Vitreomacular Adhesion and Its Association With Age-Related Macular Degeneration in a Population-Based Setting: The Alienor Study

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Purpose. The purpose of this study was to describe vitreomacular adhesion (VMA), diagnosed with spectral-domain optical coherence tomography (SD-OCT), its risk factors, and its association with AMD in a population-based study of French elderly subjects.

Methods. Six hundred twenty-two of 624 (99.7%) participants of the Alienor study (Bordeaux, France), ≥75 years of age, had gradable SD-OCT scans of the macula in at least one eye. VMA was defined as visible perifoveal vitreous separation with remaining vitreomacular attachment and unperturbed foveal morphologic features. Late AMD was classified from retinal color photographs, SD-OCT, and ophthalmologic history. Early AMD was classified from retinal photographs and defined by the presence of large drusen and/or reticular drusen and/or pigmentary abnormalities.

Results. The prevalence of VMA was 15.8%, decreased with age (18.1% in subjects 75 to 84 years of age versus 8.9% after 85 years of age), and was higher in men than women (20.6% vs. 12.8%). VMA also tended to be less frequent in eyes with a history of cataract surgery (odds ratio [OR] = 0.66, $P = 0.05$), after adjustment for age and sex. No associations of VMA with other risk factors (cardiovascular risk factors, dietary intake of omega-3 fatty acids, lifetime ultraviolet radiation exposure, major AMD genetic polymorphisms) were found. After multivariate adjustment, VMA was not significantly associated with early or late AMD (OR = 1.14, $P = 0.70$ and OR = 0.78, $P = 0.51$ for early and late AMD, respectively).

Conclusions. VMA was visible on SD-OCT in 16% in this sample of elderly French subjects but was not associated with AMD. Prospective studies of the associations of VMA with AMD are needed.

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

With age, the vitreous cortex may detach gradually from the retina, leading to posterior vitreous detachment (PVD). This detachment starts in the perifoveal area and progresses after months or years to a total PVD.[1] It is only with the development of ultrasound examinations and, more recently, with spectral-domain optical coherence tomography (SD-OCT) that the detailed examination of the vitreous and the vitreomacular interface has improved.

The International Vitreomacular Traction Study (IVTS) group has developed an OCT-based classification of the vitreomacular interface.[2] In this classification, vitreomacular adhesion (VMA) is defined as perifoveal vitreous separation with remaining vitreomacular attachment and unperturbated foveal morphologic features.

Several studies have suggested a link between VMA and exudative AMD. Krebs et al. showed a higher frequency of VMA in patients with AMD: OCT detected persistent central vitreoretinal adhesion in 18 (36%) of 50 eyes with exudative AMD, significantly higher than in nonexudative AMD (4 of 57 [7%]) and in controls (6 of 56 [10%]).[3] In a retrospective case-control study, Mojana et al.[4] found that the hyaloid adhesion was associated with AMD: VMA was present in 28% in patients with AMD compared with 16% in the control group. Robison et al.[5] evaluated vitreomacular adhesion in different stages of AMD. VMA was present in 11 (38%) of 29 of eyes with exudative AMD and in only 3 (10%) of 29 eyes with nonexudative AMD. In a paired study performed to reduce the effects of genetics and environmental factors, Lee et al. compared the rate of VMA in the AMD eye with the fellow non-AMD eye. Exudative AMD was mostly present in eyes with vitreomacular adhesion (44 of 53, 83%) and rarely found in eyes without vitreomacular adhesion (6 of 53, 11.3%).[6] These previous publications were case-control studies with major limitations. There was no population-based study. Case-control studies are well known to be associated with a high risk of bias, because of the selection of cases (often overrepresenting the most severe cases) and controls (which may not be comparable to the cases in many respects, thus generating differences linked to the selection rather than the disease status). Moreover, when the person classifying the risk factor

(here VMA) is not masked to the case/control status, this may induce an observer bias (differential classification according to the case or control status). Finally, VMA is a recent concept, and population-based data such as prevalence or risk factors are lacking. The purpose of our study is to describe the prevalence of VMA, its risks factors and its associations with AMD in a population-based study of French elderly subjects.

