

# Smoking and the Long-term Incidence of Age-Related Macular Degeneration

## *The Blue Mountains Eye Study*

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**Objective:** To assess the association between smoking and long-term incident age-related macular degeneration (AMD).

**Methods:** Of 3654 Australians 49 years and older examined at baseline (January 14, 1992, through December 18, 1993), 2454 were examined 5 years later (January 11, 1997, through February 23, 2000), 10 years later (July 10, 2002, through November 4, 2005), or both. Retinal photographs were taken to assess AMD. Smoking status was recorded at each interview.

**Results:** After controlling for age, sex, and other factors, current smokers had a 4-fold higher risk of late AMD than never smokers (relative risk, 3.9; 95% confidence interval, 1.7-8.8). Past smokers had a 3-fold higher risk of geographic atrophy (relative risk, 3.4; 95% confi-

dence interval, 1.2-9.7). Joint exposure to current smoking and (1) the lowest level of high-density lipoprotein (HDL) cholesterol, (2) the highest total to HDL cholesterol ratio, or (3) low fish consumption was associated with a higher risk of late AMD than the effect of any risk factor alone. However, interactions between smoking and HDL cholesterol level, ratio of total to HDL cholesterol, and fish consumption were not statistically significant.

**Conclusion:** Smoking strongly increased the long-term risk of incident late, but not early, AMD, with a possibly greater effect in persons with a low HDL cholesterol level, a high ratio of total to HDL cholesterol, and low fish consumption.

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**A**GE-RELATED MACULAR DEGENERATION (AMD) is the leading cause of blindness in the Western world.<sup>1</sup> The exact etiology of AMD is unknown. Population-based studies<sup>2-6</sup> have shown strong cross-sectional associations between smoking and AMD. Population-based longitudinal data are limited, however, on the smoking-AMD association.<sup>7-9</sup> The Beaver Dam Eye Study<sup>9</sup> was the first large population-based study to examine the long-term associations between smoking and incident AMD and reported a modest positive association between smoking and early, but not late, AMD incidence. In addition to smoking, AMD is postulated to share other risk factors with cardiovascular disease,<sup>10</sup> such as elevated cholesterol level<sup>11</sup> and hypertension.<sup>12,13</sup> Smoking may also interact with AMD gene susceptibility<sup>14,15</sup> and other environmental risk factors.<sup>16</sup>

The Blue Mountains Eye Study is a population-based cohort study. We previously reported the association between

smoking and AMD observed from the study baseline<sup>4</sup> and 5-year follow-up<sup>8</sup> data. In the present study we examine the association between smoking and the 10-year incidence of AMD in the same cohort and possible joint effects on AMD risk between smoking and some common cardiovascular risk factors. Detailed analyses of associations between cardiovascular disease/risk factors and long-term incident AMD are reported separately.

## METHODS

The Blue Mountains Eye Study is a population-based cohort study of vision, common eye diseases, and other health outcomes in an Australian population. Study methods and procedures have been described elsewhere.<sup>17</sup> At baseline (January 14, 1992, through December 18, 1993), 3654 individuals 49 years and older were examined (82.4% participation). Of these participants, 2335 (75.1% of survivors) and 1952 (53.4% of the original cohort; 76.6% of survivors) underwent 5-year (January 11, 1997, through February 23, 2000) and 10-year (July 10, 2002, through Novem-

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ber 4, 2005) follow-up examinations, respectively. A total of 2454 participants (67.2% of the original cohort) attended follow-up at least once and had retinal photographs available for AMD assessment. Mean follow-up was 5.1 years and 10.5 years for the 5- and 10-year follow-up examinations, respectively. This study followed the recommendations of the Declaration of Helsinki and was approved by the Human Research Ethics Committee of the University of Sydney. Written informed consent was obtained from all the participants.

