Objective: To describe the risk factors and associated population attributable risk for age-related maculopathy (ARM) and age-related macular degeneration (AMD) in Australians aged 40 years and older.

Methods: Residents were recruited from 9 randomly selected urban clusters and 4 randomly selected rural clusters in Victoria, Australia. At locally established test sites, the following information was collected: visual acuity, medical and health history, lifetime sunlight exposure, dietary intake, and fundus photographs. Age-related maculopathy and AMD were graded from the fundus photographs using an international classification and grading system. Backwards logistic regression was used to identify the independent risk factors for ARM and AMD.

Results: The participation rate was 83% (n=3271) among the urban residents and 92% (n=1473) among the rural residents. Gradable fundus photographs of either eye were available for 4345 (92%) of the 4744 participants. There were 656 cases of ARM, giving a weighted prevalence of 15.1% (95% confidence limit [CL], 13.8, 16.4); and there were 30 cases of AMD, giving a weighted prevalence of 0.69% (95% CL, 0.33, 1.03). In multiple logistic regression, the risk factors for AMD were as follows: age (odds ratio [OR], 1.23; 95% CL, 1.17, 1.29), smoked cigarettes for longer than 40 years (OR, 2.39; 95% CL, 1.02, 5.57), and ever taken angiotensin-converting enzyme inhibitors (OR, 3.26; 95% CL, 1.33, 8.01). The magnitude of all of these risk factors was slightly less for ARM, and having ever taken blood cholesterol-lowering medications was also significant (OR, 1.67; 95% CL, 1.12, 2.47; P = .001).

Conclusion: Smoking is the only modifiable risk factor for ARM and AMD, among the many environmental and systemic factors that were assessed.


LATE AGE-RELATED maculopathy (ARM) or age-related macular degeneration (AMD) is the most common cause of vision impairment in most developed countries, including Australia.1,2 With the changing demographic profiles that will lead to a further increase in the number of elderly persons, AMD will become even more common in the future. We do not know how to prevent ARM or AMD, and treatment is only partially effective for a few patients with AMD. Therefore, research efforts need to be directed at the primary and secondary prevention of AMD.

Several studies3-11 have reported the risk factors for ARM and AMD in population-based and case-control studies. There have been numerous other reports of specific risk factors, modifiable and nonmodifiable, for ARM and AMD. They include genetic influences,12-13 refractive error,14-16 iris color,17-19 heart disease and hypertension,20-22 smoking,23-25 alcohol consumption,26-28 and sunlight.29-31 Antioxidants have been shown in some studies25-30 to be protective for ARM and AMD. Despite this extensive body of research into the risk factors for ARM and AMD in various study populations, to our knowledge, there have been only 2 reports24,40 of the population attributable risk associated with any of these risk factors. Mitchell et al40 recently estimated that the attributable risk for AMD in former and current smokers ranges from 20% to 68%. This information is necessary to design appropriate public health interventions to maximize the potential for decreasing the prevalence and incidence of ARM and AMD in the community.

This study describes the risk factors and associated population attributable risk for ARM and AMD in a population-based sample of representative Australians aged 40 years and older.
PARTICIPANTS AND METHODS

The detailed methods used for the Visual Impairment Project were published previously. In summary, 9 pairs of urban census collector districts and 4 pairs of rural census collector districts were randomly selected from which to recruit residents in Victoria, Australia, aged 40 years and older to participate. Residents were identified and recruited through a household census. At locally established test sites, the following information was collected: demographic details, visual acuity when first seen and best-corrected visual acuity on a 4-m LogMAR chart, intraocular pressure, visual fields, personal health history and use of medications, dietary intake, lifetime history of time spent outdoors and ocular protection behaviors while outdoors, and clinical eye examination results. The study protocol was approved by the Royal Victorian Eye and Ear Hospital Human Research and Ethics Committee.

