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REVIEW

Smoking and age-related macular degeneration: a review of association

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Abstract

Purpose **Age-related macular degeneration (AMD) is the leading cause of severe and irreversible vision loss in the Western world. As there is no effective treatment for all types of AMD, identifying modifiable risk factors is of great importance. This review evaluates the epidemiological evidence associating smoking with AMD.**

Methods **Systematic review of published epidemiological studies evaluated against established criteria for evidence of a causal relationship.**

Results **In total, 17 studies (cross-sectional studies, prospective cohort studies, and case–control studies) were included in the review. A total of 13 studies found a statistically significant association between smoking and AMD with increased risk of AMD of two- to three-fold in current-smokers compared with never-smokers. Five studies found no association between smoking and AMD. There was also evidence of dose-response, a temporal relationship and reversibility of effect.**

Conclusion **The literature review confirmed a strong association between current smoking and AMD, which fulfilled established causality criteria. Cigarette smoking is likely to have toxic effects on the retina. In spite of the strength of this evidence, there appears to be a lack of awareness about the risks of developing eye disease from smoking among both healthcare professionals and the general public.**

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Introduction

Early signs of age-related maculopathy (ARM) are common in the elderly eye and age-related macular degeneration (AMD) is the leading cause of severe and irreversible vision loss in the developed world. The prevalence of neovascular AMD and/or geographic atrophy in the US population aged ≥ 40 years is estimated to be 1.47%, with 1.75 million citizens having AMD.[1] In the UK, AMD is the most common cause of blindness registration.[2] Owen at al,[3] estimated that 214 000 people in the UK may have visual impairment caused by AMD.

Recent therapeutic developments for AMD have concentrated on high-technology interventions such as photodynamic therapy (PDT), macular rotational surgery, and radiotherapy, with new therapies such as intravitreal antivascular endothelial growth factor (VEGF) administration currently undergoing evaluation or registration. These costly treatments provide only partial clinical benefit to selected patients; at best they slow progression of disease and cannot restore vision. Therefore, attention is focusing on identification of modifiable risk factors for AMD.

Age is the most important, but clearly nonmodifiable, risk factor for AMD.[4] Genetic susceptibility, as indicated by a positive family history of AMD, is associated with a high risk of the disease.[4] While progress is being made on consolidating the chromosomal locations of several AMD susceptibility loci, the role of genetic factors in AMD is likely to result from the combined effects exerted by multiple gene variants interacting with environmental factors.[5,6] Considering modifiable risk factors, low dietary intake or low plasma concentrations of antioxidants may be associated with AMD.[4] Dietary and micronutrient supplementation is

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increasingly considered as preventive intervention although the protective effect of direct vitamin interventions remains uncertain.[7] Cardiovascular disease and AMD may share a common risk factor profile, for example, obesity, dietary fat, alcohol consumption, and smoking.[4] Dietary fat may also be a risk factor independent of its relation to cardiovascular disease, with both animal and vegetable fats implicated.[8]

Smoking is a major risk factor for many chronic diseases, especially respiratory and cardiovascular disease.[9] The effects of smoking on the eye are not well recognised. This paper evaluates the evidence for a causal association between smoking and AMD.

Methods

Searching and review of studies

MEDLINE (1966 to July 2003) and EMBASE (1980 to July 2003) were searched using combinations of the key words of 'smoking', 'macular degeneration', and 'age-related maculopathy'. Bibliographies were checked for further relevant studies.

Studies were included if they were epidemiological studies (case–control, cohort or cross-sectional studies) published in English, assessed the relationship between tobacco smoking and AMD or ARM, and included an estimate of the degree of association (odds ratio (OR) or relative risk (RR)). The outcome measure was the presence of ARM or AMD as defined by the investigators of each study. The evidence was reviewed against a framework for assessing the evidence for causality derived from Hill[10] and subsequently modified by Susser[11] (see box).

