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Purpose. The aim of this study was to investigate the prevalence of subretinal drusenoid deposits (SDD) and to identify associated factors in an elderly population.

Methods. The participants of the population-based Montrachet study underwent an exhaustive ophthalmologic examination, including color fundus photography and macular spectral domain-optical coherence tomography (SD-OCT), coupled with infrared reflectance imaging. The presence of SDD and other age-related macular degeneration lesions, according to the European Eye Epidemiology SD-OCT classification of macular diseases, and subfoveal choroidal thickness were recorded. Moreover, the association of SDD and both clinical and demographic factors as well as plasma levels of vitamin E and lutein/zeaxanthin (L/Z) were analyzed.

Results. The mean age of patients was 82.3 ± 3.8 years and 62.7% were female. The prevalence of SDD was 18.1% ($n = 205$) in the subjects with at least one eye interpretable ($n = 1135$). In multivariate analysis, SDD was positively associated with increasing age (OR, 4.6; 95% CI, 2.8–7.7; $P < 0.001$ for subjects aged >85 years), female sex (OR, 1.7; 95% CI, 1.2–2.4; $P = 0.005$), and plasma L/Z level (OR, 1.2; 95% CI, 1.0–1.5; $P = 0.039$), and negatively associated with lipid-lowering drugs use (OR, 0.5; 95% CI, 0.3–0.9; $P = 0.014$ for statin medications) and subfoveal choroidal thickness (OR, 0.8; 95% CI, 0.7–0.9; $P = 0.002$).

Conclusions. The prevalence of SDD was high in subjects older than 75 years, more frequent in women, and was associated with a thinner choroid. The association with lipid-lowering drugs deserves further investigation.

Keywords: subretinal drusenoid deposits, reticular pseudodrusen, prevalence, age-related maculopathy, age-related macular degeneration, optical coherence tomography, population-based study

AMD is one of the leading causes of vision loss in developing and developed countries,[1] and accounts for approximately 45% of all cases of visual impairment in Europe.[2] Early AMD is a macular disease characterized by small yellowish spot-like lesions called "drusen" or/and alterations of RPE, which is usually asymptomatic and discovered during fundus examination.[3] Drusen classically accumulate under the RPE and have numerous components that are mainly lipids such as esterified cholesterol, unesterified cholesterol, and phosphatidylcholine.[4,5]

Reticular pseudodrusen were first described in 1990[6] and identified as an unusual, yellowish, indistinct, deep interlacing lesions typically along the superior vascular arcades and better seen on blue light channel fundoscopy. In the Wisconsin age-related maculopathy grading system, reticular pseudodrusen is classified as a separate entity.[7] SDD is associated with a 2-fold increased risk of developing a late form of AMD in the fellow eye of neovascular AMD.[8] They are associated with both forms of AMD either due to geographical atrophy[9] or choroidal neovascularization.[10] Furthermore, one can report a spatial relationship between the presence of SDD and the future development of geographic atrophy.[11,12] Recent studies using multimodal imaging methods, such as spectral domain optical coherence tomography (SD-OCT), have shown that reticular pseudodrusen were in fact subretinal drusenoid deposits (SDD)[13,14] and have improved their identification and their progression.[15,16] Theories have been proposed for the etiology of SDD, namely, loss of regulatory immune responses (para-inflammation),[17,18] choroidal vascular abnormalities leading to choroidal atrophy and RPE dysfunction,[19–21] or impaired outer retinal lipid homeostasis.[4,22]

Since historical epidemiologic studies are based on color fundus photography, population-based studies have underreported the prevalence of SDD among patients with AMD and/or early AMD.[23,24] Few population based-studies evaluated the prevalence of SDD using new multimodal imaging,[9,25,26] which leads to better sensitivity and specificity for SDD detection.[16,25]

Therefore, we conducted a study to estimate the prevalence and associated factors of SDD in an elderly population using color fundus photography and SD-OCT coupled with infrared reflectance (IR) imaging.