Methods

Study Population

The Alienor (Antioxydants, Lipides Essentiels, Nutrition et maladies OculaiRes) Study is a prospective population based-study aiming at assessing the associations of age-related eye diseases with nutritional factors.[7] It also takes into account other major determinants of eye diseases, including gene polymorphisms, lifestyle, and vascular factors. Subjects of the Alienor Study were recruited from an ongoing population-based cohort, the Three-City (3C) Study, on the vascular risk factors of dementia.[8] The 3C study included 9294 subjects ≥65 years of age from three French cities (Bordeaux, Dijon, Montpellier), among whom 2104 were recruited in Bordeaux. They were initially recruited between 1999 and 2001 and were followed-up every 2 years since baseline. Each examination consisted of a cognitive evaluation, assessment of vascular risk factors, nutritional factors, and lifestyle.

The Alienor Study consists of eye examinations, which are offered to all participants of the 3C cohort in Bordeaux since the third follow-up (wave 1, 2006–2008). Among the 1450 participants reexamined between October 2006 and May 2008, 963 (66.4%) participated in the Alienor Study's baseline eye examination. This examination consisted of the evaluation of age-related eye diseases: AMD, glaucoma, cataract, and dry eye syndrome. Detailed characteristics of participants and nonparticipants have been published elsewhere.[7] At the fourth follow-up (wave 2, 2009–2010), an SD-OCT examination of the macula and the optic nerve was included in the eye examination. Among the Alienor participants still alive, 624 subjects (69.1%) accepted this second eye examination. They were ≥75 years of age.

This research adhered to the tenets of the Declaration of Helsinki. The design of the Alienor study has been approved by the Ethical Committee of Bordeaux (Comité de Protection des Personnes Sud-Ouest et Outre-Mer III) in May 2006. Participants gave written informed consent for their participation in the study.

Eye Examination

Each subject underwent an ophthalmologic examination including measurement of refraction by an auto-refractometer (Speedy-K, Luneau, France), best-corrected visual acuity (Early Treatment of Diabetic Retinopathy Study [ETDRS] scale), intraocular pressure by a noncontact tonometer (KT 800, Kowa, Tokyo, Japan), and macular and optic disc photography by a nonmydriatic retinograph (TRC NW6S; Topcon, Tokyo, Japan). The SD-OCT examination was performed using Spectralis (Software Version 5.4.7.0; Heidelberg Engineering, Heidelberg, Germany).

SD-OCT Imaging

SD-OCT examinations were performed using Spectralis (Software Version 5.4.7.0; Heidelberg Engineering). This device has an acquisition rate of 40,000 A-scans per second, with a depth resolution of 7 μm in tissue and a transversal resolution of 14 μm by using a superluminescence diode with an 870-nm bandwidth. The instrument combines OCT technology with a confocal scanning laser ophthalmoscope (CSLO). The Spectralis OCT provides an automatic real-time (ART) function that adjusts for eye movement and increases image quality. All OCT assessments were performed by the same experienced technician without pupil dilation. For the macular cube acquisition, the following conditions were used: resolution mode, high speed; scan angle, 20°; size X, 1024 pixels (5.7 mm); size Z, 496 pixels (1.9 mm); scaling X, 5.54 μm/pixel; scaling Z, 3.87 μm/pixel; number of B-scans, 19; pattern size, 20 × 15° and distance between B-scans, 236 μm.

Classification of VMA

VMA was graded as defined by the IVTS and is characterized by an "elevation of the cortical vitreous above the retinal surface, with the vitreous remaining attached within a 3-mm radius of the fovea without retinal abnormalities."[2] The evidence of VMA was based on the macular cube and was subclassified by size of the adhesion in focal (<1500 μm) or broad (>1500 μm).

Classification of VMA was performed by a trained ophthalmologist. The ophthalmologist performing VMA evaluation had no access to the AMD classification or any other clinical or risk factor data.

Classification of AMD

Retinal photographs were interpreted according to the International Classification and a modification of the grading scheme used in the Multi-Ethnic Study of Atherosclerosis for drusen size, location, and area.[9,10] Eyes were classified according to one of three exclusive groups: no AMD, early AMD, and late AMD.