The Visual Impairment Project model to quantify lifetime ocular exposure to UV-B was modified to quantify lifetime ocular exposure to visible light. This was accomplished with the use of total global radiation data, ocular exposure ratios for visible light that revealed no protective effect for hats, and information about the transmittance of visible light through sunglasses.

Clinical examinations and fundus photography were performed by 2 trained ophthalmic research fellows using a standardized protocol. A retinal camera (Topcon TRC FET; Topcon America Corp, Paramus, NJ) and film (Kodachrome 64 ASA; Kodak Australia, Mourebank, New South Wales) were used to obtain stereoscopic photographs of the central fundus area and macular arcades. All photographs were then graded according to the Wisconsin Age-Related Maculopathy Grading System. Poor-quality photographs were not graded. A plastic grid, comprising 3 concentric circles of radii 500, 1300, and 3000 μm, and 4 radial lines that divided the photograph into subfields were placed over each stereoscopic pair of slides and centered on the fovea. Only ARM lesions present within the grid were noted. Photographs were considered gradable if the fovea and two thirds of the macula were visible.

Age-related maculopathy and AMD were classified according to an international classification and grading system. Age-related macular degeneration was classified as “wet” (neovascular) or “dry” (atrophic), but was combined for analysis in the present report. Neovascular AMD included serous or hemorrhagic detachment of the retinal pigment epithelium or sensory retina, intraretinal and/or subretinal and/or sub-retinal pigment epithelial hemorrhages, or subretinal fibrous scars. Early ARM was defined as the presence of soft distinct, soft indistinct, or reticular drusen or the presence of any retinal pigmentary abnormalities in the absence of signs of AMD lesions. Small hard drusen alone were not considered as early ARM.

Interview data were entered directly into a data entry system (Paradox; Carel Corp, Ottawa, Ontario) with internal consistency checks. The following variables were created from the smoking information: current, past, or never smoker; pack-years of smoking; total years of smoking; and years since quitting smoking. Pack-years of smoking and total years of smoking were categorized into 10-year groups, through to greater than 40 years. All other data were entered twice and verified. A 5% random sample of the fundus photographs was graded twice to assess reliability. The more severely affected eye was used for the analysis.

SAS statistical software (SAS Institute Inc, Cary, NC) was used for all statistical analyses. The χ² statistic was used to evaluate the agreement between the 2 photogrades. Prevalence estimates were weighted to the 1996 Australian Bureau of Statistics data to reflect the population of Victoria. Univariate analyses included the t test and the χ² test. Backwards logistic regression was used to assess the independent risk factors for ARM and AMD. The Smith serially additive expected dose model was used to evaluate the association between average annual ocular visible light exposure and ARM or AMD for case and control subjects for each year of life. Attributable risk estimates were calculated according to the methods of Bruzzi et al.

Nonparticipants differed from participants only in language spoken at home; they were more likely to speak a language other than English at home. The participation rate for people who spoke Greek at home was 76% compared with 85% for people who spoke English at home. The study population is representative of the Victorian population and of Australia as a whole.

The urban residents ranged in age from 40 to 98 years (mean, 59 years), and 1511 (46%) were men. The rural residents ranged in age from 40 to 95 years (mean, 59 years), and 701 (48%) were men.

Gradable fundus photographs of either eye were available for 4345 (92%) of the 4744 participants. In multivariate analyses, 2 factors remained significantly associated with the availability of gradable fundus photographs: age and rural residence (P = .001 for both). There was no significant difference in the frequency of the diagnosis of ARM or AMD on clinical examination (P = .94) in those subjects who had or did not have gradable photographs. There were 656 cases of ARM, giving a weighted prevalence of 15.1% (95% confidence limit [CL], 13.8, 16.4); and 30 cases of AMD, giving a weighted prevalence of 0.69% (95% CL, 0.33, 1.03). The number of people with any pigmentary abnormalities was 356; 316 people had soft distinct drusen, 178 had soft indistinct drusen, and 266 had large drusen (=125 μm). These features are not mutually exclusive.

