Development and Validation of a Risk Score for Age-Related Macular Degeneration: The STARS Questionnaire

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See the appendix for the members of the STARS Survey Group.

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Purpose. To develop and validate a risk score for AMD based on a simple self-administered questionnaire.

Methods. Risk factors having shown the most consistent associations with AMD were included in the STARS (Simplified Théa AMD Risk-Assessment Scale) questionnaire. Two studies were conducted, one in Italy (127 participating ophthalmologists) and one in France (80 participating ophthalmologists). During 1 week, participating ophthalmologists invited all their patients aged 55 years or older to fill in the STARS questionnaire. Based on fundus examination, early AMD was defined by the presence of soft drusen and/or pigmentary abnormalities and late AMD by the presence of geographic atrophy and/or neovascular AMD.

Results. The Italian and French samples consisted of 12,639 and 6897 patients, respectively. All 13 risk factors included in the STARS questionnaire showed significant associations with AMD in the Italian sample. The area under the receiving operating characteristic curve for the STARS risk score, derived from the multivariate logistic regression in the Italian sample, was 0.78 in the Italian sample and 0.72 in the French sample. In both samples, less than 10% of patients without AMD were classified at high risk, and less than 13% of late AMD cases were classified as low risk, with a more intermediate situation in early AMD cases.

Conclusions. STARS is a new, simple self-assessed questionnaire showing good discrimination of risk for AMD in two large European samples. It might be used by ophthalmologists in routine clinical practice or as a self-assessment for risk of AMD in the general population.

Keywords: age-related macular degeneration, epidemiology, risk factors

AMD is the leading cause of blindness in Western populations.[1] Worldwide, the number of people with AMD is projected to increase by approximatively 40% from 2020 to 2040.[2] There are two late-AMD phenotypes, neovascular and atrophic AMD, generally preceded by several morphologic changes (drusen and pigmentary abnormalities) called early AMD.

In the recent decades, major progress has been made in the understanding and treatment of this disease.[3] In particular, the use of antiangiogenic agents, administered through intravitreal injections, has revolutionized the management of neovascular AMD.[3] While these agents allow stabilizing or even improving visual acuity in the majority of patients, their efficacy is highly dependent on an early diagnosis of neovascular lesions before major retinal damage has occurred. Moreover, numerous risk factors have been investigated in epidemiologic studies, including smoking, family history of AMD, cardiovascular disease, and risk factors (such as body mass index [BMI], hypertension, hypercholesterolemia) and ocular risk factors (in particular iris color, cataract surgery, refractive errors). Some of these risk factors have shown very consistent associations with AMD (in particular smoking and family history of AMD), while for others, results were less consistent.[3,4] More than 50 genetic polymorphisms have also been identified as associated with AMD.[5]

Therefore, an early and simple identification of high-risk subjects now seems desirable in order to offer those subjects increased ophthalmologic follow-up (in particular for an early diagnosis and treatment of neovascular AMD, if needed). Risk scores have been proposed in order to determine individual level risk for AMD, allowing for a personalized medicine approach.[6–10] While the proposed models show good discrimination for AMD, most of models rely on assessment of genetic polymorphisms, which are currently not readily available to ophthalmologists and their patients in routine clinical practice. By contrast, although many clinical, lifestyle, and ocular risk factors have been associated with AMD, most risk scores include only a limited set of such risk factors (mainly smoking and BMI).

In the present study, we developed a simple, self-administered 13-item questionnaire to assess personalized risk for AMD in routine clinical practice. A scoring system was derived from a first sample of more than 12,000 Italian subjects and validated on a second sample of more than 6000 French subjects.

Materials and Methods

Study Design and Participants

The two cross-sectional observational studies used in the current study have been conducted according to the principles expressed in the Declaration of Helsinki. The collected data were completely deidentified and did not necessitate any medical examination beyond usual care. These studies therefore did not require patient-level consent nor institutional review board approval. Approval was obtained from the Commission Nationale Informatique et Libertés for the constitution and use of the database and from the Comité Consultatif sur le Traitement de l'Information en Matière de Recherche dans le Domaine de la Santé for the interest of the research in the field of health.

