

## SCIENTIFIC REPORT

# 28 000 Cases of age related macular degeneration causing visual loss in people aged 75 years and above in the United Kingdom may be attributable to smoking

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**Background:** Age related macular degeneration (AMD) causing visual impairment is common in older people. Previous studies have identified smoking as a risk factor for AMD. However, there is limited information for the older population in Britain.

**Methods:** Population based cross sectional analytical study based in 49 practices selected to be representative of the population of Britain. Cases were people aged 75 years and above who were visually impaired (binocular acuity  $<6/18$ ) as a result of AMD. Controls were people with normal vision (6/6 or better). Smoking history was ascertained using an interviewer administered questionnaire.

**Results:** After controlling for potentially confounding factors, current smokers were twice as likely to have AMD compared to non-smokers (odds ratio 2.15, 95% CI 1.42 to 3.26). Ex-smokers were at intermediate risk (odds ratio 1.13, 0.86 to 1.47). People who stopped smoking more than 20 years previously were not at increased risk of AMD causing visual loss. Approximately 28 000 cases of AMD in older people in the United Kingdom may be attributable to smoking.

**Conclusion:** This is the largest study of the association of smoking and AMD in the British population. Smoking is associated with a twofold increased risk of developing AMD. An increased risk of AMD, which is the most commonly occurring cause of blindness in the United Kingdom, is yet another reason for people to stop smoking and governments to develop public health campaigns against this hazard.

of severe AMD and to compare them to a population based control group.

## METHODS

The MRC trial of the assessment and management of older people in the community is a large cluster randomised trial taking place in 106 general practices from the MRC General Practice Research Framework.<sup>7</sup> The practices in the study were selected to be representative of the mortality (SMR) and Jarman scores of general practices in Britain (England, Wales, and Scotland). The aim of the trial was to compare the cost effectiveness of different methods of assessment and management of older people in the context of the 1990 contract of service which required general practitioners to offer an annual health check to patients aged 75 years and over. The study compared two different types of multi-dimensional assessment (targeted versus universal) and two different management models (primary care team versus multidisciplinary geriatric evaluation team). Randomisation was at the practice level and stratified by SMR and Jarman score. All patients aged 75 years or over on the general practitioner list were invited to participate in the trial, unless they were in long stay hospital or nursing homes, or were terminally ill.

People in the 53 practices allocated to the “universal” arm of the trial were given a visual acuity test as part of a detailed health assessment by the practice nurse. Visual acuity was measured at 3 metres with a Glasgow acuity chart which measures the minimal angle of resolution on a logarithmic scale (logMAR).<sup>8</sup> Binocular vision was measured first, followed by vision in the right and left eyes. All vision measurements were conducted with usual spectacle correction. People with visual acuity of 0.5 or more in either eye (equivalent to less than 6/18 Snellen acuity) were retested with a pinhole occluder. If vision did not improve to less than 0.5, and the cause of visual loss had not previously been investigated, the person was referred to an ophthalmologist. If vision improved to less than 0.5, the patient was advised to see an optometrist. Visual impairment was defined as presenting binocular acuity of less than 6/18 (logMAR score 0.5 or more). In 49 practices, the cause of visual impairment was assessed by medical record review.<sup>9</sup> The trial and additional data collection on causes of visual loss were approved by the relevant local research ethics committees.

People with AMD causing visual impairment were considered as “cases” and compared to a “control” group. There were two different options for selection of the control group. Firstly, to compare people visually impaired due to AMD with the rest of the MRC trial study population. This control group would include people visually impaired as a result of other

**Abbreviations:** AMD, age related macular degeneration; ARM, age related maculopathy

Visual impairment is common in older people in Britain.<sup>1</sup> Its prevalence increases progressively with increasing age. Age related macular degeneration (AMD) is the most important cause of visual impairment.<sup>2</sup> Currently there are estimated to be approximately 200 000 people aged 75 years and above visually impaired due to AMD in the United Kingdom.<sup>3,4</sup> There is no treatment that can restore visual loss in people with AMD.<sup>5</sup> In order to develop preventive strategies we need to understand why some people develop AMD and others do not.

Previous studies have identified smoking as a risk factor for AMD.<sup>6</sup> However, these studies have not included many people aged 75 years and above, which is the population group that bears the burden of AMD in the United Kingdom. In addition, to our knowledge there have been no published studies in the British population that have examined this risk factor specifically.