RISK FACTORS FOR ARM AND AMD

The following potential risk factors for any ARM and AMD were assessed with univariate analyses: age, sex, rural residence, educational level, country of birth, parents’ country of birth, iris color, smoking history, alcohol intake, family history of AMD, body mass index, glaucoma, self-reported diagnosed hypertension, self-reported diagnosed diabetes, use of blood cholesterol-lowering medications, use of hormone replacement therapy, refractive status (myopia or hyperopia), intake of dietary and supplementary antioxidants, cataract, prior cataract surgery, and average annual ocular visible light exposure. After controlling for age, borderline significant (P < .10) univariate risk factors are summarized in Table 1 and Table 2.
The Smith serially additive expected dose model was used to explore the relationship of lifetime ocular sun exposure and ARM. Although the mean annual ocular sun exposure was greater for people with ARM than for people without ARM for those aged 28 to 80 years, the finding was not significant \((P=.76)\). We conducted a restricted analysis of the sunlight data to determine if more recent sunlight exposure was associated with ARM. We found that the mean annual ocular sun exposure (expressed in Melbourne sun years) over the previous 20 years was not significantly different between people with and without ARM (mean, 0.33 and 0.32, respectively; \(t=0.84\); \(P=.40\)).

The significant \((P<.10)\) univariate risk factors were then placed into a logistic regression model. Family history of AMD was not included in the multivariate models because the data were not available for most of the cohort. The following risk factors were found to be significantly associated with the prevalence of any ARM: age \((P=.001)\), having smoked cigarettes for longer than 40 years \((P=.03)\), angiotensin-converting enzyme (ACE) inhibitor use \((P=.001)\), and use of blood cholesterol-lowering medication \((P=.01)\) (Table 3). The magnitude of all of these risk factors was greater for AMD, except for blood cholesterol-lowering medication use, which was not significant \((P=.71)\) (Table 3).

The attributable risk estimates reveal that age has the greatest impact on the prevalence of ARM in the community, followed by ACE inhibitor use and smoking (Table 3). The population attributable risks were all higher for AMD (Table 3). The multivariate risk factors were further evaluated by using the definition of ARM that was used by the Beaver Dam Eye Study and the Blue Mountains Eye Study. The results were nearly identical, although use of blood cholesterol-lowering medication was no longer statistically significant \((P=.18)\; data not shown).
The association of smoking and ARM and AMD was explored further by evaluating the age-adjusted odds ratios (ORs) for various categories of smoking behavior (Table 4 and Table 5, respectively). These data reveal that only the duration, not the amount, of smoking is associated with ARM and AMD. Current smoking status was not related to ARM, and although persons with AMD were more than 2 times more likely to be current smokers than never smokers, this finding was not statistically significant (P = .11). In ever smokers, a dose-response relationship with years of cigarette smoking was observed for ARM (Mantel-Haenszel \( \chi^2 = 33.6; P < .001 \)) but not for AMD (P > .10). Significant dose-response relationships were not observed for any of the other measures of cigarette smoking (data not shown, P > .10).

The risk factors for women were modeled in separate multivariate logistic regression models. Women who reached menopause at or before the age of 40 years were found to have a higher prevalence of ARM or AMD (OR, 1.78; 95% CL, 1.16, 2.74). The number of years between menarche and menopause was not significant (P = .57) in multivariate analyses (data not shown).

The potential effect of the cluster sampling strategy was evaluated by including in the logistic model a fixed term for the cluster and by modeling the risk factors separately by cluster. There was no significant difference in the results (data not shown).

**COMMENT**

To our knowledge, this is the first population-based study to report the risk factors and the population attributable risk associated with these risk factors for ARM. An advantage of the Visual Impairment Project is that the sam-
gling scheme has provided a study population that is representative of Victorians and Australians aged 40 years and older. That allows meaningful interpretation of the attributable risk estimates that can then be used for public health planning in Australia.