In both studies, participating ophthalmologists included all their patients aged 55 years or older over a period of 1 week. First, between May and September 2010, 12,639 patients were enrolled prospectively by 127 ophthalmologists in Italy. This first sample was used to derive the STARS (Simplified Théa AMD Risk-Assessment Scale) scoring system (derivation set). Second, between March 2013 and March 2014, 6837 patients were enrolled by 80 French ophthalmologists. This second sample was used to validate the scoring system derived from the Italian sample (validation set).

The STARS Questionnaire

The STARS questionnaire was developed with the help of two experts in the field: Cecile Delcourt, who specializes in ophthalmic epidemiology, and Francesco Bandello, a retina specialist. The included items (Table 1) were selected on the basis of a literature search and represent the risk factors that have shown the most consistent associations with AMD.[3,4] The questionnaire was designed to be simple, quick, and easy to fill in. The studied risk factors included demographic data (age, sex, BMI, and ethnicity), family history of AMD, personal medical history (smoking, BMI, hypertension, myocardial infarction, hypercholesterolemia), and eye-related parameters (iris color, cataract, refraction).

The data were collected on a single form; the first part, with questions on demography, medical history, and lifestyle, was filled in by the patient. The ophthalmologist then performed the eye examination and filled in the second part of the questionnaire (iris color, cataract extraction, refraction, fundus examination). Early AMD was defined by the presence of drusen and/or pigmentary abnormalities, whereas late AMD was defined by the presence of neovascular and/or atrophic AMD, based on fundus examination by the participating ophthalmologist.

Statistical Methods

The analysis strategy was stratified in three steps. First, a multivariate logistic regression was applied to the Italian data (derivation set). Subjects with early and late AMD were compared to those without AMD using polytomous nominal logistic regression with adjustment for age and gender. Two-sided tests were used. Multivariate analyses were conducted, including all factors demonstrating associations ($P < 0.20$) with risk for early or late AMD in age- and gender-adjusted analyses. Backward stepwise selection was used to remove nonsignificant variables ($P \geq 0.05$) from the multivariate model. Adjustments for age and gender were maintained in the final multivariate model.

Second, a predictive function was built by using the final model retained during the multivariate analysis. The regression coefficients of the final model were scaled and rounded to integers to create a score easy to implement. Optimal scaled and rounded coefficients were calculated using the algorithm proposed by Cole.[11] This algorithm finds the smallest common multiplier, k, that permits each estimated coefficient to be transformed into an integer without too much loss of precision. The predictive value of this new scoring system was evaluated using this set of data. The performance of this prognostic score was assessed using the C statistic that is identical to the area under the receiver operator characteristic curve in the case of a binary outcome.

Third, external validation of the predictive function was assessed on the French sample. The predictive function was applied on French data sample (validation set). The Hosmer-Lemeshow calibration statistics were calculated to measure the significance of the deviation between predicted and observed outcomes.

Finally, to make the use of the STARS risk scale easier, three categories were created. The first cutpoint (10) was chosen to

Table 1. The STARS Questionnaire

Part 1: Risk Factors (filled by the patient)
Age, y
55–65
Between 65 and 74
Between 75 and 85
>85
Gender
Male
Female
Ethnicity
Caucasian
North-African
Family history of AMD
Father
Mother
Brother/sister
BMI (weight/height^2 [m])
<25
Between 25 and 30
>30
Smoking
Current
Past:
<5 y
Between 5 and 10 y
>10 y
Personal medical history
Myocardial infarction
Hypertension
Atherosclerosis
Hypercholesterolemia
Part 2: Eye examination (filled by the ophthalmologist)
Iris color
Light
Dark
Cataract surgery
Yes
No
Refraction
Myopia
Hyperopia
Fundus examination
Soft drusen
Pigmentary abnormalities
Late AMD