Late AMD was defined by the presence of neovascular AMD or geographic atrophy within the grid (3000 μm from the foveola). Neovascular AMD included serous or hemorrhagic detachment of the RPE or sensory retina, subretinal or sub-RPE hemorrhages, and fibrous scar tissue. Geographic atrophy was defined as a discrete area of retinal depigmentation, 175 μm in diameter or larger, characterized by a sharp border and the presence of visible choroidal vessels. In addition, SD-OCT macular scans (vertical and horizontal lines, macular volume) were interpreted by a retina specialist for signs of retinal atrophy and neovascular AMD (subretinal fluid, subretinal tissue, pigment epithelium detachment, intraretinal fluid). Finally, classification of late atrophic and neovascular AMD was based on all available information (ophthalmologic history and treatments, retinal photographs, OCT scans).

Early AMD was classified from retinal photographs and defined by the presence of soft distinct drusen and/or soft indistinct drusen and/or reticular drusen and/or pigmentary abnormalities. Soft distinct and indistinct drusen were larger than 125 μm in diameter and with uniform density and sharp edges or decreasing density from the center outward and fuzzy edges, respectively. Pigmentary abnormalities were defined as areas of hyperpigmentation and/or hypopigmentation (without visibility of choroidal vessels). This definition of early AMD is similar to those used in other large epidemiologic studies of AMD, such as the Blue Mountains Eye Study, the Rotterdam Study, or the EUREYE Study, to facilitate comparisons with these studies.[11–13] This definition is also similar to the definition of intermediate AMD proposed by Ferris et al.[14]

Other Variables

Potential risk factors were selected, based on factors associated with AMD in the Alienor study and/or with VMA on basis of a literature search.[15–19] They included age, sex, smoking, body mass index (BMI), hypertension, plasma high-density lipoprotein (HDL)-cholesterol, plasma low-density lipoprotein (LDL)-cholesterol, dietary intakes of omega-3 polyunsaturated fatty acids (PUFAs), diabetes, the polymorphisms Complement Factor H (CFH) Y402H, age-related maculopathy susceptibility 2 (ARMS2) A69S, and cataract extraction. Cataract extraction was verified at slit lamp. Data on general characteristics, lifestyle, and cardiovascular risk factors were collected during a face-to-face interview using a standardized questionnaire administered by a trained psychologist or nurse. General data included demographic characteristics and smoking. BMI (kg/m^2) was calculated as weight per height^2. Two separate measures of blood pressure in a seated position were performed in all participants. The first blood pressure measurement was recorded at the beginning of the interview and the second one at the end, using a digital electronic tensiometer (OMRON M4; Omron Sante France SAS, Rosny-sous-Bois, France). The average systolic blood pressure (SBP) was the average of these two SBP measures. The same calculation was made for the average diastolic blood pressure (DBP). Hypertension was defined as average SBP $\geq$ 140 mm Hg and/or average DBP $\geq$ 90 mm Hg and/or antihypertensive medication use at baseline examination. Plasma lipids and glucose were measured at a central laboratory from fasting blood samples collected at home. Diabetes was defined as fasting blood glucose $\geq$7 mmol/L and/or medication use and/or self-reported diabetes. Regarding lifetime UV radiation exposure, as previously published,[20] for each participant, average annual ambient UV radiation exposure was estimated using the residential history by weighing annual ambient UV radiation at each location (estimated from the Eurosun UV database [www.eurosun-project.org]) by the time spent at that location.

Dietary intakes of omega-3 PUFAs were estimated from a 24-hour dietary recall performed by dieticians in 2002–2003.[21] Genetic polymorphisms were determined by the Lille Génopôle from the DNA samples collected in 1999–2001.

Statistical Analysis

Associations of VMA with potential risk factors were estimated using logistic generalized estimating equation (GEE) models (which allow taking into account the data from both eyes and their intraindividual correlations), adjusted for age and sex.

