LMICs. It is therefore important to be able to identify people at high risk of AMD in order to consider targeted approaches for prevention and/or treatment. Furthermore, rehabilitation services need to be planned for people developing visual loss as a result of AMD. Unfortunately, data to plan these services are currently lacking. The incidence of AMD has been investigated in seven cohort studies of eye disease worldwide,[6-16] with no data from the African continent. There are large variations in the prevalence, phenotypes and incidence of AMD in different populations, [6-16] making extrapolation of findings from studies in other regions of the world to an African setting difficult.

The aim of this current study was to estimate the six-year cumulative incidence of AMD in Nakuru, Kenya, as well as identify risk factors for incident disease.

Methods/Design

The following examination protocols were implemented at both baseline and follow-up with detailed methodology available elsewhere[21] and in the supplementary material:

Ophthalmic and General Examination

All participants underwent LogMAR visual acuity (VA) testing on each eye separately and corrected VA when <20/40 Snellen equivalent.

Detailed interviews were undertaken in the local language covering demographic details, information on risk factors, socio-economic status (SES) and full past medical history.

A nurse recorded the blood pressure, weight, height and waist and hip circumferences.

Participants had two non-stereoscopic digital 45^0 fundus photographs (one disc and one macula centred) taken per eye by an ophthalmic clinical officer. Digital images were graded at an approved grading centre.

The senior grader (NS) graded all images for the presence of AMD. All eyes classified as having late-stage AMD were adjudicated by the MEHRC clinician (TP). The adjudicator also graded 5% of randomly selected images to ensure quality control..

Definitions of AMD Used

A modified version of the International Classification and grading system for age-related maculopathy and AMD was used for image grading at baseline and follow-up.[24] Drusen were categorized based on size, uniformity of colour and margins.

Patients were classified into hard or soft drusen categories: small drusen <63µm were considered to be hard. Large drusen with a uniform density, sharp margins, and a nodular surface texture were placed in the soft distinct category, whereas those without sharp margin were classified as indistinct. When end-stage disease was apparent, patients were classified as having Geographic Atrophy (GA) in the presence of well-demarcated regions with diameters >175µm, within which large choroidal vessels were clearly visible, owing to the atrophy of the overlying choriocapillaris and Retinal Pigment Epithelium. Neovascular AMD was graded as present when exudative features, such as serous fluid, haemorrhage, lipid exudates or fibrosis were seen to be originating primarily from the subretinal, pigment and epithelial tissue layers.

Case definitions were based on the eye with more severe status if both eyes were gradable and on the gradable eye if only one was gradable. “Early AMD” was defined as the presence of large, soft drusen, the presence of pigmentation >63µm, and “Late AMD” the presence of GA or neovascular AMD.

Incident AMD was defined on the absence of AMD features at baseline on retinal images and subsequent presence of these features at follow-up. Incident Late AMD was defined as the combination of i) no or Early AMD at baseline and ii) signs of Late AMD at follow-up.

Dealing with loss to follow-up

Logistic regressions corrected for the survey-design were used to calculate p-values to assess differences between participants seen and those lost to follow-up (LTFU) and those known to have died.

An inverse probability-weighting (IPW) model was used to allow estimation of cumulative incidence while accounting for those LTFU. Those who had died between

baseline and follow-up were excluded from the analysis. Multivariable logistic regression was used to identify independent baseline covariates associated with LTFU. Covariates for which there was evidence of association with the outcome ($p<0.1$) were kept in a multivariable model. Individuals without a complete set of the baseline covariates included in the final multivariable model were excluded from any estimations based on the weighted analysis. From this final model, the probability of being followed was estimated, based on the presence or absence of each of these baseline covariates. The inverse of this probability formed the weighting to be applied in order to account for those LTFU.

The final step was to exclude those individuals LTFU from the analysis, and apply the IPW to account for those LTFU. A sensitivity analysis for this approach involved a complete records analysis (i.e. only including those people who had complete records for outcome and all variables in the analysis).