Table 2. Characteristics of Derivation and Validation Samples

Characteristics	Italian Sample (Derivation) N = 12,639, (%)	French Sample (Validation) N = 6837, (%)
AMD		
No	5095 (40.3%)	4900 (71.7%)
Early	6061 (48.0%)	1250 (18.3%)
Late	1483 (11.7%)	687 (10.0%)
Gender		
Male	6051 (47.9%)	2590 (40.0%)
Female	6588 (52.1%)	3891 (60.0%)
Age		
55–64 y	3937 (31.1%)	2101 (31.0%)
65–74 y	3962 (31.3%)	2009 (29.6%)
75–85 y	3303 (26.1%)	2007 (29.6%)
>85 y	1437 (11.4%)	671 (9.9%)
Ethnicity		
Caucasian	10960 (91.6%)	6341 (94.5%)
North-African	1011 (8.4%)	309 (4.6%)
Family history of AMD		
No	7705 (61.0%)	6133 (89.7%)
Yes	4934 (39.0%)	704 (10.3%)
BMI		
<25 kg/m^2	3202 (26.9%)	2715 (41.9%)
[25–30] kg/m^2	5959 (50.1%)	2785 (43.0%)
>30 kg/m^2	2732 (23.0%)	979 (15.1%)
Smoking		
Never smoker	5021 (39.7%)	4179 (63.6%)
Former smoker >10 y	2616 (20.7%)	1479 (22.5%)
Former smoker ≤10 y	2800 (22.2%)	266 (4.0%)
Current smoker	2202 (17.4%)	644 (9.8%)
History of myocardial infarction		
No	11287 (89.3%)	6267 (94.9%)
Yes	1352 (10.7%)	340 (5.1%)
History of hypertension		
No	6374 (50.4%)	3976 (60.3%)
Yes	6265 (49.6%)	2615 (39.7%)
History of atherosclerosis		
No	10210 (80.8%)	5979 (91.1%)
Yes	2429 (19.2%)	586 (8.9%)
History of hypercholesterolemia		
No	7717 (61.1%)	4981 (75.9%)
Yes	4922 (38.9%)	1582 (24.1%)
Iris color		
Dark	7108 (56.9%)	3246 (49.6%)
Light	5377 (43.1%)	3300 (50.4%)
Cataract surgery		
No	7046 (61.2%)	4507 (71.1%)
Yes	4463 (38.8%)	1830 (28.9%)
Myopia		
No	7379 (58.4%)	4911 (75.6%)
Yes	5260 (41.6%)	1588 (24.4%)
Hyperopia		
No	7932 (62.8%)	3688 (56.7%)
Yes	4707 (37.2%)	2811 (43.3%)

be highly sensitive (sensitivity above 90% in the derivation sample). The second cutpoint (20) was chosen to be highly specific (specificity above 90% in the derivation sample). This led to three groups: low risk (0–9 points), moderate risk (10–19 points), high risk (20+).

The statistical tests were bilateral with a risk of 5% error. All statistical analyses were performed with analytic software (SAS 9.3; SAS Institute Inc., Cary, NC, USA).

Results

As shown in Table 2, patients with an early or late AMD represented respectively 48.0% and 11.7% in the Italian sample and 18.3% and 10.0% in the French sample. About 31% of patients were younger than 65 years, or between 65 and 75 years, with a slight majority of women (52% for Italian sample and 60% for French sample). The distribution of ethnic groups showed a vast majority of Caucasian subjects (91.6% for Italian sample and 94.5% for French sample).

The distribution of risk factors appeared to be somewhat different in the Italian and French samples. Indeed, Italian patients declared more current smoking (17.4 vs. 9.8%), history of myocardial infarction (10.7% vs. 5.1%), hypertension (49.6% vs. 39.7%), atherosclerosis (19.2% vs. 8.9%), and hypercholesterolemia (38.9% vs. 24.1%). Italian patients also reported much more frequently a family history of AMD (39.0% vs. 10.3%), dark eyes (56.9% vs. 49.6%), cataract surgery (38.8% vs. 28.9%), and myopia (41.6% vs. 24.4%) but declared less hyperopia (37.2% vs. 43.3%) than did the French patients.

As a first step, a multivariate model was estimated on the derivation (Italian) sample. After adjustment for age and gender, all risk factors showed significant associations with AMD and were introduced in the final multivariate model (data not shown). The final multivariate model was applied on the derivation sample of 10,223 Italian patients without any missing data on any of the risk factors. Table 3 gives the odds ratio (OR) and the 95% confidence interval (CI) for the studied risk factors in the multivariate model for the derivation dataset.

Female sex was associated with an increased risk for late, but not early, AMD (OR = 1.36 and OR = 0.92, respectively). Older age was associated with an increased risk for both early and late AMD ($P < 0.001$ for all age groups). The North-African ethnic group was significantly related to early and late AMD (OR = 3.43 and OR = 3.70, respectively, $P < 0.0001$). A family history of AMD was significantly associated with an increased risk for early and late AMD (OR = 3.93 and OR = 6.99, respectively; $P < 0.0001$). Subjects with BMI >30 kg/m^2 were at increased risk for early and late AMD (OR = 1.23 and OR = 1.89, respectively; $P < 0.0001$). Smoking, whether current or past (≤10 years or >10 years), was significantly associated with an increased risk for early and late AMD. All four cardiovascular diseases and risk factors were significantly associated with early and late AMD, with OR between 1.52 and 2.54 ($P < 0.0001$).