Box. Criteria for causal attribution[10,11]

- Consistency of findings: between study types, settings, populations and time
- Strength of association
- Evidence of dose-response: greater intensity and/or duration of smoking associated with greater effect
- Evidence of reversibility: reduced risk with removal of exposure (ie among ex-smokers compared with current-smokers)
- Temporal relationship: evidence that exposure preceded effect
- Biological plausibility: evidence of supporting biological evidence from animal and tissue models or other sources

Results

Design of studies

In total, 23 studies examined the link between smoking and AMD. Two studies were excluded from the review as they were not published in the English language.[12,13] One study was excluded because it was a case series.[14] Three studies did not report an OR or RR.[15–17] We attempted to calculate crude ORs for these studies using the available data. Pauleikhoff *et al*[15] did not contain sufficient data to allow calculation of an OR. In the study by Hirvela *et al*,[16] there were very large differences in smoking between men and women but there were insufficient data to calculate a sex-specific OR. However, the authors reported there was no association between smoking and AMD in a stepwise logistic regression analysis. The fourth study was a very small (30 cases) individually matched case–control study. A valid OR (allowing for matching) could not be calculated as this would have required access to the raw data.[17] Thus, 17 studies were included in the review.

Study designs were cross-sectional (seven studies—Table 1), prospective cohort (four studies, including one study which reported results from two time points—Table 2), and case–control (six studies—Table 3).

Most studies originated from North America (eight studies), Europe (five studies) or Australia (two studies). For the cross-sectional and prospective cohort studies, subjects were recruited from the general population or through selected occupations such as watermen,[18] physicians[19] and nurses.[20] For the case–control studies, cases were recruited through eye clinics, and hospital controls were recruited through eye clinics[21–24] or general medicine clinics.[25]

The age range for subjects in most studies was 40–80 years. The sex of subjects was not always reported, but approximately equal numbers of males and females were included in studies where data were available. Some studies recruited only males[18,19,25] or females.[20]

We also reviewed two pooled analyses of the findings of three large cross-sectional studies[26] and their subsequent extension into cohort studies.[27]

Association between smoking and AMD

What is the strength and consistency of the association?
Of seventeen included studies, 13 found a statistically significant association between smoking and one or more types of AMD, with increased risks for current-smokers or ever-smokers compared with non-smokers or never-smokers (RR/OR 1.06–4.96).[19–22,24,25,28–34] A significant positive association between smoking and the risk of developing AMD was observed in six out of seven cross-sectional studies (RR/OR 1.30–4.96), three out of four cohort studies (OR/RR 1.70–3.70), and four out of six case–control studies (OR/RR 1.25–2.97).

In total, 10 studies evaluated 'all AMD' or 'all late AMD' and smoking; six studies found an

Table 1 Cross-sectional studies examining the association between smoking and AMD: current-smokers *vs* never-smokers (unless stated otherwise)

Study	*Subjects*	*AMD type*	*Number with AMD*	*Odds ratio (95% CI)*	*Adjusted for confounders?*
Chesapeake Bay Watermen Study, USA[18]	769	All AMD	96	Ever-smokers *vs* never-smokers: 0.61 (0.35–1.05)	Yes
Copenhagen Study, Denmark[34]	773	All AMD	112	2.4 ($P<0.05$)	No
		Atrophic AMD	88	2.5 ($P<0.01$)	
		Neovascular AMD	24	1.5 (NS)	
Beaver Dam Eye Study, USA[28]	4771	Early ARM	745	Ever-smokers *vs* never-smokers: M 1.29 (0.98–1.70) F 1.02 (0.81–1.29)	Yes
		Neovascular AMD	58	Current-smokers *vs* never-smokers or ex-smokers: M 3.29 (1.03–10.50) F 2.50 (1.01–6.20) Ever-smokers *vs* never-smokers: M 2.86 (0.64–12.7) F 2.06 (1.03–4.10)	
Rotterdam Study, The Netherlands[29]	6174	Neovascular AMD	65	RR 3.6 (1.8–7.4)	Yes
		Atrophic AMD	36	RR 1.5 (0.6–3.9)	
Blue Mountains Eye Study, Australia[30]	3654	Early ARM	231	1.89 (1.25–2.84)	Yes
		All late AMD	58	4.46 (2.20–9.03)	
		Atrophic AMD	19	4.94 (1.29–18.82)	
		Neovascular AMD	47	3.26 (1.45–7.33)	
POLA Study, France[31]	2196	All late AMD	41	3.5 (1.0–12.2), $P=0.04$	Yes
Visual Impairment Project, Australia[32]	4744	Any ARM including AMD	685	1.01 (0.80–1.29)	Yes
		AMD	30	2.38 (0.83–6.80)	

