

## Case-control study of the risk factors for age related macular degeneration

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### Abstract

**Aim**—A case-control study was initiated to determine the risk factors for the development of age related macular degeneration (AMD).

**Methods**—Study participants, who were all white, aged 50–85 years, and were recruited from private ophthalmology practices. Each practitioner enrolled patients with bilateral AMD, who were then matched with controls for sex and age. Environmental factors and systemic and ocular histories were screened. All patients had bilateral red-free fundus photographs and fluorescein angiography. Photographs were classified into pigment epithelium alterations, drusen, geographic atrophy, and exudative AMD. Statistical analysis included the identification of risk factors for AMD. A multivariate analysis was performed at the end of the study. Analysis included the entire study population and was carried out for each stage of AMD.

**Results**—1844 controls were compared with 1844 patients with AMD. Mean age was 71 years for controls and 72 for cases. Logistic regression identified six major risk factors for AMD (whole population): arterial hypertension (odds ratio (OR)=1.28), coronary disease (OR=1.31), hyperopia (OR=1.33), light coloured irises (OR=1.22), and lens opacities or previous cataract surgery (OR=1.55). The significance of vascular risk factors was increased for late stages of AMD, especially the atrophic forms (coronary disease, OR=3.19).

**Conclusions**—This large case-control study confirms some of the risk factors previously identified and may contribute to the determination of methods for prevention of AMD.

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Age related macular degeneration (AMD) is the most common cause of blindness in people over 55 years of age in developed countries. The pathogenesis of this condition is still putative<sup>1</sup> and, in absence of therapy, there is a need to identify risk factors associated with AMD in an effort to preclude its development.

Following the Framingham Eye Study,<sup>2</sup> a number of epidemiological studies have attempted to identify risk factors for AMD.<sup>2–23</sup> These studies, which were case-control and population based, have provided informative

but controversial data. The goals of the present study were to further explore the possible link between environmental factors and systemic and ocular conditions that may be risk factors for AMD in a European population.

Based upon previously published reports, we studied the following risk factors in a case-control study: present and past smoking habits, coronary artery disease, systemic hypertension, ametropia, iris colour, and lens status.

### Subjects and methods

#### PARTICIPATION OF OPHTHALMOLOGISTS

Biopharma initiated this project and provided logistic and financial support with no financial interest.

The goals and methods of the study were presented to participating ophthalmologists (n=859) at several regional meetings by members of the scientific committee and by regional coordinators.

#### INCLUSION AND EXCLUSION CRITERIA

Each ophthalmologist first had to select a day for recruitment. The first patient satisfying the inclusion criteria examined on this day or on the following day, was included. Inclusion criteria were bilateral AMD features: drusen (minimum of five in each eye), pigment epithelium alteration, geographic atrophy, or exudative maculopathy. Visual acuity was measured but not taken in account for inclusion.<sup>21 22</sup> The corresponding control (that is, without any age related change) was the next patient seen after the AMD case who was of the same sex and of comparable age (plus or minus 5 years). Both controls and cases had to be white, non-diabetic, and 50–85 years of age. Cooperation and good photographic documentation of fundus status were required. The majority of the control group was seen for refractive problems; few of them had retinal problems, mainly arteriolosclerosis modifications (Table 1).

Table 1 Fundus pathology in the controls

Pathology	No of patients
Central serous chorioretinopathy	1
Choroidal myopic abnormality	11
Inherited macular dystrophy	7
Acute multifocal placoid pigment epitheliopathy	1
Pseudophakic macular cystoid oedema	5
Epiretinal premacular membrane	23
Macroaneurysm	2
Branch vein occlusion	37
Central retinal venous occlusion	22
Hypertensive retinopathy or atherosclerosis	187
Parafoveal telangiectasis	1
Toxoplasmosis	2
Macular hole	2

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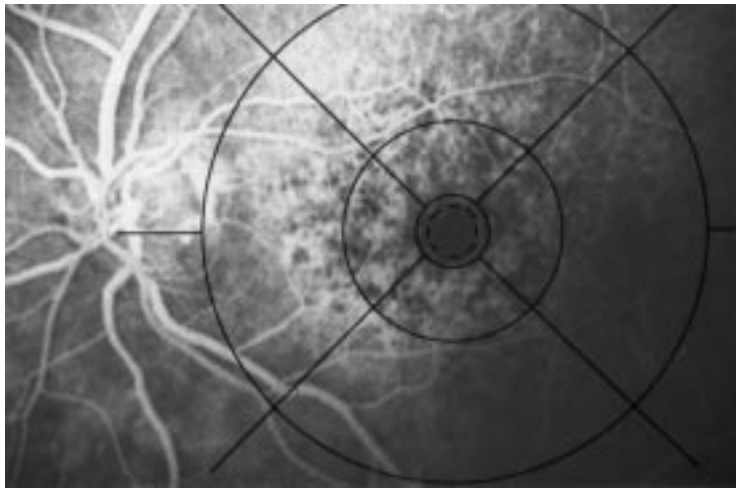