At each visit participants underwent an eye examination after pupil dilation, and 30° stereoscopic retinal photographs of the macula and other retinal fields of both eyes were taken, as described previously,<sup>17</sup> using a fundus camera (Zeiss FF3; Carl Zeiss, Oberkochen, Germany). At the baseline, 5-year, and 10-year examinations, photographs of both eyes were obtained in 97.6%, 97.5%, and 84.5% (1649/1952) of participants, respectively, and photographs of at least 1 eye were obtained in 99.0%, 98.8%, and 86.5% (1689/1952) of participants, respectively.

### AMD DEFINITION

Details of the photographic grading for AMD lesions were reported<sup>17</sup> and closely followed the Wisconsin Age-Related Maculopathy Grading System.<sup>18</sup> When any lesions were identified at either follow-up examination, a side-by-side grading of the baseline and 5-year photographs and of the baseline and 10-year photographs was performed. Assessments of intergrader and intragrader reliability showed good agreement for identifying AMD lesions.<sup>17</sup>

Late AMD was defined to include neovascular AMD and geographic atrophy (GA), as described in the international classification.<sup>19</sup> All detected late AMD cases were adjudicated and confirmed by a retinal specialist (P.M.). Incident late AMD was defined by the appearance at follow-up of neovascular AMD or GA in either eye of persons without late AMD lesions in either eye at previous examinations.<sup>20</sup> Incident neovascular AMD was defined after excluding baseline neovascular AMD cases but not cases with baseline GA because we considered that neovascular AMD could still develop in eyes with GA. Persons with both GA and neovascular AMD at either the baseline or follow-up examination were not considered to have incident GA.

Early AMD was defined as the presence at the macula<sup>18</sup> of large (>125 μm in diameter), indistinct soft or reticular drusen or combined large, distinct soft drusen and retinal pigmentary abnormalities,<sup>19</sup> without late AMD signs. Incident early AMD was defined by the appearance at follow-up of these lesions in either eye of persons without late or early AMD at previous examinations and without late AMD at follow-up.<sup>20</sup> Incident early AMD also included patients with distinct soft drusen or retinal pigmentary abnormalities, but not both lesions, at baseline who then developed complementary lesions that together composed a diagnosis of early AMD. The incidence of principal early AMD lesions, soft indistinct or reticular drusen, or retinal pigmentary abnormalities was defined by the appearance of these lesions at follow-up in either eye of persons without late or early AMD at baseline or follow-up and without corresponding lesions in either eye at previous examinations.

### EXPOSURE MEASUREMENT

Smoking status was assessed using an interviewer-administered questionnaire. Participants were asked whether they had ever smoked and, if so, at what age they started smoking, what form their tobacco intake took (ready-made cigarettes, hand-rolled cigarettes, cigars, or pipe), and the quantity per day usually smoked. Participants who had quit smoking were asked when they had quit. Pack-years were calculated by

multiplying the total time smoked (years) by the usual daily cigarette-equivalent intake, divided by 20. Current smokers were defined as participants who currently smoked or had stopped smoking less than 1 year before the examination.

Nonexposed skin color was assessed by a single examiner (P.M.) as very fair, fair, light olive, dark olive, or brown-black. Weight, height, and blood pressure were measured by a trained examiner. A standardized questionnaire was used to ascertain medical, family, and social history. Fasting blood specimens were collected for clinical biochemistry assessment. Age was defined at baseline; body mass index was calculated as weight in kilograms divided by height in meters squared; physical inactivity was categorized as answering negatively to the questions, "In the past 2 weeks, did you walk for recreation or exercise?" and "In the past 2 weeks, did you engage in vigorous activity or exercise that made you breathe harder or puff and pant?"

Participants also completed a 145-item, semiquantitative food frequency questionnaire (FFQ) modified from an early FFQ by Willett et al<sup>21</sup> for Australian diet and vernacular. The FFQ was attempted and returned by 3267 participants at baseline (89.4%), with 2900 (88.8% of those who attempted the FFQ; 79.4% of those who attended examination) usable FFQs. Characteristics of the FFQ respondents and exclusion criteria have been reported elsewhere.<sup>22,23</sup>