The reported odds ratios are presented as a pooled estimate for males (M) and females (F) except where reported separately; NS = nonsignificant.

association[19,20,30–32,34] and two studies did not find an association.[18,23] Hyman *et al*[21] found an association in men only and Christen *et al*[19] found an association only at high intensities of smoking. In total, 10 studies evaluated neovascular AMD and six of these found a positive association;[22,24,25,28–30] five studies evaluated atrophic AMD and four found a positive association.[24,30,33,34] In addition, some studies found the association was different for men or women. These variations could have been caused by random fluctuation because of relatively small numbers after stratifying by lesion type.

The results were not completely consistent and five studies found no association or only a very weak link between smoking and AMD.[18,23,35–37] Of these, West *et al*[18] found a nonsignificant decreased risk of AMD in ever-smokers in a small cross-sectional study, and Blumenkranz *et al*[35] found a small nonsignificant increase among current-smokers in a small case–control study. More importantly, a generally well-conducted large French case–control study found only a weak and nonsignificant association between previous and current smoking with AMD after adjustment for confounding factors.[23] Finally, although the Beaver Dam Eye Study found a strong association between smoking and neovascular AMD at baseline,[28] the association at the 5- and 10-year follow-up examinations was weaker.[36,37]

Findings from the three large well-executed cross-sectional studies from Europe, Australia, and the USA demonstrate a consistent association between smoking and AMD.[28–30] The populations from these three key studies were combined giving a pooled population of 12 468 subjects.[26] Apart from age, smoking was the only factor that retained a clear (three-fold) association with AMD (Table 4). The association with current smoking was stronger for neovascular AMD compared with atrophic AMD.

Is there a temporal relationship?

The prospective cohort study design is best for demonstrating that smoking preceded the development of AMD. The three key cross-sectional studies (the Beaver Dam Eye Study, the Rotterdam Study, and the

Table 2 Prospective cohort studies examining the association between smoking and AMD: current-smokers *vs* never-smokers (unless otherwise stated)

Study	*Follow-up (years)*	*Subjects*	*AMD types*	*Number with AMD*	*Relative risk (95% CI)*	*Adjusted for confounders?*
Physicians' Health Study, USA[19]	7	21 157	All AMD	268	Current-smokers <20/day *vs* never-smokers: 1.26 (0.61–2.90) Current-smokers ≥20/day *vs* never-smokers: 2.46 (1.60–3.79)	Yes
			Neovascular AMD	64	1.95 (0.89–4.24)	
Nurses' Health Study, USA[20]	12	31 843	All AMD	65	1.70 (1.20–2.50)	Yes
Beaver Dam Eye Study, USA[36]	5	3583	Incidence early ARM	265	M 1.53 (0.81–2.88) F 0.74 (0.40–1.35)	Yes
			Progression of ARM	188	M 2.34 (1.00–5.44) F 1.00 (0.50–2.01)	
Beaver Dam Eye Study, USA[37]	10	3684	Incidence early ARM	345	1.37 (0.98–1.94)	Yes
			Progression of ARM	365	1.34 (0.94–1.91)	
Blue Mountains Eye Study, Australia[33]	5	2335	Early ARM	193	0.94 (0.70–1.20)	Yes
			Atrophic AMD	17	3.60 (1.10–11.30)	
			Neovascular AMD	23	1.60 (0.40–5.70)	
			Any late lesions	34	2.50 (1.00–6.20)	
			Incidence late ARM	26	1.50 (0.40–5.30)	

The reported relative risks are presented as a pooled estimate for males (M) and females (F) except where reported separately.