Several studies\textsuperscript{5,10-13} have revealed a possible genetic link for ARM. Although the persons with ARM in our study were more than twice as likely as controls to report a family history of ARM, we were not able to explore this relationship in multivariate analyses because of missing data. Many members of the study population were not asked further questions about family history of AMD because they had never heard of the disease. Identification of a gene for AMD could lead to screening programs for the early detection and treatment of AMD.

We did not find a significant association with sex in our multivariate analyses. Similar results were also observed in the pooled data from the Beaver Dam Eye Study, the Rotterdam Study, and the Blue Mountains Eye Study.\textsuperscript{51} However, when the analyses were rerun using the same definition of ARM as given in these 3 studies, we did find a significantly increased risk of ARM in women (OR, 1.37; 95% CI, 1.02, 1.84). Age-related maculopathy was defined in these 3 studies as the presence of soft indistinct or reticular drusen or the presence of soft distinct and retinal pigmentary abnormalities. In the international classification of ARM that we used,\textsuperscript{47} ARM was defined as the presence of soft indistinct or reticular drusen, soft distinct drusen, or retinal pigmentary abnormalities. The definition that we used resulted in more cases of early ARM.

There have been 2 reports\textsuperscript{7,2} in the literature of a possible association between estrogen and AMD, with a suggestion of an indirect link between estrogen use, cardiovascular disease, and AMD. In the Eye Disease Case-Control Study,\textsuperscript{7} researchers found that persons with AMD were more likely to be former or current estrogen users. In the Blue Mountains Eye Study,\textsuperscript{2} researchers found a protective effect for early AMD, with increasing years from menarche to menopause. In the present study, persons with ARM were slightly less likely than controls to have ever taken hormone replacement therapy and had more years between menarche and menopause. However, we did not find a significant relationship between iris color and ARM or AMD.\textsuperscript{20} Two previous studies\textsuperscript{6,7} have demonstrated nonsignificant inverse associations between educational level attained and AMD. We did not find a significant relationship between educational level and ARM.

Avascular basis for AMD has been suggested in several studies,\textsuperscript{2,6,9,10,16,17} although there is no underlying hypothesis for this association. Although persons with ARM in the present study were significantly more likely in univariate analyses to have hyperopia, even when controlling for the presence of a nuclear opacity ($\chi^2 = 4.4, P = .04$), this finding was not significant in multivariate analyses.

Age-related macular degeneration has been found to be associated with cataract and cataract surgery in several studies,\textsuperscript{6,9,10,16,22} although the results have been inconsistent in the type of lens opacity associated with AMD. In the present study, we found that prevalent cataract of each type and prior cataract surgery were significantly associated with ARM in univariate analyses, but not in multivariate analyses. Prospective data from the Beaver Dam Eye Study revealed that cataract surgery was significantly associated with the progression of ARM and late AMD, but that no specific lens opacities were associated with the incidence or progression of ARM.\textsuperscript{25}

Although an association between light-colored irides and AMD has been demonstrated in several studies,\textsuperscript{5,9,10,19} an association was not observed in either the Eye Disease Case-Control Study\textsuperscript{7} or the National Health and Nutrition Examination Survey in the United States.\textsuperscript{6} There is no agreed hypothesis as to why iris color might be related to AMD, although it has been suggested that there might be an indirect link with skin sun sensitivity or the ability to repair sun-induced damage.\textsuperscript{19} Recent data on macular pigment density could be considered to underlie this finding. In the present study, we did not find a significant relationship between iris color and ARM or AMD.

Two previous studies\textsuperscript{6,7} have demonstrated nonsignificant inverse associations between educational level attained and AMD. We did not find a significant relationship between educational level and ARM or AMD. Cross-sectional findings related to socioeconomic status are difficult to interpret because the higher socioeconomic groups live longer and are, therefore, able to participate in studies. Prospective data are needed to properly assess the potential association of education or other sociodemographic variables with the incidence of ARM, after accounting for selective mortality.

