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Joint Contribution of Genetic Susceptibility and Modifiable Factors to the Progression of Age-Related Macular Degeneration over 10 Years

The Three Continent AMD Consortium Report

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Purpose: To assess joint effects of genetic and modifiable factors on the 10-year progression of age-related macular degeneration (AMD).

Design: Individual and pooled data analyses of 2 population-based cohorts.

Participants: Blue Mountains Eye Study (BMES) and Rotterdam Study (RS) participants (n = 835).

Methods: Participants of the BMES and RS were followed up over 10 years or more. At baseline and follow-up visits, interviews using questionnaires and eye examinations with retinal photography were performed. Age-related macular degeneration was assessed by trained photographic graders and verified by retinal specialists. Genetic susceptibility to AMD meant carrying 2 or more risk alleles of the *CFH* or *ARMS2* SNPs, or both (rs1061170 and rs10490924), relative to 0 or 1 risk allele. Discrete logistic regression models were used to investigate the joint associations of genetic susceptibility and either smoking, fish consumption, dietary intake of lutein–zeaxanthin, or combined environmental risk scores from the 3 modifiable factors with the risk of AMD progression. Odds ratios (ORs) with 95% confidence intervals (CIs) and synergy indexes are reported.

Main Outcome Measure: Ten-year progression of AMD, categorized as any (≥1 step) or 2-step (≥2 steps) progression on the Three Continent AMD Consortium 5-step severity scale.

Results: Older age, the presence of AMD genetic susceptibility, and baseline AMD status were associated strongly with AMD progression ($P < 0.0001$). In analyses of pooled data, each additional score from the combined environmental risk scores was associated with an increased risk of 2-step progression over 10 years (OR, 1.26; 95% CI, 1.02–1.56). The copresence of AMD genetic susceptibility and combined risk score of 3 or more was associated with a substantially higher risk of 2-step progression compared with the presence of either factor alone. There was a significant synergistic effect (OR, 4.14; 95% CI, 1.07–15.95) and interaction ($P = 0.025$) between genetic susceptibility and environmental risk score of 3 or more.

Conclusions: Among persons with AMD genetic susceptibility and pre-existing early AMD lesions, presenting with high environmental risk scores from 3 modifiable factors (smoking, infrequent consumption of fish, low lutein–zeaxanthin intake) were associated with an increased risk of 2-step progression over 10 years. *Ophthalmology Retina 2017;■:1–10 © 2017 by the American Academy of Ophthalmology*

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Age-related macular degeneration (AMD) is a multifactorial disease and a leading cause of visual impairment in developed countries.[1–5] The progression of AMD has been documented in a number of population-based studies.[6–10] However, few studies have examined the joint contribution of AMD genetic and environmental factors to AMD progression over the long term (≥10 years).[7,10,11] Age-related macular degeneration is known to be associated with genetic and lifestyle risk factors. Genetic susceptibility to AMD is not modifiable; however, lifestyle and dietary factors are. Modifiable factors are of

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particular interest because they can be targeted for the prevention or slowing of progression to late AMD, that may lead to blindness. Twin studies have demonstrated discordance in the development of AMD in identical twins,[12] suggesting the involvement of environmental exposure mechanisms in AMD pathogenesis.[13] Another twin study in the United States demonstrated that worse stages of AMD were more prominent in an identical twin who smoked compared with the fellow twin who did not smoke,[14] implying that environmental factors can influence AMD risk independent of genetic factors.[14]

A few studies have examined the joint contribution of genetic susceptibility, lifestyle, and dietary factors to the risk of late AMD,[15–17] and few specifically focused on AMD progression in persons or eyes with early AMD lesions present. No consistent patterns of joint contribution have emerged, likely because of the relatively small sample sizes of the studies and therefore being underpowered. Using 2 population-based cohorts that used comparable examination methods and had long-term follow-up, we aimed to examine factors associated with AMD progression over the long term among participants with early AMD lesions in either eye at baseline. In particular, we focused on the joint contribution of genetic and modifiable factors to the progression.

Methods

In the Three Continent AMD Consortium (3CC), we included the Blue Mountains Eye Study (BMES) and Rotterdam Study (RS),[18,19] in both of which dietary data were collected. Written informed consent was obtained from each participant at each visit in the two studies. Both studies adhered to the tenets of the Declaration of Helsinki.