Table 3 Case–control studies examining the association between smoking and AMD: current-smokers *vs* never-smokers (unless otherwise stated)

Study location	*Cases*	*Controls*	*AMD types*	*Odds ratio (95% CI)*	*Adjusted for confounders?*
USA[21]	162	175	AMD with vision loss	All subjects 1.20 (0.80–1.89) M 2.60 (1.15–5.75) F 0.84 (0.48–1.47)	No
France[35]	26	23	Neovascular AMD	1.25 (0.30–4.40)	No
Eye Disease Case–Control Study, USA[22]	421	615	Neovascular AMD	2.20 (1.40–3.50), $P = 0.002$	Yes
France[23]	1844	1844	All ARM and AMD	1.09 (0.83–1.42)	Yes
Japan[25]	56	82	Neovascular AMD	2.97 (1.0–8.84), $P < 0.05$	Yes
Age-Related Eye Disease Study, USA[24]	340	1115	Early ARM	Ever-smokers *vs* never-smokers: 1.25 (1.09–1.44), $P \leq 0.01$	Yes
			Atrophic AMD	Ever-smokers *vs* never-smokers: 1.61 (1.06–2.42), $P \leq 0.05$	
			Neovascular AMD	Ever-smokers *vs* never-smokers: 1.91 (1.57–2.33), $P \leq 0.01$	

The reported odds ratios are presented as a pooled estimate for males (M) and females (F) except where reported separately.

Blue Mountains Eye Study) were subsequently extended into longitudinal studies; two studies reported results from further analysis of smoking and the risk of AMD after 5[33,36] and 10 years[37] follow-up. In the Blue Mountains Eye Study, the association between all ARM and atrophic AMD (but not neovascular AMD) was still

Table 4 Age-adjusted associations between smoking and AMD—pooled analysis of three studies (current-smokers *vs* never-smokers and ex-smokers *vs* never-smokers): odds ratios (95% CI)

	Pooled analysis of cross-sectional studies[26]	*Pooled analysis of cohort studies at 5 years*[27]
All AMD		
Current *vs* never	3.12 (2.10–4.64)	2.35 (1.30–4.27)
Ex *vs* never	1.36 (0.97–1.90)	1.29 (0.79–2.11)
Atrophic AMD		
Current *vs* never	2.54 (1.25–5.17)	2.83 (1.15–6.93)
Ex *vs* never	1.58 (0.90–2.79)	1.01 (0.44–2.31)
Neovascular AMD		
Current *vs* never	4.55 (2.74–7.54)	1.90 (0.88–4.14)
Ex *vs* never	1.54 (0.97–2.44)	1.59 (0.88–2.85)

present 5 years from baseline.[33] A further pooled analysis of the 5-year results from these three studies found a continued three-fold association of current smoking with development of AMD (Table 4).[27] The Physicians' Health Study[19] and the Nurses' Health Study[20] also observed positive associations between smoking and AMD after 7 years of follow-up.

Is there a dose–response effect?

Eight studies investigated a dose–response by comparing different levels of smoking, classified using pack-years (Table 5).[19,20,25,29,31,32,36,37] All except the 10-year follow-up of the Beaver Dam cohort study identified a dose–response effect. In the 5-year follow-up results from the Beaver Dam study, the relative risk of early ARM increased as the amount smoked (measured in cigarette pack-years) increased.[36] However, there appeared to be a negative association between the incidence of late ARM and the amount smoked in the 10-year follow-up.[37] In female current-smokers and ex-smokers, an increasing number of cigarettes smoked was associated with an increased risk of developing AMD.[20] In men, current smokers of <20 cigarettes per day had a smaller relative risk of AMD compared with subjects who smoked ≥ 20 cigarettes per day.[19] When the length and duration of smoking were combined as pack-years, compared with never-smokers, there was an increasing risk of AMD as the number of pack-years increased from 0.25 to >40 (P for trend <0.001).[19]

Only one study has examined the age at onset of AMD in relation to smoking.[33] In the Blue Mountains Eye Study, participants who were current smokers at the baseline examination and were free of late AMD, developed disease signs around 10 years younger than nonsmokers (mean ages 67 and 77 years, respectively).