Cataract surgery, myopia, and hyperopia were associated with increased risk for early and late AMD with OR between 1.48 and 3.48 ($P < 0.0001$). Patient eyes with a light-colored iris were associated with early AMD (OR = 1.27, $P < 0.0001$) but not with late AMD (OR = 1.14, 95% CI (0.97–1.33).

As a second step, we determined rounded scores for each risk factor, based on the regression coefficients for late AMD in the final multivariate model. The algorithm calculating a simpler score from the final model leads to an optimal scaling multiplier (k), unique and equal to 3.85 (Table 4). The obtained scores are then rounded, giving the final scores for each risk factor. For instance, for gender, the β coefficient is 0.30. It is multiplied by 3.85, giving 1.15, which is then rounded to 1. Thus, males will be attributed a score of 0 and females a score of 1. Similarly, regarding age, scores of 0, 2, 4, and 9 will be attributed to subjects aged 55–64, 65–74, 75–85, >85 years or more, respectively. Finally, for a given patient, the STARS score predicting late AMD is easily provided by summing the scaled rounded coefficients for the patient's observed risk factors.

As a third step, the performance of the STARS score to discriminate patients with AMD from patients without AMD was tested using receiving operating characteristic (ROC) curves. The area under the ROC curve for the STARS score was

Table 3. Multivariate Associations of Risk Factors With Early and Late AMD (Derivation Sample)

Characteristics	Early AMD OR [95%CI]	Late AMD OR [95%CI]	Global *P*
Gender			
Male	1.00, ref	1.00, ref	
Female	0.92 [0.82; 1.02]	1.36 [1.16; 1.59]	<0.0001
Age			
55–64 y	1.00, ref	1.00, ref	
65–74 y	1.71 [1.51; 1.94]	1.61 [1.27; 2.03]	<0.0001
75–85 y	2.08 [1.81; 2.40]	3.02 [2.39; 3.81]	<0.0001
>85 y	4.09 [3.3; 5.06]	11.29 [8.49; 15.02]	<0.0001
Ethnicity			
Caucasian	1.00, ref	1.00, ref	
North-African	3.43 [2.64; 4.46]	3.70 [2.70; 5.07]	<0.0001
Family history of AMD			
No	1.00, ref	1.00, ref	
Yes	3.93 [3.48; 4.44]	6.99 [5.85; 8.34]	<0.0001
BMI			
<25 kg/m^2	1.00, ref	1.00, ref	
[25–30] kg/m^2	1.09 [0.97; 1.23]	1.24 [1.02; 1.51]	<0.0001
>30 kg/m^2	1.23 [1.06; 1.43]	1.89 [1.51; 2.37]	<0.0001
Smoking			
Never smoker	1.00, ref	1.00, ref	
Former smoker >10 y	1.21 [1.05; 1.40]	1.50 [1.20; 1.86]	<0.0001
Former smoker ≤10 y	1.77 [1.52; 2.06]	2.28 [1.83; 2.85]	<0.0001
Current smoker	1.40 [1.21; 1.62]	1.63 [1.28; 2.08]	<0.0001
History of myocardial infarction			
No	1.00, ref	1.00, ref	
Yes	1.60 [1.32; 1.94]	2.30 [1.81; 2.92]	<0.0001
History of hypertension			
No	1.00, ref	1.00, ref	
Yes	1.76 [1.58; 1.95]	1.97 [1.68; 2.30]	<0.0001
History of atherosclerosis			
No	1.00, ref	1.00, ref	
Yes	1.71 [1.49; 1.96]	2.54 [2.12; 3.05]	<0.0001
History of hypercholesterolemia			
No	1.00, ref	1.00, ref	
Yes	1.52 [1.37; 1.69]	1.78 [1.52; 2.09]	<0.0001
Iris color			
Dark	1.00, ref	1.00, ref	
Light	1.27 [1.14; 1.41]	1.14 [0.97; 1.33]	<0.0001
Cataract surgery			
No	1.00, ref	1.00, ref	
Yes	2.23, [1.98; 2.50]	3.48 [2.95; 4.10]	<0.0001
Myopia			
No	1.00, ref	1.00, ref	
Yes	2.58 [2.26; 2.94]	1.48 [1.18; 1.85]	<0.0001
Hyperopia			
No	1.00, ref	1.00, ref	
Yes	3.15 [2.75; 3.62]	3.27 [2.62; 4.08]	<0.0001

ref, reference.