### STATISTICAL METHODS

We examined the association of baseline smoking status and pack-years smoked with the 10-year incidence of early AMD, late AMD, and each specific lesion. Person-specific incidence rates were calculated using Kaplan-Meier methods. Multivariate-adjusted relative risks (RRs) and 95% confidence intervals (CIs) were calculated using discrete linear logistic models. Several factors were considered as potential confounders, including age; sex; white blood cell count; heavy alcohol consumption ( $\geq 4$  vs  $< 4$  drinks daily); physical inactivity (yes vs no); body mass index; weekly aspirin use ( $\geq 3$  vs  $< 3$  times per week); total and high-density lipoprotein (HDL) cholesterol, triglyceride, and fibrinogen levels; self-reported medical history of diabetes mellitus, acute myocardial infarction, stroke, gout, or hypertension; AMD history among first-degree relatives (present vs absent); fasting glucose level; systolic and diastolic blood pressure; very fair skin (compared with fair skin or darker); and dietary fish intake ( $< 1$  vs  $\geq 1$  serving per month). The final multivariate model retained significant factors and included age, sex, white blood cell count, HDL cholesterol level, AMD family history, dietary fish intake, and very fair skin. Tests of trend for increasing pack-years of exposure were assessed treating pack-year strata as ordered categories scaled to the median for each stratum.

Interactions between smoking and other cardiovascular risk factors were assessed using additive and multiplicative scales and by stratification. To examine statistical interaction as a departure from joint multiplicative effects, cross-product interaction terms were added into the models. To assess interaction as a departure from joint additive effects, we estimated the Rothman synergy index (S)<sup>24</sup> and its 95% CI<sup>25</sup>:

$$S = \frac{[RR(AB) - 1]}{[RR(Ab) - 1] + [RR(aB) - 1]}$$

where *A* and *B* denote presence of the 2 risk factors; *a* and *b*, absence of the 2 risk factors. In the absence of additive interaction, *S* = 1. Analyses of interaction between HDL cholesterol and smoking were further controlled for total cholesterol level and heavy alcohol consumption because serum HDL cholesterol level is directly associated with alcohol consumption.<sup>26</sup> A computer program (SAS version 9; SAS Institute Inc, Cary, North Carolina) was used for all the analyses.

**Table 1. Smoking Status by Age and Sex at the Baseline Examination (1992-1994), Blue Mountains Eye Study<sup>a</sup>**

Sex and Age, y	Participants, No. (n = 2454) <sup>b</sup>	Never Smoked, %	Past Smokers, %	Current Smokers, %
Female				
<60	436	60.6	22.9	16.5
60-69	557	65.5	23.3	11.1
70-79	345	66.1	27.2	6.7
≥80	75	68.0	28.0	4.0
Subtotal	<b>1413</b>	64.3	24.4	11.3
Male				
<60	333	39.9	38.4	21.6
60-69	442	29.9	55.0	15.2
70-79	217	31.8	59.9	8.3
≥80	46	47.8	52.2	0
Subtotal	<b>1038</b>	34.3	50.6	15.1

<sup>a</sup>Percentages may not total 100% because of rounding.

<sup>b</sup>Smoking history was unavailable for 3 participants.

**Table 2. Comparison of Baseline (1992-1994) Characteristics Between Participants Followed Up and Not Followed Up Across 10 Years, Blue Mountains Eye Study**

Baseline Characteristic	Followed Up (n = 2454)	Not Followed Up or No Photographs (n = 429)	P Value <sup>a</sup>	Died (n = 771)
Age, mean (95% confidence interval), y	64.4 (64.0-64.7)	62.1 (61.3-62.9)	<.001	74.3 (73.6-75.0)
Smoking status, %				
Never	51.5	43.4	.02	42.7
Past	35.5	35.9	.90	38.8
Current	12.9	20.7	<.001	18.5
Women, %	57.6	62.5	.06	50.6
Living alone, %	25.6	24.1	.50	35.5
Walking disability, %	3.3	4.2	.30	21.7
Regular use of community services, %	2.5	2.8	.70	13.8
History of stroke, %	3.3	3.8	.60	12.8
History of heart disease, %	14.3	10.3	.02	24.6
History of cancer, %	7.5	7.2	.90	12.6
History of diabetes mellitus, %	6.4	9.6	.02	11.3
Presence of hypertension, %	43.5	45.9	.40	54.4

<sup>a</sup>P values were obtained by comparing those who were not followed up or had no photographs with those who were followed up, excluding those who died.