Cumulative incidence estimation

The six-year cumulative incidence of AMD was estimated by dividing the total (weighted) number of individuals who were classified as having AMD at follow-up by the (weighted) number AMD free at baseline and examined at follow-up. The six-year cumulative incidence was then used to estimate the expected number of new AMD cases per year. First, the size of the at-risk population in Kenya was estimated, using the baseline prevalence of AMD from this cohort and the 2015 Kenyan population estimates for those over 50 years old. The six-year incidence was then multiplied by this at-risk population and divided by six, with the assumption that cumulative incidence was constant over time. Annual cumulative incidence was also estimated separately for men and women and in ten-year age categories (50-59, 60-69, 70-79 and 80+).

The incidence of progression from Early AMD to Late AMD was calculated by examining participants with Early AMD at baseline who were followed up and had a valid AMD status at follow-up.

Assessing risk factors associated with AMD incidence

The age-adjusted association between AMD incidence and each covariate was estimated using a Poisson regression model. A multivariable model was created using backward stepwise selection, using the likelihood ratio test and a threshold of $p<0.05$ for retention of a variable in the model.

Results

At baseline, 4,414 participants had a complete assessment, of whom 3,304 (75%) had an AMD assessment from retinal imaging (Figure 1). Of these, 404 (12%) had AMD at baseline, the majority (n=366; 91%) had early AMD and 38 (9%) had late AMD. A further 2,900 participants did not have AMD at baseline and were therefore at risk of developing AMD at follow-up.[5]

Characteristics of participants and non-participants at six-year follow-up are shown in Table 1. Non-participants were divided into those who had died, and those who had not but did not attend the examination clinic (e.g. due to mass displacement in the period of post election violence after the baseline study period) and/or those without a valid AMD assessment (e.g. cataract obstructing a view of the retina). Compared with those followed-up, participants who had died during follow-up were older, more likely to be male, to have lower education levels and higher systolic blood pressure and have diabetes, but had lower BMI. Compared with participants seen, those lost to follow-up were less likely to be Kikuyu or Kalenjin speakers, had lower levels of education, and were more likely to be from urban areas and be from either the highest or lowest socioeconomic quartile. People seen at follow-up were less likely to have VI at baseline (3.7%) compared with either those who died before follow-up (13.3%) or those not seen at follow-up (7.0%).

In total, 1,453 (50%) of the people at-risk of AMD were followed up after six-years (Figure 1), and 1,282 had data on AMD at follow-up. Of these, 202 developed early AMD and no participants developed late AMD. The six-year cumulative incidence of early AMD, after taking account of LTFU by using IPWs, was 164.2 per 1000 people (95% CI: 136.7-195.9).

In addition, 366 participants with early AMD were at risk of progressing to late AMD at follow-up, of whom 173 were followed up and 142 had a valid AMD assessment (25 of 31 who did not have an AMD assessment had a lens opacity obscuring the retinal images). Two cases with early AMD from the 142 at-risk had developed late

AMD at follow-up (Figure 1), giving a six-year cumulative incidence of progression from early to late AMD of 24.5 per 1000 people (95%CI: 5.0-111.7).

Of the 38 people with late AMD at baseline, 17 (45%) participants were followed up, five (13%) died and 16 (42%) were not located for follow-up. Of the 17 followed up, four did not have a valid AMD assessment (due to obstructing lens opacities), 11 remained classified as late AMD, and two as "critical eye difficult to grade due to image quality, but most likely to be stable end-stage" AMD. The visual status at baseline and follow-up is shown in eTable1.

Cumulative incidence of AMD (80+: 243.8 per 1,000 [115.8-442.4] vs. 50-59: 139.3 per 1,000 [105.3-181.9]) strongly correlated with age (Table 2). The cumulative incidence of AMD was higher for females than males in each age group (Female: 197.0 per 1,000 [156.7-244.7] vs. Male: 130.5 per 1,000 [104.1-162.4]), with an overall six-year cumulative incidence of 197 new cases per 1,000 people (95%CI: 157 to 245) in females compared to 131 new cases per 1,000 people (95%CI: 104 to 162) in males, giving an unadjusted risk ratio of 1.51 (95% CI: 1.14 to 2.00). For each increase in age category the risk ratio was estimated to be 1.19 (95% CI: 1.00 to 1.42).

Based on extrapolations of these results to census data and population estimates in 2015 (assuming incident cases annually is proportional to the cumulative incidence), we estimate that in Kenya 103,070 new cases of AMD (at any severity) develop every year in the people aged ≥50 years, of whom 65,720 (64%) are among women (Table 3).