Reversibility—what is the effect of stopping smoking?

In total, 11 studies examined the risk of AMD in ex-smokers;[19,20,22,25,29–33,36,37] ex-smokers still had an increased risk of developing AMD compared with never-smokers but it was considerably lower than in current-smokers (Table 6). In the pooled analysis of the three large cross-sectional studies and their associated cohort studies, ex-smokers had an only slightly increased risk of AMD compared with never-smokers (Table 4).[26,27] Further, in the 5- and 10-year follow-up of the Beaver Dam Eye Study,[36,37] and in the 5-year follow-up of the Blue Mountains Eye study,[33] ex-smokers had a similar risk of developing AMD as never-smokers.

The risk of developing AMD was higher in ex-smokers who reported having smoked >25 cigarettes/day compared with <25 cigarettes/day.[20] The Physician's Health Study evaluated the risk of AMD in ex-smokers taking into account their previous intensity of smoking and the time since smoking cessation (years).[19] Subjects who had smoked ≥ 20 cigarettes/day still appeared to have an increased risk of AMD even when they had stopped smoking >20 years previously. Ex-smokers who had smoked <20 cigarettes/day, regardless of when they stopped smoking, had a similar risk of AMD compared with never-smokers. Similarly, in the POLA study, former smokers seemed to remain at high risk for AMD for up to 20 years after stopping smoking.[31]

Discussion

The evidence fulfils established causality criteria and strongly suggests an association between smoking and AMD. The association is mostly consistent across a range of populations studied using different study types by different investigators. Depending on the type of AMD, the risk of developing the disease for current-smokers is two- or three-times the risk for never-smokers. The pooled analysis found a greater than four-fold increased risk for neovascular AMD.[26] Long-term follow-up of subjects in longitudinal studies demonstrates that exposure to smoking precedes the development of AMD. A dose–response effect has been demonstrated: the risk of developing AMD increases as the intensity of smoking increases.

The three large cross-sectional studies and their related cohort studies and pooled analyses provide particularly important evidence because of their large number of subjects, and the strength and rigour of the study designs.[28–30]

There was evidence that ex-smokers had a lower risk of AMD, suggesting reversibility of effect. Further evidence of the reversibility of the risk on removing the exposure comes from the Macular Photocoagulation Study (MPS).[38] The MPS investigators noted a higher rate