## RESULTS

Baseline characteristics of the 2454 participants included in the analysis of AMD incidence are given in **Table 1**. Smoking history was incomplete for 3 participants who reported being ever smokers but did not provide further information to be classified as either current or past smokers. Men were slightly more likely to currently smoke (15.1% vs 11.3%;  $P = .006$ ) and were significantly more likely to have smoked in the past (50.6% vs 24.4%;  $P < .001$ ). The proportion of participants reporting a history of current smoking decreased with increasing age ( $P < .001$  for men and women).

**Table 2** compares baseline characteristics of participants followed up at least once ( $n = 2454$ ) and those alive but lost to follow-up ( $n = 429$ ) or who died without any reexamination ( $n = 771$ ). Compared with participants who were followed up, those alive but lost to follow-up were more likely to have been younger, to have been current

smokers, and to have had diabetes mellitus but were less likely to have reported a history of heart disease.

**Table 3** provides the association between smoking status and incident early and late AMD. Current smoking at baseline was found to be associated with a 4-fold higher risk of late AMD than never smoking. When each late AMD lesion was analyzed separately, a significant association was observed between current or past smoking and incident GA but not neovascular AMD. The mean age of participants with incident late AMD was 68.8 years (95% CI, 65.5-72.1 years) among current smokers at the baseline examination, 74.8 years (95% CI, 72.4-77.2 years) among past smokers, and 73.5 years (95% CI, 71.1-75.9 years) among those who reported having never smoked ( $P = .01$ ). The mean age of incident late AMD cases of past smokers was not significantly different from that of never smokers ( $P = .71$ ).

We assessed the effect of duration of smoking cessation on the risk of late AMD and GA in past smokers.

**Table 3. Relation Between Smoking Status at Baseline (1992-1994) and 10-Year Incident AMD, Blue Mountains Eye Study**

AMD Stage or Lesion and Smoking Status	At Risk, No.	Cases, No.	10-y Cumulative Incidence, %	RR (95% CI) <sup>a</sup>	Multivariate RR (95% CI) <sup>b</sup>
Any late AMD					
Never	1239	32	3.0	1 [Reference]	1 [Reference]
Past	849	25	3.8	1.4 (0.8-2.5)	1.6 (0.8-3.0)
Current	304	15	6.4	4.9 (2.5-9.7)	3.9 (1.7-8.8)
Neovascular AMD					
Never	1243	24	2.3	1 [Reference]	1 [Reference]
Past	850	11	1.5	0.9 (0.4-1.8)	0.8 (0.4-1.9)
Current	306	8	3.6	3.2 (1.4-7.5)	1.9 (0.6-5.3)
Geographic atrophy					
Never	1226	11	1.1	1 [Reference]	1 [Reference]
Past	842	14	2.4	2.2 (0.9-5.0)	3.4 (1.2-9.7)
Current	300	7	2.9	7.1 (2.6-19.8)	10.3 (2.7-39.1)
Early AMD					
Never	1168	146	14.4	1 [Reference]	1 [Reference]
Past	801	94	14.6	1.0 (0.8-1.4)	0.9 (0.7-1.3)
Current	283	26	11.3	1.2 (0.8-1.9)	1.2 (0.7-2.0)
Soft indistinct/reticular drusen					
Never	1178	127	12.4	1 [Reference]	1 [Reference]
Past	806	74	11.3	0.9 (0.7-1.3)	0.8 (0.6-1.2)
Current	284	24	10.3	1.4 (0.9-2.2)	1.5 (0.9-2.6)
Pigmentary abnormality					
Never	1109	226	23.9	1 [Reference]	1 [Reference]
Past	745	137	23.0	0.9 (0.7-1.2)	0.9 (0.7-1.1)
Current	265	46	21.2	1.2 (0.8-1.7)	1.1 (0.7-1.7)

Abbreviations: AMD, age-related macular degeneration; CI, confidence interval; RR, relative risk.