Associations of AMD with VMA were estimated using logistic GEE models. Subjects without any AMD were considered as the reference group. GEE models were adjusted first for age and sex (model 1). In model 2, we performed additional adjustment for cataract surgery. Finally, model 3 was adjusted for age, sex, cataract surgery, CFH Y402H, ARMS2 A69S, omega-3 PUFA intake, smoking, diabetes, and HDL-cholesterol.

All statistical analyses were performed using statistical software SAS (version 9.2; SAS Institute, Inc., Cary, NC, USA).

Results

Among the 624 subjects of the ALIENOR study, 622 (99.7%) had gradable SD-OCT examinations for VMA. These subjects were aged 82.2 years on average, 158 (25.3%) subjects were aged more than 85 years, and the proportion of women was 62.7%. Among the 1244 eyes, 540 (43.4%) had undergone cataract surgery and were pseudophakic. With regard to AMD classification, 538 subjects (86.5%) had gradable photographs in at least one eye, among whom 176 (32.7%) subjects had early AMD, 24 (4.5%) had geographic atrophy, and 32 (5.9%) had neovascular AMD.

Table 1. Prevalence of VMA According to Age and Sex, Alienor Study

Characteristics	Age 75–84, y, *n* (%)	Age > 85, y, *n* (%)	Total, *n* (%)
Men	*N* = 188	*N* = 45	*N* = 233
Any VMA	43 (22.9)	5 (11.1)	48 (20.6)
Focal VMA	15 (8.0)	1 (2.2)	16 (6.9)
Broad VMA	27 (14.4)	3 (6.7)	30 (12.9)
Uncertain subtype*	1 (0.5)	1 (2.2)	2 (0.8)
Women	*N* = 277	*N* = 112	*N* = 389
Any VMA	41 (14.8)	9 (8.0)	50 (12.9)
Focal VMA	10 (3.6)	2 (1.8)	12 (3.1)
Broad VMA	23 (8.3)	5 (4.4)	28 (7.2)
Uncertain subtype*	8 (2.9)	2 (1.8)	10 (2.6)
Total	*N* = 465	*N* = 157	*N* = 622
Any VMA	84 (18.1)	14 (8.9)	98 (15.7)
Focal VMA	25 (5.4)	3 (1.9)	28 (4.5)
Broad VMA	50 (10.8)	8 (5.1)	58 (9.3)
Uncertain subtype*	9 (1.9)	3 (1.9)	12 (1.9)

* Subtype (focal or broad) was judged uncertain when the site of vitreous attachment was not clearly visible on one or both sides of the detachment.

As shown in Table 1, the prevalence of VMA was 15.8%. VMA was more frequent in men (20.6%) than women (12.8%). The prevalence of VMA was higher before 85 years (18.1%) than after (8.9%). Approximately 60% of VMA was broad (size of the adhesion > 1500 μm) and approximately 30% was focal (size of the adhesion $\leq$ 1500 μm), whereas subtype could not be classified in approximately 10% of the cases, because the site of vitreous attachment was not clearly visible on one or both sides of the detachment. Because of the small numbers of affected subjects in subgroups (in particular, only 28 with focal VMA), we could not differentiate focal from broad VMA in further analyses.

We then compared socio-demographic and biological characteristics of participants according to the presence of VMA (Table 2). Subjects with VMA were younger than those without VMA (80.0 vs. 82.5 years, $P < 0.0001$) and were more often male (49.0% vs. 35.3%). Cataract extraction status was available for 599 patients (96.3%). Participants with VMA were less often operated on than subjects without VMA (39.2% vs. 58.2%, $P = 0.0006$). Subjects with and without VMA did not differ for the other characteristics (diabetes, hypertension, BMI, smoking, omega-3 PUFA dietary intake, plasma lipids, genetic polymorphisms).

The associations of VMA with the various potential risk factors are shown in Table 3. After adjustment for age and sex, only the history of cataract surgery was significantly associated with VMA at the limit of statistical significance ($P = 0.05$). No associations were found with diabetes ($P = 0.21$), other cardiovascular risk factors (hypertension, BMI, smoking, plasma lipid levels), omega-3 PUFA intake, or genetic polymorphisms.