The population based MRC trial of the assessment and management of older people in the community<sup>7</sup> offered the opportunity to identify a large number of representative cases

**Table 1** Cases and controls by age and sex

Age group	Controls			Cases		
	Male	Female	Total	Male	Female	Total
75–79	1344	1504	2848	26	48	74
80–84	511	633	1144	47	112	159
85–89	123	187	310	45	131	176
90+	21	41	62	20	87	107
Total	1999	2365	4364	138	378	516

“Cases” are people with AMD causing visual impairment. “Controls” are people with 6/6 vision or better (binocular acuity). Data from the 49 practices taking part in vision add-on study to the MRC Trial of the Assessment and Management of Older People in the Community.

causes and people not visually impaired. The second option considered was to compare people visually impaired due to AMD with people with good vision (that is, visual acuity of 6/6 or better).

The signs and symptoms of AMD form a continuous spectrum. Dichotomising the disease, as in many other conditions, is essentially arbitrary. In this study, relatively severe AMD cases were selected because a cut-off point of visual acuity worse than 6/18 was used to identify them. It is likely that a small proportion of people with vision worse than 6/6 and better than, or equal to, 6/18 will have AMD and a larger proportion will have early age related maculopathy (ARM)—that is, drusen and pigmentary changes putting them at increased risk of developing AMD.<sup>10</sup> For this reason, in order to minimise the number of controls who have AMD or ARM, a control group of people with good vision—that is, binocular visual acuity of 6/6 or better, was selected.

Smoking history was ascertained using an interviewer administered questionnaire. The questions used came from the Whitehall study.<sup>11</sup> Participants were asked whether they smoked currently. For people who responded no, they were asked whether they had ever smoked cigarettes. Age smoking started and stopped was also elicited and the number of cigarettes (ounces (g) tobacco) smoked a day. One ounce (28 g) of tobacco was assumed to correspond to 30 cigarettes.

The following variables were created:

- Smoking status 1 = never smoked 2 = ex-smoker 3 = current smoker.
- Pack years were calculated from the number of years participants had smoked, multiplied by the usual daily cigarette equivalent intake, and divided by 20. This gives a measure of the lifetime exposure dose received.
- The number of years since stopping smoking was calculated from the current age minus the age stopped smoking. People who were still smoking had a value of 0; people who had never smoked were excluded from this variable.

The following confounding factors were considered because they have been reported in other studies as putative risk factors for AMD: socioeconomic status, alcohol consumption, cardiovascular disease and its risk factors. Data

were not available on antioxidant micronutrient intake, exposure to light (visible or ultraviolet), and family history of AMD.

All regression analyses took account of the extra variation introduced by the cluster design of the study using the “svy” commands in Stata version 8.0 (Stata Corporation, TX, USA). “Svy” commands calculate robust standard errors using the “linearisation” variance estimator (based on a first order Taylor series linear approximation).

## RESULTS

Controls were younger and less likely to be women (table 1); 9.0% of the study population were current smokers. Smoking decreased with increasing age ( $p < 0.001$ ) and was higher in men (11.2%) than women (7.3%) ( $p < 0.001$ ). Table 2 shows the association between current smoking and risk of AMD causing visual impairment by age.

After controlling for potentially confounding factors, current smokers were twice as likely to be a case compared to non-smokers (odds ratio 2.15, 95% CI 1.42 to 3.26) (table 3). There was little or no association for ex-smokers (odds ratio 1.13, 0.86 to 1.47). There was an increased chance of AMD causing visual loss with increasing pack years of smoking, however, this increase was not seen consistently after controlling for confounding factors.

There was an increased association of AMD with decreasing years since stopping smoking (test for linear trend  $p < 0.001$ ). People who stopped smoking more than 20 years previously did not have increased odds of AMD causing visual loss. There was a moderately increased odds ratio for AMD for people who stopped smoking 10–20 years ago. The adjusted odds ratio comparing people who had stopped smoking 10–<20 years ago with those who had stopped smoking 20 years ago or more or who had never smoked was 1.46 (95% CI 1.03 to 2.07). Comparing people who were current smokers, or who had stopped smoking less than 10 years ago, with people who had stopped smoking 20 years ago or more, or who had never smoked, gave an adjusted odds ratio of 2.29 (95% CI 1.69 to 3.10).

Based on current estimates of the number of people with AMD causing visual loss in the United Kingdom,<sup>3</sup> this equates to approximately 28 000 people (95% CI 17 000 to

**Table 2** AMD causing visual impairment associated with smoking by age

Age group	Odds ratio*	95% CI	p Value
75–79	2.89	1.40 to 5.94	0.003
80–84	1.85	1.09 to 3.15	0.022
85–89	1.38	0.69 to 2.78	0.361
90+	0.93	0.25 to 3.44	0.915

Mantel-Haenszel estimate of the odds ratio controlling for the effects of age = 1.78 (95% confidence intervals 1.26 to 2.52)  $p = 0.001$ .