Figure 1 Simplified grid derived from the Wisconsin grid. The central area is localised inside the innermost continuous circle, the peripheral area is outside the inner circle.

#### DATA COLLECTION

##### Standardised questionnaire

The past or present professional activity, current medication use, and all major diseases (ophthalmological or systemic) were noted. The general practitioner was informed of the study, and gave written information on the systemic conditions and past and current medications. Angina pectoris was diagnosed by questioning the patient; infarction was diagnosed electrocardiographically. Hypertension was defined according to World Health Organisation guidelines. A hypertensive subject was thus defined as having a systolic blood pressure greater than 160 mm Hg and/or a diastolic blood pressure greater than 95 mm Hg at three separate measurements taken during at least two different consultations. The aim of antihypertensive treatment was to obtain a diastolic blood pressure less than or equal to 90 mm Hg.

All patients were asked questions about environmental or general factors using a standard questionnaire:

- Do you take medication for high blood pressure?
- Have you ever had heart disease, such as angina or a myocardial infarction?
- Do you smoke regularly?

If yes, since what age and how many cigarettes do you smoke a day?

If no, have you ever smoked previously (duration and amount)?

A complete ophthalmological examination was performed and results were recorded. Both eyes were studied and the eye with the worse distance visual acuity was included in the study. An eye was randomly chosen in case of equal acuity. Examination included optical correction, distance and reading acuity test (Monoyer and Parinaud charts), possible amblyopia, iris colour (light or dark; light iris colour included grey, blue, and green), and intraocular pressure. Mean distance visual acuity measured with a Monoyer chart (from 0 to 10) was right eye and left eye 4.3 (SD 3.2) for cases and right eye 7.4 and left eye 7.3 (2.5) for controls. An attempt was made to assess the presence or absence of lens opacities as well as

the nuclear colour (white, yellow, or brown) and the localisation of the opacities (nuclear, cortical, or capsular). The time of cataract extraction and the type of correction (glasses, contact lenses, or intraocular lens) were recorded. Sixty three pairs with missing information were not included.

##### Reading centre

Photographic examination included red-free frames of both maculas and fluorescein angiography (FA) of both eyes of patients with AMD. Red-free or colour frames but not FA of both maculas were required for controls. FA was considered relevant for control. Centralised reading of the photographs was performed independently by three pairs of ophthalmologists (HB and GC; MAE-B and AH; JS and GS) after testing for interobserver and intraobserver classification consistency. A simplified grid derived from the Wisconsin grid was used to localise atrophic, hypopigmented, or hyperpigmented lesions.<sup>24 25</sup> The slide of the grid was superimposed over the videoprojected fundus photographs. The centre of the circles corresponded to the centre of the macula and the outer circle was tangential to the temporal border of the optic disc (Fig 1).

All elementary lesions were assessed in the eye with the worse visual acuity and cases were divided into four different types according to the most severe or most extensive lesion<sup>26 27</sup>:

- Drusen (minimum of five for inclusion) were classified as hard or soft, and as isolated or confluent.<sup>28</sup> Hard drusen, with sharp borders, corresponded to a window defect on FA; soft drusen had fuzzy edges and were characterised by delayed and late staining on FA. Controls were drusen free on fundus examination as well on red-free or colour frames.
- Pigment epithelium alterations included hypo- or hyperpigmentation or both. Hypopigmentation corresponded to a window defect that allowed observation of the choriocapillaris on FA. Hyperpigmentation was identified as granules or clumps of pigment in or beneath the retina that resulted in blocked fluorescence on FA.<sup>29</sup>
- Geographic atrophy (GA) appeared on ophthalmoscopy as sharply demarcated zones of decreased coloration with exposure of the underlying large choroidal vessels. These areas were hyperfluorescent on FA owing to a window defect. This form has been described as "the natural end result of AMD in the absence of clinical evidence of choroidal neovascularisation."<sup>30</sup> Therefore, areas of retinal pigment epithelium (RPE) atrophy adjacent to a disciform scar were not considered to be "geographic atrophy", but rather RPE depigmentation.<sup>25-30</sup>
- Exudative maculopathy included macular serous detachment of the retina and/or RPE. On the red-free or colour frame, exudative macular degeneration was defined as the presence of a macular retinal serous detachment. This retinal serous detachment was associated with an RPE detachment, or with retinal, subretinal, and/or subRPE haemor-