As shown in Table 4, after adjustment for age and sex (model 1), VMA was not associated with any stage of AMD (odds ratios ranging from 0.64 to 0.83 according to type of AMD, all $P > 0.20$). These associations were not affected by further adjustments for cataract surgery (model 2) or for all potential confounders (model 3).

Table 2. Characteristics of Participants According to VMA Status

Characteristics	With VMA, $N = 98$	Without VMA, $N = 524$	*P* Value
Age, y	80.0 (3.8)	82.5 (4.22)	<0.0001
Sex			
Men	48 (49.0%)	185 (35.3%)	0.01
Women	50 (51.0%)	339 (64.7%)	
Cataract surgery ($N = 599$)			
Yes	38 (39.2%)	292 (58.2%)	0.0006
No	59 (60.8%)	210 (41.8%)	
Diabetes ($N = 521$)			
Yes	17 (20.7%)	73 (16.6%)	0.37
No	65 (79.3%)	366 (83.4%)	
Hypertension ($N = 611$)			
Yes	53 (55.2%)	253 (49.1%)	0.54
No	42 (43.7%)	257 (49.9%)	
BMI, kg/m^2 ($N = 598$)			
<25	42 (43.7%)	241 (48.0%)	0.38
25-30	37 (38.5%)	198 (39.4%)	
>30	17 (17.7%)	63 (12.5%)	
Smoking, pack-years ($N = 617$)			
0	56 (58.3%)	342 (65.6%)	0.38
<20	21 (21.9%)	92 (17.7%)	
>20	19 (19.8%)	87 (16.7%)	
Omega-3 PUFA dietary intake, g/d ($N = 607$)	1.28 (1.63)	1.17 (1.24)	0.46
Plasma lipids, mmol/L ($N = 506$)			
HDL cholesterol	1.46 (0.39)	1.50 (0.37)	0.30
Triglycerides	1.26 (0.57)	1.26 (0.53)	0.99
Total cholesterol	5.38 (1.08)	5.52 (1.18)	0.33
CFH Y402 H ($N = 569$)			
TT, low AMD risk	42 (45.6%)	216 (45.3%)	0.64
TC, intermediate AMD risk	35 (38.0%)	199 (41.7%)	
CC, high AMD risk	15 (16.3%)	62 (13.0%)	
ARMS2 A69S ($N = 520$)			
GG, low AMD risk	54 (65.8%)	298 (68.0%)	0.66
GT, intermediate AMD risk	24 (29.3%)	127 (29.0%)	
TT, high AMD risk	4 (4.9%)	13 (3.0%)	

n (%) or average (SD) in the Alienor Study (Bordeaux, France, 2009–2010). Mean (SD) for continuous variables, *n* (%) for categorical variables.

Table 3. Age- and Sex-Adjusted Associations of VMA With Potential Confounders in the Alienor Study

Characteristics	OR	95% CI	*P* Value
Age, y*	0.85	0.79; 0.92	**<0.0001**
Sex†	0.67	0.44; 1.05	0.08
Cataract surgery	0.66	0.43; 1.00	0.05
Diabetes	1.22	0.68; 2.17	0.51
Hypertension	1.30	0.83; 2.04	0.26
BMI, kg/m^2			
<25	1.00	Reference	
25-30	0.84	0.51; 1.37	0.49
>30	1.01	0.55; 1.87	0.97
Smoking, pack-y			
0 (never smoker)	1.00	Reference	
<20	0.97	0.53; 1.79	0.93
>20	0.99	0.53; 1.87	0.99
Omega-3 PUFA intake, g/d	1.05	0.91; 1.21	0.53
Plasma lipids, mmol/L			
Total cholesterol	0.98	0.78; 1.25	0.90
HDL-cholesterol	1.04	0.77; 1.39	0.80
Triglycerides	0.96	0.58; 1.59	0.88
CFH Y402 H			
TC, intermediate risk of AMD	1.13	0.68; 1.87	0.63
CC, high risk of AMD	1.12	0.58; 2.14	0.74
ARMS2 A69S			
GT, intermediate risk of AMD	0.93	0.54; 1.58	0.78
TT, high risk of AMD	1.76	0.57; 5.46	0.33

Bolded value indicates statistical significance. CI, confidence interval; OR, odds ratio.