<sup>a</sup>Adjusted for age and sex.

<sup>b</sup>Adjusted for age, sex, white blood cell count, family history of AMD, high-density lipoprotein cholesterol level, very fair skin color, and fish intake.

Past smokers were dichotomized about the median (17.0 years) for years of smoking cessation. The risk of late AMD was 1.9 (95% CI, 0.8-4.4) and 1.2 (95% CI, 0.6-2.7) for past smokers who quit less than 17 years and 17 years or more before baseline, respectively, compared with never smokers. The corresponding risks for GA were 4.4 (95% CI, 1.2-15.8) and 2.9 (95% CI, 0.9-9.4).

The association between pack-years smoked for ever smokers and incident early and late AMD was analyzed by means of pack-year tertiles (data not shown). The results were significant only for the highest tertile ( $\geq 35$ ) of pack-years of smoking compared with never smokers for late AMD (RR, 2.4; 95% CI, 1.1-5.1) and GA (RR, 6.2; 95% CI, 1.9-20.2). When pack-years of smoking were analyzed as a continuous variable, no significant association between pack-years of smoking and late AMD was found, and neither was a dose-response pattern of the association. Findings were similar when the past and current smoking groups were analyzed separately.

Joint exposure to low HDL cholesterol and current smoking was associated with a much higher RR of late AMD than the effect of either exposure alone. Compared with nonsmoking individuals with HDL cholesterol levels of 54 mg/dL or greater (to convert to millimoles per liter, multiply by 0.0259), the RR of late AMD for current smokers increased from 2.6 (95% CI, 0.8-8.8) to 6.7 (95% CI, 2.2-20.5) for those with HDL cholesterol levels of 54 mg/dL or greater and less than 54 mg/dL, respectively (**Table 4**). A synergy index of 3.0—calculated as follows:  $S = (6.74 - 1) / [(1.31 - 1) +$

$(2.61 - 1)]$ —suggested interaction on an additive scale, although the index was not statistically significant (95% CI, 0.5-19.4). The cross-product interaction term for HDL cholesterol and smoking also was not significant. After also controlling for heavy alcohol consumption and total cholesterol level, or after excluding participants taking cholesterol-lowering drugs, the findings were essentially unchanged.

Similarly, joint exposure to an elevated ratio of total to HDL cholesterol and current smoking was associated with a higher risk of late AMD than the effect of either exposure alone. Compared with nonsmoking individuals with total to HDL cholesterol ratios of 4.30 or less, the RR of late AMD for current smokers increased from 1.5 (95% CI, 0.4-5.8) to 5.9 (95% CI, 2.1-16.5) for those with total to HDL cholesterol ratios of 4.30 or less and greater than 4.30, respectively. The cross-product interaction term for current smoking and ratio of total to HDL cholesterol was borderline nonsignificant ( $P = .06$ ). After further controlling for heavy alcohol consumption or excluding participants taking cholesterol-lowering drugs, the findings were essentially unchanged.

Joint exposure to low fish consumption and current smoking was also associated with a much higher RR of late AMD than the effect of either exposure alone. Compared with nonsmoking individuals who consumed fish at least once per month, the RR of late AMD for current smokers increased from 2.7 (95% CI, 0.9-7.7) for fish consumption of at least once per month to 7.3 (95% CI, 2.4-22.4) for fish consumption of less than once per month (**Table 4**). A synergy index of 4.2—calculated as fol-

**Table 4. Joint Effect of Baseline (1992-1994) Smoking Status and HDL Cholesterol Level or Fish Intake on Incident Late AMD, Blue Mountains Eye Study**