Table 2 Number of inclusions

	Total	Inclusion of 1 pair	Inclusion of 2 pairs	Inclusion of 3 pairs	Inclusion of 4 pairs	Inclusion of 5 pairs	Inclusion of 6 pairs
Participating ophthalmologists	859	292	275	185	89	17	1

rhage, and/or with hard exudates. No attempt was made to assess the presence of fibrous tissue.

According to FA features, choroidal new vessels (CNV) were subdivided into well defined CNV, occult CNV, and vascularised RPE detachment. Well defined CNV were characterised by early, bright choroidal hyperfluorescence with well demarcated boundaries. With progressive dye transit, the boundaries of well defined CNV became obscured by the rapid and extensive leakage and pooling of dye in the overlying subsensory retina.<sup>31</sup> Occult CNV did not display discernible hyperfluorescence on early phase angiography. Frames of the mid and late phases, however, showed diffuse, mild leakage into the overlying subsensory retinal, often with punctate or stippled hyperfluorescence in the outer retina.<sup>32</sup> The boundaries of this hyperfluorescence were poorly demarcated in most cases.<sup>33</sup> Vascularised RPE detachments were suggested by colour and red-free photographs, and characterised by an uneven and delayed filling during the course of FA. The presence of CNV was indicated by an area of early localised and accentuated hyperfluorescence. If two types of CNV were present (that is, well defined CNV in a patch of occult CNV), both were coded.

Table 3 Sex distribution by age group

	Age (years)								Total
	51–55	56–60	61–65	66–70	71–75	76–80	81–85	86–89	
Male	7	17	47	181	122	118	73	3	568
Female	14	35	102	314	300	296	205	10	1276
Total	21	52	149	495	422	414	278	13	1844

Table 4 Characteristics in relation to the stages of AMD

	Drusen (n=496)	Pigment epithelium alteration (n=333)	Geographic atrophy (n=343)	Exudative maculopathy (n=672)
Age (years)	71.1	72.1	74.8	74.0
Sex (% women)	73.2	66.4	72.0	66.2
Drusen (%):	99.6	77.2	72.6	54.6
Small hard	69.0	48.3	42.6	27.5
Large hard	88.9	64.0	63.0	47.2
Soft	54.8	27.9	26.8	12.1
Soft and confluent	31.5	10.5	10.2	5.5
Pigment epithelium detachment	2.8	—	—	15.5
Pigmentation alterations:				
Hypopigmentation (%):	27.2	94.3	13.4	11.9
Involving the foveola	5.4	35.4	3.8	4.0
Macular, not involving the foveola	16.5	82.6	8.7	9.1
Extramacular	26.0	89.5	12.5	10.9
Hyperpigmentation (%):	36.1	83.8	65.6	31.5
Involving the foveola	12.1	33.9	23.0	10.6
Macular, not involving the foveola	22.8	72.1	45.5	21.6
Extramacular	29.8	80.5	63.0	29.5
Atrophy (%):	—	—	98.5	—
Involving the foveola	—	—	67.6	—
Macular, not involving the foveola	—	—	91.5	—
Extramacular	—	—	96.5	—
CNV (%):	—	—	—	98.2
Involving the foveola	—	—	—	30.1
Macular, not involving the foveola	—	—	—	72.0

For every subtype of lesion, the term “non-applicable” was used when the lesion was either obscured or poorly identifiable.

With projection of the modified grid onto fundus photographs and angiograms, the lesions were classified topographically as peripheral (sparing the inner circle) or central (encroaching upon the inner circle), independently of the involvement of the centre of the macula.

#### POPULATION

Each participating ophthalmologist provided up to six cases and as many controls; 1844 pairs were included by 859 participating ophthalmologists evenly distributed throughout France (Table 2).

Mean age was 73 years (range 53–89) for AMD patients and 72 (range 51–89) for controls. Males accounted for 31% of cases and females for 69% (Table 3). Cases were divided into 496 drusen, 333 pigment epithelium alterations, 343 geographic atrophy, and 672 exudative maculopathy (Table 4).