Table 5 Studies examining the association between smoking and AMD: dose–response

Study	*AMD type*	*Relative risk or odds ratio (95% CI) compared with never-smokers*
Rotterdam Study, The Netherlands[29]	Neovascular AMD	1–9 pack-years: OR 2.1 (0.7–6.2) 10–19 pack-years: OR 7.1 (2.10–19.0) 20–29 pack-years: OR 8.6 (3.0–24.8) ≥30 pack-years: OR 5.7 (2.2–14.5)
POLA Study, France[31]	All late AMD	1–19 pack-years: OR 1.8 (0.5–6.2) 10–19 pack-years: OR 2.1 (0.6–7.4) ≥20 pack-years: OR 4.8 (1.8–12.9)
Visual Impairment Project, Australia[32]	Any ARM including AMD AMD	Current smoker >40 years: OR 1.30 (1.02–1.66) ≤20 pack-years: OR 0.94 (0.33–2.70) >20 pack-years: OR 1.67 (0.69–4.00) Current smoker >40 years: OR 2.39 (1.02–5.57)
Physicians' Health Study, USA[19]	All AMD	<20 cigarettes/day: RR 1.26 (0.61–2.9) ≥20 cigarettes/day: RR 2.46 (1.60–3.79)
Nurses' Health Study, USA[20]	All AMD	1–14 cigarettes/day: RR 1.6 (0.9–2.8) ≥25 cigarettes/day: RR 2.4 (1.4–4.0)
Beaver Dam Eye Study, USA[36] (5-year follow-up)	Incidence early ARM	Per 10 pack-years: M RR 1.06 (1.00–1.13), $P=0.06$ F RR 0.94 (0.84–1.06)
	Progression of ARM	Per 10 pack-years: M RR 1.09 (1.02–1.17), $P=0.014$ F RR 1.05 (0.94–1.17)
Beaver Dam Eye Study, USA[37] (10-year follow-up)	Incidence early ARM	<15 pack-years: RR 1.24 (0.89–1.72) 15–34 pack-years: RR 1.03 (0.72–1.47) ≥35 pack-years: RR 1.24 (0.89–1.74)
	Incidence late ARM	<15 pack-years: RR 0.42 (0.16–1.08) 15 to 34 pack-years: RR 0.63 (0.26–1.55) ≥35 pack-years: RR 0.76 (0.36–1.62)
Japan[25]	Neovascular AMD	Duration of smoking ≤29 years 1.86 (0.59–5.84) Duration of smoking 30–39 years 2.38 (0.77–7.35) Duration of smoking ≥40 years 3.79 (1.13–12.70), $P<0.05$

of choroidal neovascular membrane recurrence after laser photocoagulation in patients who continued smoking compared with nonsmokers (85 *vs* 50%, $P=0.02$) receiving similar laser treatment. It is uncertain whether this also occurs for PDT and other novel AMD treatments over longer follow-up periods. These data are needed and should be collected. The potential for reversibility is important especially if the risk falls substantially after smoking cessation, as suggested by the Blue Mountains and Beaver Dam studies and from the pooled analyses.[26,27] This could be a very useful public health message, as smokers with AMD in one eye might reduce their risk of progression to blinding, late-stage second eye involvement if they were able to stop smoking.

Plausible biological mechanisms support the involvement of smoking in the aetiology of AMD. Although the pathogenesis of AMD and the mechanism of action of smoking on the eye are not fully understood, the risk of developing AMD is likely to involve more than one mechanism. First, AMD may reflect accumulated oxidative damage in the retina.[39] Smoking may also reduce choroidal blood flow in the eye, and promote ischaemia, hypoxia, and micro-infarctions, all of which could increase the susceptibility of the macula to degenerative changes.[40] Decreased choriocapillaris blood

Table 6 Studies examining the association between stopping smoking and AMD: ex-smokers *vs* never-smokers

Study	*AMD type*	*Relative risk or odds ratio (95% CI)*
Rotterdam Study, The Netherlands[29]	Neovascular AMD	RR 2.1 (1.1–3.9)
	Atrophic AMD	RR 0.9 (0.4–2.2)
Blue Mountains Eye Study, Australia[30]	Early ARM	OR 1.03 (0.93–1.14)
	All late AMD	OR 1.83 (1.07–3.13)
	Atrophic AMD	OR 2.13 (0.82–5.56)
	Neovascular AMD	OR 1.26 (0.69–2.28)
Blue Mountains Eye Study, Australia[33] (5-year follow-up)	Early ARM	OR 0.9 (0.7–1.3)
	Atrophic AMD	OR 0.7 (0.2–2.4)
	Neovascular AMD	OR 0.9 (0.3–2.3)
	Any late lesions	OR 0.9 (0.4–2.1)
POLA Study, France[31]	All late AMD	OR 2.8 (1.1–6.9)
Visual Impairment Project[32]	AMD	OR 1.01 (0.42–2.40)
Physicians' Health Study, USA[19]	All AMD	RR 1.30 (0.99–1.70)
	Neovascular AMD	RR 1.06 (0.61–1.85)
Nurses' Health Study, USA[20]	All AMD	RR 1.8 (1.3–2.5)
Beaver Dam Eye Study, USA[36] (5-year follow-up)	Incidence early ARM	M RR 0.95 (0.55–1.62) F RR 1.18 (0.78–1.80)
Beaver Dam Eye Study, USA[37] (10-year follow-up)	Incidence early ARM	RR 1.1 (0.85–1.47)
	Incidence late ARM	RR 0.61 (0.33–1.13)
Eye Disease Case–Control Study, USA[22]	Neovascular AMD	OR 1.5 (1.1–2.1), $P = 0.02$
Japan[25]	Neovascular AMD	OR 2.09 (0.71–6.13)