0.78 in the Italian (derivation) sample and 0.72 in the French (validation) sample, showing good discrimination in both samples (Fig. 1). In the French (validation) sample, the Hosmer-Lemeshow statistic was 3.31 ($P = 0.91$), also indicating a good calibration.

Finally, as shown in Figure 2, in the Italian sample, less than 5% of patients with late AMD were considered at low risk for AMD, and symmetrically, less than 10% of patients without AMD were considered at high risk for AMD. In the French sample, the distribution of risk scores was somewhat different, with overall fewer patients classified as high risk. But again, only about 10% of patients with late AMD were considered at low risk, and less than 5% of those without AMD were considered at high risk. When grouping the French and Italian samples, almost 90% of those classified at high risk had early or late AMD, and symmetrically, more than 80% of those classified at low risk for AMD were free of AMD (Fig. 3). When using the high-sensitivity cutpoint of 10 points, sensitivity was 91.9% and 79.6%, specificity 43.6% and 44.7%, positive predictive value 74.1% and 36.5%, and negative predictive value 75.7% and 84.5% in the Italian and French samples, respectively.

Discussion

STARS is a new 13-item, simple questionnaire that showed good discrimination of patients with and without AMD. The first sample of patients, in Italy, was used to estimate the parameters of the scoring, and the second, independent

Table 4. Simplified Scoring System Based on Multivariate Model for Late AMD in the Italian (Derivation Sample)

Variables	OR [95% CI]	Regression Coefficients (β)	Final Scores ($k = 3.85505$)
Gender			
Male	1.00, ref	0	0
Female	1.36 [1.16; 1.59]	0.30	1
Age			
55–64 y	1.00, ref	0	0
65–74 y	1.61 [1.27; 2.03]	0.47	2
75–85 y	3.02 [2.39; 3.81]	1.10	4
>85 y	11.29 [8.49; 15.02]	2.42	9
Ethnicity			
Caucasian	1.00, ref	0	0
North-African	3.70 [2.70; 5.07]	1.31	5
Family history of AMD			
No	1.00, ref	0	0
Yes	6.99 [5.85; 8.34]	1.94	7
BMI (kg/m^2)			
<25 kg/m^2	1.00, ref	0	0
[25–30] kg/m^2	1.24 [1.02; 1.51]	0.21	1
>30 kg/m^2	1.89 [1.51; 2.37]	0.64	2
Smoking			
Never smoker	1.00, ref	0	0
Former smoker >10 y	1.50 [1.20; 1.86]	0.40	2
Former smoker ≤10 y	2.28 [1.83; 2.85]	0.82	3
Current smoker	1.63 [1.28; 2.08]	0.49	2
History of myocardial infarction			
No	1.00, ref	0	0
Yes	2.30 [1.81; 2.92]	0.83	3
History of hypertension			
No	1.00, ref	0	0
Yes	1.97 [1.68; 2.30]	0.68	3
History of atherosclerosis			
No	1.00, ref	0	0
Yes	2.54 [2.12; 3.05]	0.93	4
History of hypercholesterolemia			
No	1.00, ref	0	0
Yes	1.78 [1.52; 2.09]	0.58	2
Iris color			
Dark	1.00, ref	0	0
Light	1.14 [0.97; 1.33]	0.13	0
Cataract surgery			
No	1.00, ref	0	0
Yes	3.48 [2.95; 4.10]	1.25	5
Myopia			
No	1.00, ref	0	0
Yes	1.48 [1.18; 1.85]	0.39	2
Hyperopia			
No	1.00, ref	0	0
Yes	3.27 [2.62; 4.08]	1.18	5

ref, reference.

sample, in France, was used to validate the discriminating abilities of the score. The score showed good discrimination in both samples (area under the ROC curve of 0.78 and 0.72 in the Italian and French samples, respectively).