* Adjusted for sex.

† Adjusted for age.

Discussion

In this sample of French elderly subjects aged at least 75 years, the prevalence of VMA was 15.8%. It was higher in subjects aged 75 to 84 years, as well as in men, and tended to be lower in eyes with cataract extraction, after adjustment for age and sex. After multivariate adjustment for all potential confounders, there were no statistically significant associations of VMA with any stage of AMD.

The Beaver Dam Eye Study (BDES) recently found a higher prevalence of 26% (551 of 1540 eyes) of VMA.[22] However, subjects were younger than in the ALIENOR Study (mean age ALIENOR: 82.2 years [SD: 4.3 years] compared with a mean age of 74.1 years [SD: 7.1 years] in BDES). This result is consistent with the decline in the prevalence of VMA in the oldest old, as shown in our study.

The lower prevalence of VMA after 85 years of age may be explained by the timing of vitreous detachment. Indeed, the detachment begins around the macula, and then the vitreous detaches from the center of the macula and then the disc, and finally there is a complete detachment of the posterior vitreous in the older subjects.[1] Using SD-OCT of the macula, it is difficult to differentiate completely attached from completely detached vitreous (posterior hyaloid). When the vitreo-retinal interface is not visible, it is impossible to determine whether the vitreous is completely attached or completely detached. Thus, the lower VMA prevalence in very old subjects may represent a higher prevalence of complete posterior vitreous detachment in these subjects, although we have no means to demonstrate this on the basis of SD-OCT examinations of the posterior pole.

Our results differ from previous studies on the association between vitreomacular adhesion and AMD. The few available studies found a significant association between VMA and AMD, mainly in its neovascular form.[3–6] The authors suggested three hypotheses for this association.[3,4] First, the vitreomacular adhesion may induce chronic inflammation by confining cytokines or free radicals in the macula or by interfering in the normal oxygenation and nutrition of the macula. Indeed, studies have shown that inflammation may play an important role in the pathogenesis of AMD.[23–25] Another hypothesis is that the presence of nondetached vitreous may prevent normal oxygen diffusion and nutrients from the vitreous cavity to the macula. The last hypothesis is that the presence of an adherent vitreous may confine the proangiogenic factors within the macula contributing to neovascularization.[26] However, some authors[4,6] have the opposite hypothesis that local inflammation caused by AMD may favor the vitreous to be more adherent to the macula.

Table 4. Association of AMD With Visible VMA in the Alienor Study

Model	Any AMD	Early AMD	Late AMD	Atrophic AMD	Neovascular AMD
1					
No VMA					
Reference	1.00	1.00	1.00	1.00	1.00
VMA					
OR	0.76	0.83	0.74	0.64	0.71
95% CI	0.48; 1.20	0.51; 1.34	0.43; 1.29	0.19; 2.18	0.40; 1.26
P Value	0.23	0.45	0.29	0.48	0.24
2					
No VMA					
Reference	1.00	1.00	1.00	1.00	1.00
VMA					
OR	0.77	0.86	0.73	0.68	0.65
95% CI	0.49; 1.22	0.53; 1.39	0.42; 1.28	0.20; 2.24	0.34; 1.25
P Value	0.27	0.54	0.27	0.52	0.19
3					
No VMA					
Reference	1.00	1.00	1.00	1.00	1.00
VMA					
OR	0.94	1.14	0.78	0.74	0.74
95% CI	0.49; 1.79	0.59; 2.20	0.37; 1.63	0.16; 3.51	0.28; 1.96
P Value	0.85	0.70	0.51	0.71	0.55

Model 1: GEE adjusted for age and sex. Model 2: GEE adjusted for age, sex, and cataract surgery. Model 3: GEE adjusted for age, sex, cataract surgery, CFH Y402H, ARMS2 A69S, omega-3 PUFA intake, smoking, diabetes, and HDL-cholesterol.