flow is associated with AMD.[41,42] Nicotine administration appeared to increase severity of experimental choroidal neovascularization in a mouse model.[43] Smoking has also been shown to reduce macular pigment optical density, which reflects levels of the protective carotenoids, lutein, and zeaxanthin in the macular retina.[44,45] Weeks *et al*[46] hypothesised that the effect of smoking on the risk of developing ARM is accentuated by a gene in the 10q26 region of the genome.

Although our review provides strong evidence for an AMD link with active smoking, the evidence for passive smoking increasing AMD risk is sparse.[28,30] More recent studies of passive smoking tend to use much more comprehensive assessments of exposure in the workplace, home, and other settings. The question of whether passive smoking might cause AMD should be addressed using these methodologies before being dismissed on currently available evidence.

The presence of confounding factors presents a problem for all observational studies. Age is an accepted major risk factor for AMD and 15 studies adjusted results to account for age or age plus sex.[18–20,22–25,28–33,36,37] Smoking is known to be associated with other health risk behaviours such as poor diet and excessive alcohol consumption.[47] Poor diet is suspected of being a risk factor for AMD and hence is a potential confounding factor. However, only the Beaver Dam Eye Study, for the 5- and 10-year follow-up results adjusted for vitamin and alcohol intake.[36,37]

Reviewing the data was complicated by variation in the definitions of exposure and outcome. There was no standard definition of the smoking and non-smoking status of subjects. All studies used subject-reported smoking data and it is possible that subjects underestimated or overestimated the extent of their smoking. Although all studies used the presence of AMD as an outcome measure, this is not a homogeneous diagnosis and definitions of disease (eg, differentiation of early and late AMD) varied between studies.

Five studies identified no association or only a weak association of AMD with smoking.[18,23,35–37] Two of these studies included relatively small numbers of subjects and did not define clearly the exposure and outcome.[18,35] The large, French, multicentre private practice clinic-based,

case–control study found a very weak and nonsignificant association between current or past smoking and AMD.[23] However, this study was atypical in that its setting was private eye clinics and subjects had a very low smoking prevalence. It is possible that under-reporting of smoking occurred or that 'non-smokers' may have included patients who had recently stopped smoking. If this under-reporting occurred differentially among the AMD patients, the estimated effect of smoking could have biased the results towards no effect. In addition, selection bias was a strong possibility as controls were eye clinic patients, most of whom had vascular eye diseases, which may also have been related to smoking. Finally, given the large number of studies included in the review, at least one study would be expected to have a null finding by chance alone.

The 5- and 10-year follow-up analyses of the Beaver Dam, Eye Study[36,37] found none or a weak association of smoking with AMD in contrast with the cross-sectional baseline analysis.[28] This may be partly because of small numbers of cases—only 56% of original subjects examined at baseline were evaluated during the 10-year follow-up. Dropout in cohort studies might also cause bias towards the null or even finding a protective effect of smoking if dropout occurred more frequently among smokers at highest risk of developing AMD or occurred more frequently among AMD patients who are smokers. This could theoretically happen in any of the cohort studies, particularly those with longer follow-up periods. This might result in bias if the smokers at highest risk of developing AMD were also those at highest risk of dropout because of serious ill health or death (eg, the heaviest smokers and smokers with multiple risk factors for coronary heart and neoplastic disease). This would result in the selective loss to the study of smokers at highest risk of AMD, leading to a reduction in the observed association between AMD and smoking. Whether differential loss to follow-up because of death or illness is a cause of bias is not clear. However, it is highly plausible as there is a mass of evidence from prospective studies that smokers have greatly increased mortality and morbidity, and this is greatest in heavy and prolonged smokers. The effect of such a bias is likely to increase with prolonged follow-up. The Beaver Dam Eye Study investigators did not find that AMD was associated with increased mortality in the analysis at 5 years.[36] However, this contrasts with the findings of increased mortality among patients with AMD in the 10-year follow-up of the Rotterdam Study[48] and 6.5-year follow-up in the AREDS.[49]