As expected, all selected risk factors were significantly associated with early and/or late AMD. Besides age, the most consistent risk factors for AMD are family history of AMD and smoking,[12] both of which show very strong associations with early and late AMD in the present study. Previous studies have suggested that not only current smokers, but also past smokers are at increased risk for smoking.[13] Several studies have suggested that it takes more than 20 years for past smokers to return to the level of risk of those who never smoked.[14–18] The present study further confirms that AMD risk remains increased in past smokers for more than 10 years after cessation. It also suggests that recent quitters (less than 10 years) may actually be at higher risk than current smokers. Previous studies showed similar associations, with higher[14–16] or similar[17] risk in recent quitters compared with current smokers. Overall, these data suggest that there is a lag between smoking cessation and decrease in AMD risk (probably about 10 years) and then a slow decrease, with a return to the risk of nonsmokers only after more than 20 years. The observation of an increased risk in recent quitters may be due to a different profile of quitters by comparison with current smokers (more intense and longer exposure to smoking, occurrence of

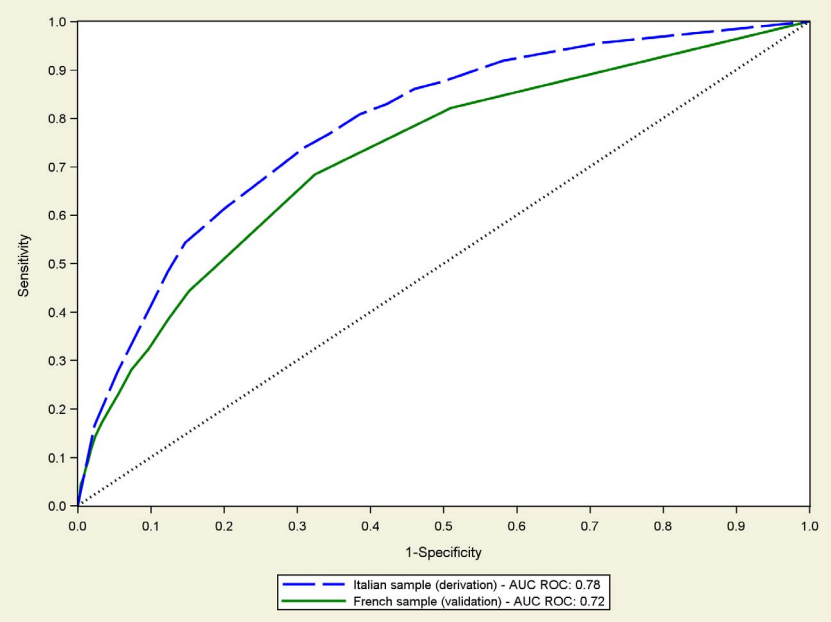

FIGURE 1. ROC curve for the discrimination of AMD according to the STARS risk score.

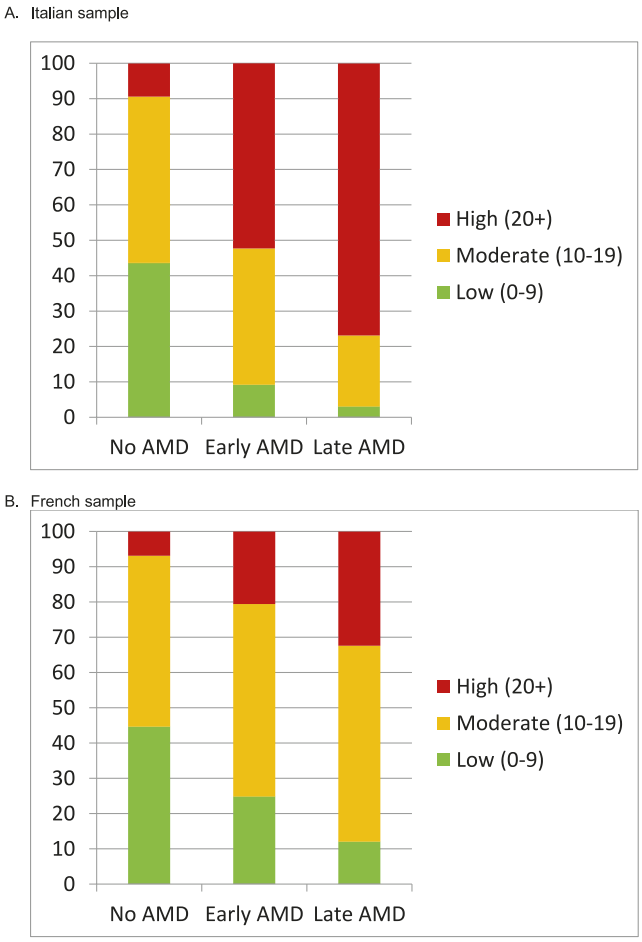

FIGURE 2. Distribution of the risk score categories (low, moderate, high) according to AMD status.