	Smoking Status	At Risk, No.	Cases, No.	Multivariate RR (95% CI)	
				Joint Exposure	Stratified
HDL cholesterol ≥54 mg/dL	Never	638	16	1 [Reference]	1 [Reference]
	Past	378	11	1.4 (0.6-3.4) <sup>a</sup>	1.4 (0.6-3.4) <sup>a</sup>
	Current	141	5	2.6 (0.8-8.8) <sup>a</sup>	2.4 (0.7-8.3) <sup>a</sup>
<54 mg/dL	Never	524	13	1.3 (0.6-3.1) <sup>a</sup>	1 [Reference]
	Past	416	12	2.2 (0.9-5.5) <sup>a</sup>	1.8 (0.7-4.7) <sup>a</sup>
	Current	135	9	6.7 (2.2-20.5) <sup>a</sup>	5.6 (1.7-17.9) <sup>a</sup>
Fish intake ≥Once a month	Never	828	20	1 [Reference]	1 [Reference]
	Past	613	16	1.3 (0.6-2.7) <sup>b</sup>	1.3 (0.6-2.8) <sup>b</sup>
	Current	184	6	2.7 (0.9-7.7) <sup>b</sup>	2.7 (0.9-7.7) <sup>b</sup>
<Once a month	Never	188	5	0.8 (0.3-2.5) <sup>b</sup>	1 [Reference]
	Past	118	7	2.3 (0.9-6.2) <sup>b</sup>	2.8 (0.7-12.1) <sup>b</sup>
	Current	64	5	7.3 (2.4-22.4) <sup>b</sup>	9.4 (1.9-47.0) <sup>b</sup>

Abbreviations: AMD, age-related macular degeneration; CI, confidence interval; HDL, high-density lipoprotein; RR, relative risk.

<sup>a</sup>Adjusted for age, sex, white blood cell count, family history of AMD, very fair skin, and fish consumption.

<sup>b</sup>Adjusted for age, sex, white blood cell count, family history of AMD, very fair skin, and HDL cholesterol level.

lows:  $S = (7.25 - 1) / [(0.79 - 1) + (2.69 - 1)]$ —suggested greater than additive joint effects of smoking and low fish consumption, although the index was not statistically significant (95% CI, 0.5-36.8). The cross-product interaction term for fish consumption and smoking also was not significant.

There were no other interactions found between smoking and other cardiovascular risk factors, including sex, diabetes mellitus, hypertension, and baseline history of cardiovascular disease. No significant association was found between smoking and incident early AMD except for 35 pack-years or more of smoking among current smokers compared with never smokers (RR, 2.2; 95% CI, 1.2-4.1). In analyses stratified by sex, multivariate analyses were not possible for late AMD due to insufficient numbers. The age-adjusted RR of late AMD for current vs never smokers was 3.9 (95% CI, 1.7-8.8) in women and 12.2 (95% CI, 2.8-53.7) in men. In fully adjusted models, the corresponding RR of early AMD was 0.9 (95% CI, 0.4-1.9) in women and 2.0 (95% CI, 0.9-4.4) in men.

#### COMMENT

To our knowledge, this is only the second (after the Beaver Dam Eye Study<sup>9</sup>) prospective population-based study to assess the long-term association between baseline smoking and incident AMD. In the present study, current smokers had a nearly 4-fold higher risk of late AMD than never smokers and developed AMD, on average, 5 years earlier than never smokers. These findings are consistent with other studies<sup>11,27-30</sup> and previous observations from the 5-year follow-up examinations of the same population, when current smokers were found to develop AMD approximately 10 years earlier than never smokers.<sup>8</sup>

The present findings suggest a possible threshold effect at 35 pack-years rather than a convincing dose-

response pattern between pack-years smoked and incident AMD. The lack of association between pack-years and AMD is most likely due to measurement error (estimating pack-years is much more difficult for respondents than is reporting current, past, or never smoking habits). Although not evident after 5 years,<sup>8</sup> we found a statistically significant association between past smoking and incident GA after 10 years. The risk from smoking seemed to persist above that of never smokers for a considerable time after quitting smoking. We also demonstrated some benefit from smoking cessation to reduce the effect magnitude of the smoking-late AMD risk. This finding supported a likely causal effect of smoking on the development of AMD.