Specific features of AMD that appear or regress over the study period were recorded (eTable 2). Small drusen were noted to have a six-year cumulative incidence of 59.1% (95%CI: 53.7-64.3%) and a cumulative risk of 24.1% (95%CI:20.6-28.0%) for regression. Hyperpigmentation and hypopigmentation both had a high cumulative

risk of resolution over the six-year follow-up period (77.0%; 95%CI:59.5-88.4% and 58.1%; 95%CI:39.7-74.4% respectively) but low incidence (3.5%; 95%CI:2.5-5.0% and 5.0%; 95%CI:3.5-7.1% respectively).

Multivariable analysis of factors associated with incident AMD indicated an increasing incidence of AMD with older age (p-value (for trend) = 0.02), female gender (p=0.001) and having diabetes mellitus (p=0.04) (Table 4).

Of those who developed incident VI in the cohort (n=234), 162 had an available AMD assessment at follow-up (69%). Of the 162 cases, 52 (32%) had AMD and three of these were classified as blind. It was not possible to infer whether vision loss was solely due to AMD or a combination of other ocular co-morbidities. Change in vision category from baseline to follow-up in all those with a valid AMD status at baseline and follow-up is described in eTable3.

202 participants developed incident AMD in the cohort, of whom 192 had normal vision at baseline. 27 (14%) of the 192 developed visual impairment by follow-up. 1,080 participants did not develop AMD with 1,040 of this group having normal vision at baseline. Of these 1,040, 83 (9%) developed VI.

Discussion

The Nakuru Eye Disease Cohort Study provides longitudinal data on AMD from sub-Saharan Africa from a population-based cohort. While there is 50% loss to follow-up, and few cases developing late AMD (resulting in wide confidence intervals for that outcome), there are limited data on these outcomes from this region. With those caveats in mind, over six years, one in six adults over the age of 50years developed early manifestations of AMD with women having a higher incidence than men. Increasing age was strongly related to both the prevalence and incidence of AMD. The majority of incident cases of AMD were defined on the basis of the development of large drusen (>64μm). Late AMD was infrequent at baseline and consistent with this pattern, only two cases of incident late AMD were found at follow-up. Both incident cases developed in people with early AMD at baseline, and no case was identified that progressed from no AMD to late AMD.

Our data estimate a higher incidence of AMD than other (non-African) cohort studies of eye disease (eTable 4). A likely explanation is that the Nakuru Cohort includes only people aged ≥50years, similar to the next two highest cumulative annual incidence estimates, which were also from older samples in Copenhagen [6] and Reykjavik [11]. Furthermore, in the Nakuru study there was a higher incidence of early AMD and a lower incidence of late AMD compared to other populations. This observation is consistent with the baseline finding, which indicated a comparatively high prevalence of early AMD but low prevalence of late AMD [5], [6-16] The two participants who progressed from early to late AMD were both above the age of 80, and since few people in the Nakuru cohort were in this age group it may explain the low incidence of late AMD, since age is the leading risk factor for incident AMD.

A high prevalence of early AMD at baseline and high incidence of early AMD at follow-up may suggest that the population under investigation has a higher risk of developing AMD. The relatively high prevalence and incidence may possibly be attributed to greater ultra violet light exposure, earlier biological aging, greater genetic predisposition or greater susceptibility to inflammatory processes, which have been attributed with AMD.[25] The proportion of people suffering vision loss due to AMD is relatively low as a factor of overall vision loss being primarily due to

conditions such as cataract that are largely under control in more developed health systems. Of those with AMD, 14% developed VI over the six-year study period compared to 9% over 14 years in a well-developed health system in Copenhagen. It should be noted however that this VI cannot be attributed to AMD alone.

Strengths and limitations

This study was conducted under challenging circumstances with limited infrastructure. It provides independently graded digital image based analysis of AMD in an east African cohort that is diverse and largely representative of the population from which it was sampled. Detailed ophthalmic, demographic and anthropometric assessment of each participant has enabled valuable analyses of associations and risk factors.