A vascular basis for AMD has been suggested in several studies, with associations between hypertension,\textsuperscript{2,6,9,20,22} cerebrovascular disease,\textsuperscript{3,6} atherosclerosis,\textsuperscript{7,22} serum cholesterol level,\textsuperscript{2,21} plasma fibrinogen level,\textsuperscript{20} and AMD having been documented. Underlying mechanisms proposed for this association have included effects on the choroidal circulation and lipid deposition within Bruch’s membrane. However, the data have not been consistent for the systemic diseases and the medications for these

### Table 5. Relation of Smoking and AMD*

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>AMD (n = 3649)</th>
<th>No AMD or ARM (n = 3649)</th>
<th>Age-Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>14 (46.7)</td>
<td>1757 (48.2)</td>
<td>1.00 (Referent)</td>
</tr>
<tr>
<td>Current</td>
<td>6 (20.0)</td>
<td>1757 (48.2)</td>
<td>2.38 (0.83, 6.80)</td>
</tr>
<tr>
<td>Past</td>
<td>10 (33.3)</td>
<td>1219 (33.4)</td>
<td>1.01 (0.42, 2.40)</td>
</tr>
<tr>
<td>Pack-years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smoked</td>
<td>14 (46.7)</td>
<td>1757 (48.2)</td>
<td>1.00 (Referent)</td>
</tr>
<tr>
<td>≤20</td>
<td>6 (20.0)</td>
<td>927 (25.4)</td>
<td>0.94 (0.33, 2.70)</td>
</tr>
<tr>
<td>&gt;20</td>
<td>10 (33.3)</td>
<td>965 (26.4)</td>
<td>1.67 (0.69, 4.00)</td>
</tr>
<tr>
<td>Cigarette smoker</td>
<td>10 (33.3)</td>
<td>311 (8.5)‡</td>
<td>2.31 (1.05, 5.40)</td>
</tr>
</tbody>
</table>

*AMD indicates age-related macular degeneration; ARM, age-related maculopathy; OR, odds ratio; and CI, confidence limit.‡Data are given as the number (percentage) of participants.†n = 3648.
systemic diseases. Similarly, in the present study, we found that use of either ACE inhibitors or blood cholesterol–lowering medications was significantly associated with the prevalence of ARM and AMD, but the presence of the systemic diseases (hypertension or hypercholesterolemia) was not significantly related to ARM in multivariate analyses. The statistically significant finding with ACE inhibitors is potentially spurious due to the many factors investigated. Prospective data are needed to confirm the significance and temporality of these cross-sectional observations and to address the issue of causality.

One of the most consistently observed risk factors for AMD that has been documented in epidemiologic studies is smoking, possibly directly due to oxidative stress, indirectly due to the promotion of atherosclerosis, or due to its effect in decreasing macular pigment density. In the present study, we found that number of pack-years of smoking was not related to the prevalence of ARM. Although the total duration of smoking, regardless of amount, was significantly associated with the prevalence of ARM. Although people with AMD were 2.4 times as likely to be current smokers in our study, this finding was not statistically significant, probably because of the relatively few cases. Although not statistically significant, the magnitude of the OR for current smoking and late AMD observed in the present study is not significantly different from the OR of 4.46 for current smoking and AMD in the Blue Mountains Eye Study, the OR of 2.2 for neovascular AMD in the Eye Disease Case-Control Study, the OR of 3.6 for late AMD in the POLA Study, the OR of 3.6 for neovascular AMD in the Rotterdam Study, and the OR of 2.5 for women and 3.29 for exudative AMD in the Beaver Dam Eye Study.