A case-control study of Krebs et al. coupling ultrasonography and time-domain OCT compared 107 cases of AMD and 56 controls.[3] This study found a higher rate of VMA (36%) in patients with wet AMD than those with nonexudative AMD (7%) or without AMD (10%). Mojana et al., in a study based on SD-OCT, compared 94 cases of AMD with 50 controls.[4] They found a higher rate of VMA in AMD patients than in the control group (28% vs. 16%). These studies have many methodologic limitations. In particular, there was no matching on age and sex, whereas our study shows that the prevalence of VMA is strongly associated with age and sex, as is AMD. Age and sex thus represent major potential confounders in the association of VMA and AMD and need to be taken into account in any such analyses. Another reason for the difference between the present study and previous studies may be the age range. Indeed, all previous studies included patients much younger than the Alienor Study. This may thus correspond to an earlier stage of vitreous detachment. In particular, in the Alienor Study, subjects with AMD may have had AMD for numerous years, with VMA at the moment they developed AMD, which then progressed to complete posterior vitreous detachment.

In an attempt to control potential sociodemographic or genetic confounders, Lee et al. and Robison et al. selected patients with unilateral exudative AMD. They compared the prevalence of VMA between both eyes.[5,6] Lee et al. found a higher rate of VMA in eyes with AMD than in control eyes (44 of 53 vs. 6 of 53). Similar results were found in the study by Robison et al. (38% vs. 10% in the control group). However, these studies did not compare the eyes with exudative AMD to normal eyes but with a set of controls including healthy eyes but also early AMD, atrophic AMD, and fibrous scars.

The main strength of our study is that this is the first population-based study. All previous studies on VMA were case control with the methodologic limitations of these studies, particularly the selection of the control group. Moreover, in our study, VMA classification was performed independently of AMD classification, with blinding of the VMA grader to the AMD status and all other variables. It is not clear whether such independent grading of VMA and AMD was performed in previous studies. This could lead to an overestimation of VMA in patients with AMD.

Another strength of our study is the adjustment for potential confounders. All major AMD risk factors found in the literature were used as adjustment variables (age, sex, cataract surgery, CFH, ARMS 2, ω3 PUFA intake, smoking, diabetes, and HDL-cholesterol).[15,16,19–21] Cataract surgery and diabetes have been reported to be associated with PVD in previous studies and were also taken as adjustment factors.[27,28] Although these adjustments had no effect on the associations observed in our study, it cannot be excluded that failure to take them into account in previous studies resulted in bias in their observations. In particular, cataract surgery is strongly associated both with VMA and AMD and needs to be taken into account.

One limitation of our study could come from the representativeness of the sample. The Alienor subsample tends to overrepresent younger subjects and high socioeconomic status, compared with the parent cohort (the 3C study).[7] The individuals included in this study may accordingly be healthier and present different lifestyles, mainly concerning their diet and physical activity, by comparison with the general population. However, the age- and sex-specific prevalence rates of AMD in the Alienor Study were similar to those observed in other studies performed in Europe and other industrialized countries.[11,29,30]

Another limitation is the limited number of late AMD cases, in particular, neovascular AMD. Thus, statistical power was low for the detection of an association between vitreomacular adhesion and late AMD, as shown by the relatively wide confidence intervals (from 0.43 to 1.63 in the final multivariate model). Moreover, this is a cross-sectional study, and thus it does not allow assessing the temporal relationship of VMA and AMD. A prospective design would be superior, by demonstrating that VMA could precede and

predict the occurrence of AMD. No such studies are currently available.

Finally, SD-OCT examination of the macula does not differentiate a complete vitreous detachment from a complete attachment of the vitreous. However, this has no direct effect on our results. Indeed, the aim of our study was to investigate the association between the VMA and AMD and not between posterior detachment of vitreous and AMD.

Conclusions

In conclusion, to our knowledge, this is the first population-based study on the relationship between VMA and AMD. VMA was frequent in this sample of elderly subjects, but was not significantly associated with prevalent AMD. A possible association between AMD and VMA may be masked by occurrence of a complete PVD after the onset of AMD. Therefore, prospective studies of the associations of VMA with AMD are needed.

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