Despite these strengths, limitations in the current study may have contributed to an underestimation of the true incidence of AMD and AMD lesions. First, the main limitation of our study is the large loss of participants at follow-up. Of the 4,414 persons who participated in the baseline study, only 2,171 persons participated in the follow-up examination, of whom 1,424 had gradable images at baseline and follow-up, the majority being excluded from analysis as a result of camera failure at baseline, lack of electricity access and/or ungradable images due to media opacities. Only those who had gradable images at both time points were included in the analysis.

A complete case record analysis was conducted without weighting for LTFU (eTable5) with results very similar to using the IPW modeling (Table 2). The results were largely similar with a possible underestimation of the incidence in females when the LTFU is not taken in to account.

Second, changes in procedures between the baseline and follow-up examination (different retinal camera) may have introduced bias. Change in cameras may have caused images with different colour profiles and saturation levels resulting in

different abilities to detect AMD features (e.g. drusen and pigment). Furthermore, the lack of stereo photographs meant cases of retinal elevation may have been overlooked. These factors may have resulted in bias toward an underestimation of the incidence of subtle early AMD lesions such as small drusen or an over estimation of pigmentation attributed to AMD. Comparison images between cameras on the same study participants at baseline and follow-up is shown in eTable6. Overall image quality was considered equivalent at the two time points in those with clear media (i.e. no lens or corneal opacity).

Third, survival bias may have caused an underestimation of the true incidence of late AMD if those who died before the follow-up and had experienced advanced AMD lesions after the first examination and it is possible that those with worsening disease were more likely to attend for follow up.

The low prevalence of late AMD at baseline and low incidence can, in part, be attributed to a lack of older people in this study population with a younger expected mortality than other populations with data on AMD incidence.

Classification bias may also be contributing to the estimates and histological studies would be required to confirm if the manifestations being attributed to AMD are consistent with other populations.

Conclusions

We estimate that in Kenya, over 100,000 new cases of AMD, mainly early AMD, will develop every year in people aged >=50 years, although a 50% loss to follow-up and wide confidence intervals for progression to late AMD limit definitive conclusions from these findings. The AMD in this population was found to be phenotypically different than in prior studies[5]. However, since the relatively high incidence was restricted to occurrence of early AMD this may not have major implications for clinical practice given the low number with associated visual loss.

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Authors Contributions

Author	Study design	Data collection	Analysis	wrote manuscript	reviewed/edit manuscript
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Wanjiku Mathenge	x	x	x		x
Kevin Wing			x		x
Madeleine Bastawrous	x	x	x		x
Hillary Rono		x			x
Helen A. Weiss	x		x		x
David Macleod			x	x	x
Allen Foster	x		x		x
Tunde Peto	x	x	x		x
Nisha Shah		x			x
Matthew Burton	x	x	x	x	x
Hannah Kuper	x	x	x	x	x

The authors have no conflict of interest to declare

The principle investigator (AB) had full access to all 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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Figure 1. Participant flowchart

Table 1: Baseline characteristics of all individuals with no AMD at baseline according to availability of AMD status at 6 year follow up (N=2900)