#### STATISTICAL METHOD

A 1–1 matched case-control study was designed by stratifying inclusions on the basis of age, sex, and referring ophthalmologist.

The relation between hypothesised risk factors (explanatory or independent variables) and the outcome of AMD (dependent variable) was investigated. All explanatory variables of this study were dichotomous or polychotomous with three or four categories. Dichotomous variables were systemic hypertension and coronary disease, and the reference group was defined as the absence of the disease. Design variables were created to represent the categories of the polychotomous variables. For smoking, spherical equivalent, iris colour, lens opacities, and/or cataract surgery statistical models were built using respectively non-smoking, emmetropia, dark iris, no lens opacities, and no cataract surgery as reference groups.

Results are expressed in terms of odds ratio (OR) with a 95% confidence interval.

For matched case-control studies, conditional maximum likelihood estimates of the OR must be computed.<sup>34</sup> Such estimates were obtained using standard logistic regression software (Statistical Analysis System).

The selection of variables followed three steps specified hereafter, considering 5% as the significance level for type I error rate:

- The selection process began with an univariate analysis of each variable. Any variable whose univariate test (Wald statistic) was significant was considered as a candidate for the multivariable model.
- For variables associated with the outcome of AMD, a second step investigated the relation

Table 5 Analysed risk factors in the study population

	Total population			
	Univariate analysis			Multivariate analysis OR (95% CI)
	AMD No (%)	Controls No (%)	OR (95% CI)	
Cardiovascular disease:				
Systemic hypertension	760 (41.5)	636 (34.8)	1.33 (1.17–1.53)	1.28 (1.09–1.50)
Coronary artery disease	247 (13.5)	168 (9.2)	1.56 (1.26–1.93)	1.31 (1.02–1.68)
Hypertension or coronary artery disease	858 (47.0)	708 (38.8)	1.40 (1.22–1.60)	
Smoking (non-smoking*):	1298 (70.5)	1341 (72.9)		
Past	340 (18.5)	296 (16.1)	1.24 (1.02–1.51)	1.12 (0.90–1.41)
Present	202 (11.0)	203 (11.0)	1.06 (0.84–1.33)	1.09 (0.83–1.42)
Spherical equivalent (emmetropia*):	352 (23.3)	419 (27.8)		
Myopia	252 (16.7)	277 (18.4)	1.08 (0.87–1.36)	0.99 (0.78–1.25)
Hyperopia	904 (59.9)	812 (53.8)	1.34 (1.12–1.59)	1.33 (1.11–1.59)
Iris colour (dark*):	809 (44.4)	869 (47.7)		
Light (blue, green, grey)	1013 (55.6)	953 (52.3)	1.15 (1.00–1.31)	1.22 (1.05–1.42)
Lens (no lens opacities and no cataract surgery*):	728 (39.9)	915 (50.2)		
Lens opacities	1002 (55.0)	822 (45.1)	1.69 (1.45–1.97)	
Cataract surgery	93 (5.1)	86 (4.7)	1.53 (1.10–2.11)	
Lens opacities or previous cataract surgery	1095 (60.1)	908 (49.8)	1.68 (1.45–1.95)	1.55 (1.31–1.84)

\*Reference group for polychotomous variables.

between pairs of variables and the outcome of AMD. Two variables and their interaction were taken into consideration in a multivariate logistic model. In case of a significant interaction, the two variables and their interaction were used in the following step of the analysis. In case of non-significant interaction, the confounder status of a variable was ascertained when, after adjustment, the relation between the other variables and the outcome variable disappeared.

- After the elimination of confounding factors, all the remaining variables and their interactions were introduced in the analysis for a more comprehensive modelling of the data. The goal of such an analysis was to statistically adjust the estimated effects of each variable of the multivariate logistic model for the other independent variables.

## Results

RESULTS FOR THE TOTAL POPULATION (1844 CASES)  
Univariate analysis (Table 5)

The odds ratio was 1.33 for systemic arterial hypertension, and 1.56 for coronary artery disease. Current smoking was not a risk factor for AMD, in contrast with a history of smoking (OR=1.24). Owing to missing values or imprecise answers as far as duration or amount of smoking was concerned, the relation between AMD and number of past years of smoking could not be studied in more detail. Odds ratio for hypermetropia was 1.34, and 1.15 for light coloured irises. Lens opacities were generally

mild in both cases and controls (81% with 1+ only), but the odds ratio for presence of lens opacities or past history of cataract surgery was 1.68.

Other factors, including profession and past medical history other than hypertension or coronary artery disease, did not have a significant association with AMD.