Although the present findings suggest a possible additive joint effect between HDL cholesterol level and smoking or fish consumption and smoking on AMD incidence, we could not confirm this statistically. Interaction on a multiplicative scale between smoking and ratio of total to HDL cholesterol, a strong predictor of coronary heart disease,<sup>31</sup> on late AMD risk was of borderline statistical significance. To our knowledge, this is the first study to explore the joint effects between smoking and other cardiovascular risk factors in population-based samples. Data from other studies<sup>6,11-13,32,33</sup> have not shown a consistent association between cholesterol level and late AMD. The present findings between lipid levels and late AMD should, therefore, be interpreted with caution, as chance findings cannot be excluded.

A biological model involving atherosclerosis could explain the joint effects of HDL cholesterol or ratio of total to HDL cholesterol and current smoking on increased AMD risk. The potential role of atherosclerosis in AMD has been postulated by Friedman<sup>34</sup> where accumulation of lipids in the sclera and the Bruch's membrane increases choroidal vascular resistance, causing leakage and deposition of proteins and lipids in the Bruch's mem-

brane. Reduced HDL cholesterol levels and increases in the ratio of total to HDL cholesterol may promote atherosclerosis.<sup>31,35</sup> Smoking is known to accelerate atherosclerosis<sup>36</sup> and to reduce levels of HDL cholesterol and increase total cholesterol levels.<sup>37</sup> Thus, reduced HDL cholesterol levels or an increase in the ratio of total to HDL cholesterol in individuals who smoke may significantly promote atherosclerosis and AMD development. A role for cholesterol in the pathogenesis of AMD, and the possibility of joint effects of AMD risk factors, is supported by animal models.<sup>38-40</sup>

High levels of polyunsaturated fatty acids in the retina support the biological plausibility of a protective effect from dietary fish intake against AMD.<sup>41</sup> Long-chain n-3 fatty acids may also have a direct or indirect antiatherosclerotic effect<sup>42,43</sup> to explain the joint effect of low fish consumption and current smoking on increased AMD risk. Animal models highlight other causal pathways. In a mouse model, nicotine increased the size and vascularity of choroidal neovascularization,<sup>16</sup> particularly when combined with platelet-derived growth factor. Fish oil may contribute to a variety of antiangiogenic mechanisms in the retina<sup>44</sup> and has been shown to inhibit platelet-derived growth factor-like protein production by vascular endothelial cells,<sup>45</sup> hence reducing the smoking-associated AMD risk. Inflammation and oxidative stress have also been implicated in AMD pathogenesis.<sup>46,47</sup> Cigarette smoke has been shown to be pro-inflammatory,<sup>48</sup> to reduce plasma antioxidant levels,<sup>49</sup> and to increase oxidative stress.<sup>50</sup> Studies<sup>44,51-53</sup> have shown that n-3 fatty acids may protect against retinal inflammation, oxidation, and degeneration. Thus, inadequate intakes of fish or other sources of long-chain n-3 fatty acids in individuals who smoke may greatly increase the risk of AMD.

The strengths of this study include its prospective nature, long follow-up, use of validated outcome measures to assess AMD,<sup>17</sup> and detailed side-by-side comparison of the baseline and follow-up examination photographs to ensure negligible misclassification for AMD diagnosis. An important source of bias in this study is the loss to follow-up of approximately 25% of survivors. Those alive but lost to follow-up were more likely to be current smokers at baseline. Therefore, these results could represent an underestimation of the relationship between baseline current smoking and AMD. Alternatively, smokers who were diagnosed as having AMD may have been more likely to attend follow-up than smokers without vision problems, leading to an apparent association between smoking and incident AMD when none was really present. The possibility of some chance findings cannot be excluded, particularly because they were based on relatively small numbers.

In summary, the findings from this large population-based prospective study add evidence to a possible causal relationship between smoking and the long-term risk of late, but not early, AMD. In addition, these results suggest joint effects of smoking with low HDL cholesterol level, elevation in the ratio of total to HDL cholesterol, or low fish intake, leading to a higher risk of AMD than due to the effect of any of these risk factors alone. This supports speculation that AMD is a condition with multiple etiologic factors, and such joint effects contribut-

ing to the pathogenesis of AMD could mirror the pathogenesis of cardiovascular disease.

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