			Participants	**Non-participants or not included in analysis**	
Baseline Characteristics		*Missing Values*	*Followed-up n=1,282 (44.2%)*	*Not followed-up Alive/Unknown/ AMD status missing n=1,393 (48.0%)*	*Deceased n=225 (7.8%%)*
Age in years, mean (SD)		0	60.7 (8.2)	61.8 (9.8)	68.5 (12.0)**
Systolic BP in mmHg, mean (SD)		26	138.4 (23.6)	139.3 (23.6)	143.3 (28.7)**
Diastolic BP in mmHg , mean (SD)		26	83.1 (13.0)	82.6 (13.1)	82.4 (16.0)
Random Blood Glucose, mean (SD)		79	5.2 (2.3)	5.2 (2.2)	5.6 (3.3)**
Sex, % (n)	Female	0	635 (49.5%)	686 (49.2%)	139 (61.8%)**
	Male		647 (50.5%)	707 (50.8%)	86 (38.2%)
BMI, % (n)	Underweight (<18.5kg/m^2)	29	139 (10.9%)	188 (13.7%)	52 (23.2%)**
	Normal (18.5-24.99kg/m^2)		648 (50.7%)	674 (49.2%)	113 (50.4%)
	Overweight (25-29.99kg/m^2)		307 (24.0%)	321 (23.4%)	40 (17.9%)
	Obese (30+kg/m^2)		184 (14.4%)	186 (13.6%)	19 (8.5%)
Vision status impaired (<6/12 better eye), % (n)	Normal	18	1233 (96.3%)	1279 (93.0%)*	195 (86.7%)**
	Impaired		48 (3.7%)	97 (7.0%)	30 (13.3%)
Tribe, % (n)	Kikuyu	0	799 (62.3%)	782 (56.1%)*	152 (67.6%)
	Kalenjin		324 (25.3%)	313 (22.5%)	52 (23.1%)
	Other		159 (12.4%)	298 (21.4%)	21 (9.3%)
Education, % (n)	None	21	119 (9.3%)	163 (11.9%)*	15 (6.7%)**
	Primary		345 (26.9%)	432 (31.4%)	91 (40.6%)
	Secondary		677 (52.8%)	608 (44.3%)	94 (42.0%)
	Higher		140 (10.9%)	171 (12.4%)	24 (10.7%)
Residence, % (n)	Rural	0	937 (73.1%)	763 (54.8%)*	161 (71.6%)
	Urban		345 (26.9%)	630 (45.2%)	64 (28.4%)
SES Quartile, % (n)	Lower	34	266 (20.9%)	324 (23.7%)*	66 (29.5%)
	Middle lower		347 (27.2%)	304 (22.2%)	55 (24.6%)
	Middle upper		345 (27.1%)	342 (25.0%)	60 (26.8%)
	Upper		317 (24.9%)	397 (29.0%)	43 (19.2%)
Smokers, % (n)	Never	15	861 (67.2%)	980 (71.1%)*	134 (59.6%)
	Former		104 (8.1%)	124 (9.0%)	22 (9.8%)
	Current		317 (24.7%)	274 (19.9%)	69 (30.7%)
Alcohol, % (n)	Never	23	524 (40.9%)	512 (37.3%)	61 (27.2%)**
	Former		549 (42.9%)	595 (43.3%)	116 (51.8%)
	Current		207 (16.2%)	266 (19.4%)	47 (21.0%)

* P-value <0.05 for association between the baseline characteristic and the odds being followed-up, amongst all participants identified as non-AMD at baseline and not known to be deceased at follow up.

** P-value <0.05 for association between the baseline characteristic and the odds of dying during the follow up period, amongst all participants identified as non-AMD at baseline, excluding the group who were not followed up.

Table 2. Age-Gender–Specific six-year cumulative incidence of AMD among the Nakuru Eye Disease Cohort Study Participants

Age Group (years)	Male N (Cases / at risk)	Risk per 1,000/6yrs (95%CI)*	Female N (Cases / at risk)	Risk per 1,000/6yrs (95%CI)	Overall N (Cases / at risk)	Risk per 1,000/6yrs (95%CI)
50-59	29 / 288	98.2(64.8,146.1)	60 / 369	172.7(129.4,226.6)	89 / 657	139.3(105.3,181.9)
60-69	33 / 221	146.6(103.6,203.4)	38 / 197	214.5(152.0,293.7)	71 / 418	179.9(142.8,224.3)
70-79	20 / 104	184.6(121.3,270.9)	13 / 66	193.0(109.3,318.0)	33 / 170	188.0(138.2,250.6)
80+	4 / 22	148.1(51.0,360.0)	5 / 15	378.8(132.6,708.7)	9 / 37	243.8(115.8,442.4)
All ages	86 / 635	130.5(104.1,162.4)	116 / 647	197.0(156.7,244.7)	202 / 1282	164.2(136.7,195.9)

Table 3. Extrapolated number of new adults, per year, aged 50 years and over in Kenya developing AMD, based on incidence data (adjusted to take account of loss to follow up) and estimates of the population in Kenya by age group in 2015.

	Male			**Female**			**Overall**		
Age Group (years)	Extrapolated number	Lower (95%CI)	Upper (95%CI)	Extrapolated number	Lower (95%CI)	Upper (95%CI)	Extrapolated number	Lower (95%CI)	Upper (95%CI)
AMD									
50-59	16460	10860	24500	31520	23630	41360	48770	36890	63700
60-69	12280	8680	17040	21800	15450	29860	33450	26540	41690
70-79	6650	4370	9750	7720	4370	12710	14550	10700	19400
80+	1520	520	3710	4550	1590	8520	5520	2620	10020
All ages over 50	38280	30530	47650	65720	52270	81620	103070	85800	123020

Table-4. Age-adjusted and multivariable analysis of a number of baseline co-variables and incident AMD in the Nakuru Eye Disease Cohort Study. (At risk = No AMD at baseline, incident AMD = early or late AMD at follow up) Sample n=1,282.