### Multivariate analysis (Table 5)

Among the previously listed significant factors, past smoking history seemed less of an influence after logistic regression analysis was performed. Multivariate analysis thus confirmed the role of the remaining characteristics with quite similar odds ratios (arterial hypertension, OR=1.28; coronary artery disease, OR=1.31; hyperopia, OR=1.33; light coloured irises, OR=1.22; and lens opacities or previous cataract surgery, OR=1.55).

RESULTS WITHIN THE VARIOUS CLINICAL GROUPS  
(TABLE 6)

### Drusen

The average age of the 496 patients with drusen was 70.8 years, with a high preponderance of women (70.8%). A total of 408 patients (79.6%) presented with hard drusen, isolated or confluent, and 231 (45.2%) with soft drusen. In a quarter of the cases (25.1%), the drusen were associated with depigmentation, and in one third of the cases (36.6%) with hyperpigmentation.

Table 6 Significant risk factors according to the various clinical groups

	Multivariate analysis			
	Drusen OR*	Pigment epithelium alterations OR*	Geographic atrophy OR*	Exudative maculopathy OR*
Cardiovascular disease:				
Systemic hypertension	NS	1.73 (1.25–2.40)	3.19 (1.81–5.64)	1.49 (1.03–2.15)
Coronary artery disease				
Hypertension or coronary artery disease				
Spherical equivalent (emmetropia†):				
Myopia	0.94 (0.58–1.50)	NS	NS	0.92 (0.63–1.35)
Hyperopia	1.42 (1.01–1.98)			1.82 (1.34–2.48)
Lens opacities or previous cataract surgery	1.78 (1.28–2.46)	1.80 (1.24–2.59)	1.78 (1.23–2.59)	1.44 (1.09–1.89)

\*OR all have 95% CI.

†Reference group for polychotomous variable.

Hyperopia (OR=1.42) and the presence of lens opacities or past history of cataract surgery (OR=1.78) were significantly associated with drusen.

#### *Alterations in retinal pigment epithelium*

There were 333 patients with alterations of the RPE; their average age was 72 years, and 65.8% were women. The majority of patients presented with a combination of depigmentation (94.5%) and hyperpigmentation (83.8%).

The only systemic risk factor associated with this group was hypertension (OR=1.73); smoking habits were not identified as risk factors. The only significant ocular risk was the presence of lens opacities or past history of cataract surgery (OR=1.80). Hyperopia or light coloured irises were not significant risk factors.

#### *Geographic atrophy (GA)*

A total of 343 cases were classified as GA; 71.4% of these patients were women. Drusen were associated with GA in 73.8% of the cases, and RPE hyperpigmentation in 67.3%; hypopigmentation was rare (12.5% cases). The average age of patients with GA was 74.3 years, making this the oldest subgroup.

A search for confounding factors showed a high link between systemic hypertension and coronary artery disease ( $p < 0.001$ ). Multivariate analysis yielded the following results: coronary disease, OR=3.19; and lens opacities or previous cataract surgery, OR=1.78.

#### *Exudative AMD*

A total of 672 eyes presented with exudative AMD. Mean age was 73.8 years, and 65.7% were female. Most eyes harboured occult CNV (72.6%), whereas approximately one third (29.7%) had well defined CNV and 16% a vascularised pigment epithelium detachment (PED). Drusen surrounded the exudative lesion in 363 (54.4%) of the eyes. RPE mottling, depigmentation, and atrophy were still visible in 33.2%, 13.5%, and 16.7% of eyes, respectively.

Multivariate analysis identified coronary artery disease (OR=1.47), hypermetropia (OR=1.83), and lens opacities or previous cataract surgery (OR=1.44) as risk factors for exudative AMD.

### **Discussion**

Several prospective, population based, or case-control studies have examined the risk factors for AMD. Clinical systemic factors for this study were chosen based on contradictory published data in the literature—that is, hypertension, past history of coronary diseases, and smoking habits. This study is the first case-control study concerning systemic and ocular risk factors performed in Western Europe.

#### AGE

The mean age of patients in the groups with drusen and with RPE alteration was 70.8 and 72.0 years, respectively. In late stages, the mean

age was 73.8 for the exudative form and 74.3 for the atrophic form, which confirms the link between severity of AMD and aging.