\*Odds of being a case if current smoker divided by odds of being a case if a non-smoker.

**Table 3** Association between smoking and AMD causing visual impairment

Risk factor	Controls	Cases	Odds ratio adjusted for age and sex			Odds ratio adjusted for confounders		
			OR	95% CI	Wald test	OR	95% CI	Wald test
Never smoked	1698	233	1			1		
Ex-smoker	2281	220	1.13	0.88 to 1.44	0.382	1.13	0.86 to 1.47	0.376
Current smoker	378	60	2.33	1.61 to 3.37	<0.001	2.15	1.42 to 3.26	0.001
Never smoked	1698	233	1			1		
<20 pack years	1286	143	1.18	0.90 to 1.55	0.214	1.17	0.86 to 1.58	0.303
20–<40 pack years	619	57	1.31	0.90 to 1.92	0.160	1.37	0.93 to 2.01	0.108
40 + pack years	627	59	1.41	0.96 to 2.05	0.075	1.24	0.80 to 1.93	0.336
Never smoked	1602	229	1			1		
Stopped 20+ years	1588	140	0.89	0.69 to 1.17	0.399	0.86	0.65 to 1.14	0.295
Stopped 15–<20 years	273	25	1.33	0.85 to 2.08	0.213	1.33	0.82 to 2.14	0.241
Stopped 10–<15 years	223	20	1.42	0.87 to 2.34	0.160	1.41	0.80 to 2.48	0.233
Stopped 5–<10 years	135	16	2.39	1.29 to 5.00	0.015	2.46	1.28 to 4.72	0.008
Stopped <5 years	92	16	2.54	1.55 to 3.20	0.008	2.24	1.01 to 4.96	0.047
Current smoker	388	61	2.37	1.63 to 3.45	<0.001	2.02	1.36 to 2.99	0.001

Data from 4364 controls and 516 cases in the 49 practices taking part in the vision add-on study in the MRC Trial of the Assessment and Management of Older People in the Community. Confidence intervals adjusted for clustered design of the study. Confounders: age (75–79, 80–84, 85–89, and 90+), sex, housing (owner, non-owner, sheltered), body mass index (quintiles), alcohol consumption (never, ex, current below median, current above median), cardiovascular disease (reported heart attack or stroke or angina as assessed by Rose questionnaire), hypertension (reported high blood pressure or current systolic >160 mm Hg or current diastolic >90 mm Hg).

36 000) (where the attributable risk % = ((OR – 1)/OR) × proportion exposed among cases).

## DISCUSSION

This is the largest study of the association of smoking and AMD in the British population and one of the largest reported to date internationally. The results fit in remarkably well with results seen in studies from other countries with different designs, ages studied, and methods of ascertainment of AMD.<sup>6 12–20</sup> Smoking is associated with a twofold increased risk of developing AMD. The benefit for stopping smoking is seen after 10 years with reductions in risk although risks do not return to that of never smokers till 20 years after stopping smoking. The result for smoking is also consistent with the known pro-oxidant damage due to tobacco—for example, through DNA damage.<sup>21 22</sup>

We estimate that approximately 28 000 cases of AMD in older people in the United Kingdom may be attributable to smoking. This is lower than estimates published in a recent editorial (54 000).<sup>23</sup> Our study provided a lower estimate of risk (twofold instead of threefold) and we used more conservative estimates of the population burden of AMD. In addition, our age range was more restricted (75 years and older rather than 70 years plus).

In contrast with other studies, we did not find a consistent dose-response relation with pack years of smoking. This may be the result of the difficulty of remembering and assessing smoking exposure over a lifetime in this elderly population.

The current study was limited by not having information on antioxidant intake. One alternative explanation is that smokers eat less fruit and vegetables and thereby increase their risk of AMD. However, other studies have been able to adjust for plasma levels of antioxidant micronutrients and have reported similar size effects for smoking.<sup>24</sup>

An increased risk of AMD, which is the most commonly occurring cause of blindness in the United Kingdom, is yet another reason for people to stop smoking and governments to develop public health campaigns against this hazard.

## CONTRIBUTORS

All authors were involved in the design, interpretation and write-up of the study; JE did the data collection and analysis and acts as guarantor of the paper; AF is the principal investigator of the MRC Trial of Assessment and Management of Older People in the Community.

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