	Study sample, n = 1,282				
	At risk of AMD (n)	**Incident AMD**	**Risk per 1,000/6yrs (95%CI)**	**Age adjusted risk ratio (95%CI)**	**Multivariable adjusted risk ratio (95%CI)***
Age					
50-59	657	89	139.3(105.3,181.9)	Baseline p=0.16	Baseline p=0.07
60-69	418	71	179.9(142.8,224.3)	1.3(1.0,1.7)	1.3 (1.0,1.7)
70-79	170	33	188.0(138.2,250.6)	1.4(0.9,1.9)	1.5 (1.0,2.1)
80+	37	9	243.8(115.8,442.4)	1.8(0.8,3.7)	1.8 (0.9,3.5)
Gender					
Male	635	86	130.5(104.1,162.4)	Baseline p=0.002	Baseline p=0.001
Female	647	116	197.0(156.7,244.7)	1.6(1.2,2.1)	1.6 (1.2,2.1)
BMI (4 missing values)					
Underweight	139	25	191.3(127.2,277.4)	Baseline p=0.84	
Normal	648	98	160.1(129.9,195.7)	0.8(0.5,1.3)	
Overweight	307	49	159.4(113.0,220.1)	0.9(0.6,1.4)	
Obese	184	30	169.1(119.0,234.6)	0.9(0.6,1.6)	
Location					
Rural	937	146	160.0(131.9,192.8)	Baseline p=0.55	
Urban	345	56	171.2(116.8,244.0)	1.1(0.8,1.7)	
SES Quartile (7 missing values)					
Lower	266	50	216.0(154.0,294.2)	Baseline p=0.07	
Lower middle	347	43	128.5(94.4,172.4)	0.6(0.4,0.9)	
Upper middle	345	59	169.1(128.1,219.8)	0.8(0.5,1.3)	
Upper	317	48	148.5(105.9,204.4)	0.7(0.5,1.1)	
Smoker					
Never	861	142	173.6(141.6,211.1)	Baseline p=0.12	
Former	104	9	83.5(39.5,167.9)	0.5(0.2,1.0)	
Current	317	51	165.7(125.5,215.7)	0.9(0.7,1.2)	
Hypertension (2 missing values)					
No	664	95	149.1(113.3,193.6)	Baseline p=0.37	
Yes	616	106	178.0(143.1,219.2)	1.2(0.8,1.6)	
Diabetic (1 missing value)					
No	1223	188	157.8(131.7,187.9)	Baseline p=0.07	Baseline p=0.04
Yes	58	14	263.9(136.3,448.9)	1.7(1.0,2.8)	1.7 (1.0,2.8)
Alcohol (2 missing values)					
Never	524	85	171.6(133.7,217.5)	Baseline p=0.59	
Former	549	81	155.2(117.5,202.2)	0.8(0.6,1.2)	
Current	207	36	169.6(116.3,240.6)	1.0(0.6,1.4)	
Ethnic group					
Kikuyu	799	126	164.7(130.5,205.6)	Baseline p=0.51	
Kalenjin	324	46	148.5(107.4,201.7)	0.9(0.6,1.3)	
Other	159	30	184.4(119.2,274.3)	1.2(0.8,2.0)	
Education level (1 missing value)					
No education	119	12	111.3(58.2,202.5)	Baseline p=0.16	
Primary	345	66	215.8(161.8,281.7)	1.8(0.9,3.4)	
Secondary	677	104	152.8(123.7,187.4)	1.3(0.7,2.5)	
College/Uni	140	20	128.5(80.7,198.4)	1.2(0.5,2.6)	

*For multivariable analysis, an initial model was fitted that included those variables shown to be associated with outcome in age-adjusted analysis (using a Wald test threshold p-value of <0.05 to indicate association). A backward stepwise approach was then applied in order to obtain a final multivariable model, removing variables with p>0.05 one-by-one.