#### SYSTEMIC HYPERTENSION

Systemic hypertension was found to be significant by multivariate analysis when the global population was considered (OR=1.26). In the Framingham Eye Study,<sup>3</sup> Sperduto and Hiller reported an association between AMD and systemic hypertension (that is, diastolic pressure higher than 95 mm Hg). While the National Health and Nutrition Examination Survey showed higher mean systolic blood pressure in patients with AMD, no significant statistical link was established.<sup>4</sup> In their case-control study, Hyman *et al*<sup>5</sup> reported a lack of association between AMD and systemic hypertension when considered alone.

In contrast with Vidaurri *et al*,<sup>6</sup> we could not establish any relation between systemic hypertension and drusen, thus concurring with the findings of the Beaver Dam Eye Study,<sup>7</sup> although an association was found for systemic hypertension and RPE alterations (OR=1.73). In patients with GA, an association with systemic hypertension was established only with univariate analysis, owing to a strong correlation with coronary artery disease. During the exudative stage of the disease, hypertension, previously reported to be significantly associated with exudative macular degeneration,<sup>8</sup> was not identified as a risk factor in this study or in the Beaver Dam Eye Study.<sup>7</sup>

#### CORONARY ARTERY DISEASE

A strong relation was found between coronary artery disease and advanced forms of AMD. The OR was 3.30 with multivariate analysis in patients with GA; in patients with exudative disease the OR was 1.5. This association was suggested previously by Hyman *et al* in two reports.<sup>5 8</sup>

While more recent studies did not identify coronary artery disease as a risk factor for CNV, they did suggest the possible influence of a cardiovascular risk factor profile on the incidence of CNV, including increased cholesterol level and exogenous estrogen intake,<sup>9</sup> haematocrit values, and leucocyte counts.<sup>7</sup>

#### SMOKING

A history of smoking was associated with AMD (OR=1.24), but only on univariate analysis for the total population. In each subgroup, OR values were quite similar but not significant.

Smoking has been related to a higher incidence of ARM in several studies.<sup>10 11</sup> In a study by Hyman *et al*,<sup>5</sup> 83% of patients with AMD were smokers, in comparison with 65% in the control group, but this was significant only for men.

A study by Shiraga *et al*<sup>12</sup> showed a dependent relation between number of cigarettes smoked and AMD; similarly, Vingerling *et al*<sup>13</sup> provided evidence for a dose-response relation between smoking and AMD, particularly for the neovascular form.

Other studies,<sup>2 14 16</sup> however, were not able to prove that smoking was a risk factor for the development of AMD.

#### IRIS COLOUR

Hyman and colleagues<sup>5 8</sup> and Weiter *et al*<sup>17</sup> found that subjects with lightly and moderately pigmented irises were at higher risk of progression of AMD to late stages, in comparison with individuals with heavily pigmented irises. Our study, as well as the Eye Disease Case-Control Study Group,<sup>9</sup> did not find a statistically significant association in any subgroup.

#### CATARACT

Lens opacities were significantly associated with all forms of AMD in our study. OR on multivariate analysis was highest for RPE alterations (1.80), geographic atrophy (1.67), and drusen (1.74), and slightly less for exudative forms (1.44). Because of the large number of investigators, classification of these cataracts into different anatomic forms was not performed.

Recently, Klein *et al*<sup>18</sup> found a similar association between nuclear sclerosis and early stages of AMD, including drusen and RPE alterations (OR=1.96), but no association with late stages of AMD (GA and the exudative form). That study differentiated nuclear sclerosis from cortical and subcapsular cataracts, and found that the latter forms were not related to either early or late stages of AMD.

Sperduto *et al*<sup>19</sup> found contrasting results, with an increased incidence of AMD in the presence of cortical lens changes and a decreased incidence of AMD with nuclear sclerosis.

#### HYPEROPIA

Hyperopia was demonstrated to be a risk factor in the global population (OR=1.33) and in patients with the exudative forms of AMD (OR=1.83). This has been reported previously by several authors.<sup>5 9 14 15 20</sup>

Previous epidemiological studies focused on the differentiation of dry and exudative forms. On the other hand, a refined classification of AMD was used in referral centres. In this study, recruitment of cases was based on non-selected ophthalmological practice, to avoid bias of referral centres. In addition, this study, which is based on angiographic features for AMD, provides the respective proportion of each form.

In conclusion, our large case-control study, which we believe reflects a cross section of the entire population of France, suggests a relation between AMD and hypertension, coronary artery disease, light coloured irises, hyperopia, lens opacities, or history of cataract surgery. Moreover, the significance of vascular risk factors is increased for late stages of AMD, especially the atrophic forms. The impact of these risk factors on the evolution of AMD must be studied by long term follow up of these patients.

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