cardiovascular diseases or cancer, which may represent an incentive to stop smoking). The relationship of the characteristics of smoking exposure with AMD risk would need to be further explored in future studies. In particular, future versions of the STARS questionnaire could add an item for long duration of smoking cessation (more than 20 years) in order to verify that the excess risk is cancelled for long durations of cessation.

The present study also shows significantly increased risk for AMD in subjects with cardiovascular disease and risk factors (obesity, hypercholesterolemia, hypertension). While epidemiologic studies have been less consistent in this field, a meta-analysis suggests that history of cardiovascular disease, obesity, and hypertension are associated with moderately increased risk for AMD. Inconsistencies of these associations in epidemiologic studies may be at least partially explained by their limited statistical power, in particular for the detection of associations of moderate strength (OR = 1.5–2). By contrast, the present study, which includes more than 12,000 participants (including

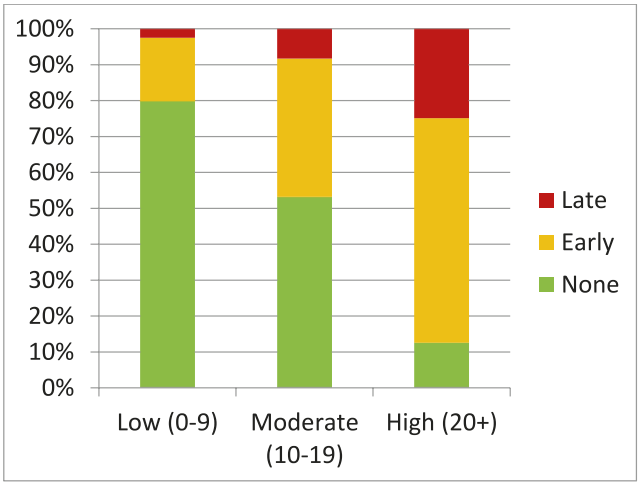

FIGURE 3. Distribution of AMD status according to the risk categories (Italian and French samples).

more than 1400 cases of late AMD), benefited from a very high statistical power (greater than 99.9% to detect OR = 1.5 for a risk factor present in 10% of the population).

Associations of AMD with ocular risk factors (iris color, cataract extraction, refraction) have been suggested in the past, often with inconsistent findings. In the present study, light iris color was significantly associated with a weakly increased risk for early AMD (OR = 1.27, 95% CI: 1.14–1.41), while its association with late AMD did not reach statistical significance (OR = 1.14, 95% CI: 0.97–1.33). Again, very large studies may be necessary to reach sufficient statistical power to detect such weak associations. In the present study, hyperopia was significantly associated with a 3-fold increased risk for early and late AMD (OR = 3.15 and 3.27, respectively). This is consistent with some previous studies,[19–25] while others found no significant associations.[26,27] In the present study, myopia was also associated with an increased risk for AMD, which represents an unexpected finding. Finally, a number of studies have suggested that subjects having undergone cataract surgery may be at higher risk for AMD,[28–33] although these findings are not completely consistent.[34] The present study further confirms these observations. The increased risk for AMD in operated eyes partially may be due to an easier diagnosis as a result of transparency of the media. It may also be due to common risk factors for cataract and AMD. Indeed, associations of AMD with lens opacities have been reported in some studies.[29] Finally, the association of AMD with cataract extraction may also be due to a higher amount of light passing through the artificial lens, leading to damage of the retina. However, this potential causal relationship cannot be demonstrated in observational studies.