Smoking is an important risk factor when considered from the public health perspective, as smoking habits in the community are potentially modifiable through intervention. Mitchell et al recently estimated that 20% of all cases of blindness in Australia may be attributable to smoking, and they advocated a new warning for cigarette packs about the risk of blindness associated with smoking. Our present data suggest that 14% of AMD cases are due to cigarette smoking for longer than 40 years. Although there is a disparity between the attributable risk estimates for ARM and AMD, the finding has public health significance because smoking was the only identified modifiable risk factor. Also, people should continue to be encouraged to quit smoking for other health reasons, including the risk of lung cancer and heart disease.

Another weak-purposed risk factor for AMD, potentially due to oxidative damage again, is alcohol use. Again, this is an important potential risk factor because of the possibility for modification of the prevalence of alcohol use in the community through education and intervention. Although we found a significant univariate association between alcohol intake and ARM, this relationship did not persist in multivariate analyses.

A third source of oxidative damage to the retina that has been suggested as a possible risk factor for AMD is ocular sunlight exposure, specifically visible light as opposed to UV light. No such association was seen in the Eye Disease Case-Control Study or in a large Australian study. In the present study, we found in univariate analyses that persons with ARM had higher annual ocular sun exposure levels than controls for most of their lives, but this finding was not statistically significant. In the Chesapeake Bay Watermen Study, researchers found that ocular sun exposure in the previous 20 years was significantly associated with the presence of AMD. We were not able to support this finding in our study.

Given the potential risk factors for AMD that are suspected of eliciting oxidative damage in the retina, it would make biological sense if antioxidants were found to be protective for AMD, as has been reported in several studies. However, several other studies have found no association between antioxidants and AMD. Given these inconsistent data, most researchers have advocated clinical trials to further assess the association of antioxidants and ARM. There are several studies under way to evaluate the effect of antioxidant supplementation on the incidence and/or progression of ARM, including the Vitamin E, Cataract, and Age-Related Maculopathy study in Australia and the Age-Related Eye Disease Study in the United States. If found to be effective, antioxidant supplementation would be one of the first opportunities for the primary prevention of AMD. In the present study, neither vitamin E or C supplementation nor total daily vitamin E or C intake was found to be associated with ARM or AMD. There is a potential for misclassification of the nutrient status of the cases and controls, however, because the dietary instrument used comprises approximately 58% of the total dietary vitamin C intake and 65% of the total dietary vitamin E intake.

Population attributable risk estimates are useful public health tools, although researchers and policy makers should be aware that attributable risk estimates from cross-sectional data may not correspond with estimates from prospective data. Valid figures allow estimates to be made of the potential decrease in disease prevalence that could be expected through intervention on a given risk factor because they combine the size of the OR and the prevalence of the risk factor in the population. They can be useful in prioritizing strategies for public health intervention and the education of health care professionals. In the present study, the highest attributable risk for ARM was associated with increasing age. Although this may reinforce the recommendation that elderly persons have regular eye examinations, it clearly is not a modifiable risk factor. The attributable risk estimates for ACE inhibitor and blood cholesterol–lowering medication use were not extremely great. More corroborative data from other studies and evidence from longitudinal studies about the significance of these potential risk factors are necessary before making any public health recommendations.

The strengths of this study lie in the representativeness of the study cohort, the relatively high response rate, and the standardized protocol that was used. The limitations of the study include the relatively few cases of AMD, which decreases the power of the study to identify significant risk factors. As with any cross-sectional study, potential for bias exists due to differential mor-
tality, ie, people with a certain risk factor or with ARM or AMD may have higher mortality rates and, thus, may not have participated in this study. Finally, self-reported data have the potential for error.

In conclusion, although several risk factors for ARM have been identified in this study, prospective data are needed to confirm the cross-sectional findings before public health and medical interventions can be recommended.

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The fundus photographs were graded by Dr Mitchell and the Blue Mountains Eye Study team, which included Dr Wang and Mireille Moffitt.

Corresponding author and reprints: Bickol N. Mukesh, PhD, Centre for Eye Research Australia, University of Melbourne, 32 Gisborne St, East Melbourne, VIC 3002, Australia (e-mail: mukeshn@unimelb.edu.au).

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