The Blue Mountains Eye Study

The BMES recruited 3654 participants (82.4% of those eligible) 49 years of age or older and living in 2 postcode regions west of Sydney during baseline examinations (1992–1994). Of these participants, 2334, 1952, and 1149 participants were re-examined after 5, 10, and 15 years, respectively. All examinations were approved by the University of Sydney and Western Sydney Area Health Service Human Research Ethics Committees.

After pharmacologic mydriasis, 30° stereoscopic color fundus photographs of the macula and optic disc and nonstereoscopic photographs of the other 4 retinal fields of both eyes were obtained using a Zeiss FF3 fundus camera (Carl Zeiss, Oberkochen, Germany) at the baseline, 5-, and 10-year visits. At the 15-year follow-up examination, 40° digital photographs were obtained with a Canon CF-60 DSi camera with DS Mark II body (Canon, Inc, Tokyo, Japan).

Rotterdam Study

At baseline (1990–1993), the RS examined 7983 participants (77.7% participation rate) 55 years of age or older, 6419 of whom underwent ophthalmic examinations and retinal photography. Re-examination visits took place between 1993 and 1995, between 1997 and 1999, and between 2002 and 2004. The mean follow-up period was 10 years. To assess 10-year progression, data from the first, third, and fourth visits were used. All examinations were approved by the Medical Ethics Committee of the Erasmus Medical Center and the Ministry of Health, Welfare and Sport of The Netherlands, implementing the Wet Bevolkingsonderzoek: ERGO (Population Studies Act: Rotterdam Study).

At the first 3 visits, after pharmacologic mydriasis, 35° stereoscopic color fundus photographs of the macula were obtained with the Topcon TRV-50VT fundus camera (Topcon Optical Co, Tokyo, Japan). For the fourth visit, 35° digital photographs were obtained with a Topcon TRC 50EX fundus camera with Sony DXC-950P digital camera (Topcon Optical Co).

Photographic Grading and Definitions of Age-Related Macular Degeneration Progression

Retinal photographs of both eyes initially were graded by trained graders of each study following the Wisconsin Age-Related Maculopathy Grading System.[20] All incident late AMD cases detected from each study initially were adjudicated and confirmed by the retinal specialists of the corresponding study team, and next were cross-confirmed by principal investigators of the Beaver Dam Eye Study, BMES, and RS.[15]

A 5-step severity scale that was developed after phenotype harmonization of AMD in the 3CC[18] was used to define AMD severity (see Appendix, available at www.ophthalmologyretina.org). The scale defines AMD by levels 10, 20, 30, 40, and 50, corresponding to no AMD, mild early AMD, moderate early AMD, severe early AMD, and late AMD. Early AMD was defined as levels 20 to 40 and late AMD was defined as level 50.[18]

Progression of AMD was defined as an increment in the steps along the severity scale from level 20 to 50 in eyes that had level 20 or higher AMD at baseline. The increment from level 10 to 20 (from no AMD to mild early AMD) was not included in this report because it was considered to be the initial development of AMD. Progression was categorized as either any progression (≥1-step increment) versus no progression or 2-step progression (≥2-step increment in the 3CC AMD severity scale) versus 1-step increment or less over a period of 10 years.

Assessment of Risk Factors

In both studies, smoking status was assessed using an interviewer-administered questionnaire. In the BMES, participants were classified as nonsmokers if they answered "no" to smoking regularly. If participants had quit smoking more than 1 year before the examination, they were classified as past smokers. Current smokers were defined as participants who currently smoked or had stopped smoking less than 1 year before the examination. In the RS, smoking status was defined as never, past, or current according to participants responses "no, never smoked," "yes, stopped smoking," and "yes, still smoking," respectively.[21,22]

Dietary information was obtained from a validated 145-item semiquantitative food frequency questionnaire in the BMES.[23] The electronic Australian Tables of Food Composition[24,25] and the United States Department of Agriculture carotenoid food composition database[26] were used to calculate the intake of most nutrients, including lutein–zeaxanthin intake, in micrograms. Data on fish consumption were obtained from the food frequency questionnaire and defined as less than 1 serving per week, termed *infrequent fish consumption*, compared with 1 serving per week or more. In the RS, dietary data were collected by a trained dietician at the research center using a 170-item validated semiquantitative food frequency questionnaire,[27] as described previously.[15] A computerized Dutch Food Composition Table was used to convert the dietary data into total energy and nutrient intakes per day.[28]

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