Finally, in the Blue Mountains Eye Study, current-smokers at the baseline examination who were still alive at follow-up were less likely to re-participate at 5 years.[33] Lower participation rates among current-smokers compared with nonsmokers is well described in epidemiological studies. This would also be likely to result in an under-estimation of the strength of any smoking–AMD association if, as seems plausible, smokers at highest risk of AMD (ie, heavier smokers) were selectively dropping out in these studies.

A further potential bias in longitudinal studies examining disease associations with smoking is that nondifferential misclassification of exposure status may occur where smokers and nonsmokers are categorised at baseline only. This will not allow for the effect of changed exposure status, such as quitting smoking during follow-up. Such changes in exposure status are especially problematic with prolonged follow-up, and will bias the measure of association towards a null finding. An example of this problem comes from a recent negative study of the effects of passive smoking, which classified exposure largely by spousal smoking at baseline and attracted considerable critical comment as a result.[50]

Conclusion and relevance for practice

The epidemiological evidence strongly suggests a causal association between smoking and the development of AMD. In the UK, using population attributable risk calculations, we previously estimated that 53 900 cases of AMD (approximately one-quarter of all UK AMD cases) and 17 800 cases of AMD-related blindness may be attributable to cigarette smoking in people aged over 69 years.[51] Most cases of AMD remain irreversible and largely medically untreatable despite the emergence of new technologies.

The current review is the most comprehensive of the causal association between smoking and AMD to date. However, this review still has a number of limitations. Only a limited set of bibliographic databases were searched, non-English language articles were not included, there was no systematic appraisal of the quality of included studies, and a quantitative summary of the studies was not attempted. We next intend to address these deficiencies by carrying out a formal systematic review of smoking and a range of eye diseases including AMD.

Both the general population and many patients attending eye clinics are unaware of the strong link between smoking and eye disease. Anecdotal reports suggest that, when warned of the risk, most patients are keen and willing to stop smoking. The fear of going blind may be more motivational than warnings about other tobacco-associated disease. The additional ocular as well as systemic hazards of smoking should be highlighted to the public and patients.[51]

Recognition of this association between smoking and eye disease has wider policy implications. The UK

government is taking action to reduce smoking. The White Paper 'Smoking Kills' (http://www.dh.gov.uk/assetRoot/04/04/16/84/04041684.pdf) sets out a package of measures, including ending tobacco advertising and sponsorship, media campaigns aimed at changing attitudes towards smoking, and investment in smoking cessation initiatives. However, it is possible that those concerned with eye health are not giving enough weight to smoking cessation, and those concerned with tobacco control and smoking cessation are not giving enough emphasis to eye health.[52] We have made efforts to address this both in correspondence to UK authorities and in efforts at raising awareness through publication[51] and in the production of a leaflet aimed at alerting eye clinic patients to the risks of smoking and helping them to quit **(**www.nwash.co.uk**)**. In Australia, efforts on television and in other media to raise the public awareness of smoking as a cause of eye disease and blindness have been encouraging.[53] In New Zealand, media publicity about smoking and blindness resulted in increased telephone calls to the national Quitline[54] and a campaign using the Australian eye television commercial (with minor modifications) was considered to have been more successful than other advertisements relating smoking to stroke and heart disease.[55]

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