A new finding from our investigations is represented by the identification of a higher risk for AMD in subjects of North-African origin. While the present study suggests that North-Africans living in Italy are at much more increased risk for AMD than subjects of European origin, these results must be taken with caution since they may be biased by different attitudes toward the consultation of ophthalmologists in these communities. Thus, the highest proportion of AMD cases in North-Africans may reflect a tendency to consult an ophthalmologist only for relatively advanced diseases (and less for a simple adaptation of eyeglasses, for instance). This finding would therefore need to be confirmed in other, truly population-based studies. If confirmed, the reasons for such increased risk will need to be identified. They may include genetic and/or environmental risk factors. We have recently shown that North-Africans living in Algeria had a lower risk for AMD than did North-Africans living in Italy, together with a generally healthier lifestyle (less obesity, smoking, cardiovascular diseases, and higher consumption of fruits and vegetables).[35] Adoption of Western lifestyle has been shown to be associated with increased risk of chronic diseases in many populations migrating from developing countries.[36]

This new short questionnaire offers several advantages. It is simple and quick, allowing its use in large population samples for early evaluation of AMD risk, such as the studies we have conducted in, overall, more than 12,000 Italian patients and more than 6000 French patients. Furthermore, this allowed for a robust estimation of the scores for each risk factor.

This new scoring of AMD risk is based on self-assessment (together with assessment of ocular risk factors by the ophthalmologist) and thus does not require any biological sampling. This is a major difference compared with other prediction models, which were all based on genetic determinations (and thus required DNA sampling). While the discriminative performances of the score are somewhat lower than in previous risk scores (AUC under the ROC curve generally between 0.80 and 0.90),[6–10] the sensitivity was high in both samples (91.9% and 79.6% in the Italian and French samples, respectively) so that the vast majority of true AMD cases would be detected. Although specificity was relatively low (43.6% and 44.7%, respectively), the negative predictive value was also high in both samples (75.7% and 84.5%, respectively), showing that among those classified at low risk, the vast majority would actually be free of AMD. Moreover, as shown in Figure 2, most of the false positives would be classified as moderate risk, and only a minority as high risk. Finally, the positive predictive values were very different in the Italian and French samples (74.1% and 36.5%), although sensitivity and specificity were in the same range in both samples. This highlights the fact that predictive values are highly dependent on the prevalence of the disease, which was quite different in the two samples (59.7% in the Italian sample and 28.3% in the French sample). Thus, the proportion of AMD cases among subjects classified as moderate or high risk may be quite different in different populations or according to the screening strategies (for instance, general public with low AMD risk or ophthalmologists specialized in retinal diseases with patients at higher risk).

This questionnaire might be used by ophthalmologists in routine clinical practice in all patients aged 50 years or more attending a routine visit to help classify patients at high, moderate, or low risk of AMD. STARS might also be used as a self-assessment for risk of AMD in the general population (through communications to the general public or general practitioners, for instance), as an incentive to visit an ophthalmologist for those subjects classified at high or moderate, risk. Such a use in the general public would, however, need to be validated, as the two studies presently used were performed among patients visiting an ophthalmologist, thus may overrepresent subjects with AMD, as well as subjects with good knowledge of AMD risk factors.

While previous risk scores were mainly based on genetic polymorphisms and a limited number of environmental factors (usually mainly smoking and BMI), the present scoring includes a comprehensive assessment of AMD risk factors, including ethnicity, family history of AMD, lifestyle, and personal medical history. It would be particularly interesting to assess in prospective studies whether this scoring is also associated with the risk of developing AMD. The combination of such a comprehensive assessment of environmental risk factors with a genetic risk scoring might also significantly improve the prediction ability of previous prediction models.

Limitations of this questionnaire include its self-reported nature. Assessment of risk factors through biomedical measurements (weight, height, blood pressure, blood lipids, etc.) would most probably increase the reliability of the scoring. However, it would also limit its future use by increasing the difficulty in assessment of risk factors. Because of the short and rapid assessment of risk factors, we were also unable to include nutritional risk factors. Indeed, there is converging epidemiologic evidence that the risk for AMD is lower in subjects with high dietary intake of antioxidants, lutein and zeaxanthin, and omega-3 polyunsaturated fatty acids.[3] However, assessment of such dietary intakes requires detailed dietary inquiries, which were not feasible in the context of these studies.

In conclusion, STARS is a new, validated, simple and quick questionnaire, allowing for self-assessment of the early risk for AMD. This questionnaire was tested in large samples of patients visiting their ophthalmologist in Italy and in France and showed good discrimination for AMD. Future studies are needed to determine the discriminative abilities in other contexts (in particular other countries and other types of population, including the general population). Prospective studies assessing the ability of such a questionnaire to predict

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future occurrence of AMD would also be particularly valuable.

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The STARS questionnaire is available upon request.

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