Methods

Study Design Population

The Montrachet (maculopathy optic nerve and nutrition neurovascular and heart disease) study is an ancillary study of the Three-City (3C) study, a population-based study designed to assess the vascular risk factors for dementia.[27] The 3C study included 9294 individuals aged 65 years and older, selected from the electoral rolls of three French cities (Bordeaux, Dijon, and Montpellier) in 1999. In Dijon, among the 4931 participants who took part in the first run of the 3C study, a subgroup of participants ($n = 1153$) were invited to participate in the Montrachet study 10 years later to investigate the relationship between age-related eye, neurologic, and heart diseases in the elderly. From October 22, 2009 to March 31, 2013 a total of 1153 volunteers were recruited in the Montrachet study. The methodology of the Montrachet study and the baseline characteristics of the participants have been described elsewhere.[28] The participants underwent a comprehensive eye examination including the collection of self-reported eye disease and treatment history, visual acuity measurement, refractive error identification, intraocular pressure measurement, visual field examination, OCT imaging, and retinal photographs. Fasting blood samples were drawn to measure plasma vitamin E, carotenoids, and fatty acids levels. Finally, all participants were asked to complete a questionnaire on lifestyle (alcohol consumption and smoking status), environment (sun protection), and nutrition (oral supplements and food frequency questionnaire). Systemic diseases and treatments considered for the present analysis were based on self-report by the participants. The body mass index (BMI) was defined as weight/height^2 in kg/m^2 and overweight was defined as BMI >25 kg/m^2. The study was approved by the regional ethics committee and was registered as number 2009-A00448-49. All participants gave their informed consent and the procedures followed were in accordance with the tenets of the Declaration of Helsinki and the STROBE statements for cross-sectional studies.[29]

Image Acquisition

Color fundus photography (one image centered on the macula, the other centered on the optic disc) were performed using a high-resolution digital nonmydriatic retinograph (TRC NW6S; Topcon, Tokyo, Japan). Color and contrast were adjusted if needed to obtain better images. All color fundus images were interpreted in duplicate by two trained and ophthalmologists in a blinded manner (FB, IBG). In the case of discrepancy, the result was adjudicated by a retina specialist (CC-G). Macular SD-OCT was performed using HRA OCT (Spectralis; Heidelberg Engineering, Heidelberg, Germany) coupled with near-infrared reflectance (NIR) imaging. The OCT acquisition had a pattern size of 20° × 15° with 19 horizontal B-scans, a distance between scans of 235 µm, and the automatic real-time (ART) mode on (15 images averaged). NIR images were obtained at 810 nm with a field size of 20° × 15°. Only images with a quality between 20 and 40 were considered. NIR macular SD-OCT images were interpreted by two independent retina specialists in a blinded fashion (PHG, LA). If there was any disagreement the result was settled by a retina specialist (CC-G). Eyes were excluded if digital images were absent or uninterpretable due to poor imaging quality.

Main Outcome Parameters

Subretinal Drusenoid Deposits. On color fundus photographs, SDD were identified as yellow, punctuated interlacing networks and typically along the superior vascular arcades (Fig. 1A). On NIR, SDD were identified as groupings of isoreflective dots with a surrounding hyporeflective annulus, often with a target configuration (Fig. 1B). On macular SD-OCT, they were identified as collections of hyperreflective material localized between the RPE–Bruch membrane and the ellipsoid zone[30] and breaking through the ellipsoid zone in more advanced stages (Fig. 1B). All stages of SDD were considered. Stage 1 was defined as a deposition of hyperreflective material between the RPE–Bruch membrane band and the ellipsoid zone. Stage 2 comprised knolls of accumulated material which deflect inwardly the contour of the ellipsoid zone. Stage 3 was determined as a conical form of the material breaking through the ellipsoid zone. In stage 4, the material was found to fade due to reabsorption and migration within the inner retinal layers.[14,15] SDD were classified as definite if at least a single SDD was visualized on SD-OCT images.

Other Variables

Classification of Age-Related Macular Degeneration. Color fundus photographs were classified using the modified Multi-Ethnic Study of Arteriosclerosis (MESA) grading system for early AMD grading, as described elsewhere.[31,32] Neovascular AMD included serous and hemorrhagic detachment of the RPE or neuroretina, 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 more, characterized by a sharp border and the presence of visible choroidal vessels.

In addition, ellipsoid zone integrity and age-related macular degeneration characteristics evaluated using SD-OCT were interpreted using the European Eye Epidemiology (E3) SD-OCT classification described elsewhere.[33] Eyes with signs of geographic atrophy (RPE atrophy and outer retinal tubulation in the absence of sign of neovascular AMD) and neovascular AMD (subretinal fluid, pigment epithelial detachment, intraretinal cystic spaces) were classified as late AMD. Finally, classification of late AMD was based on both color fundus and OCT images.

Subfoveal Choroidal Thickness

Subfoveal choroidal thickness was measured manually using enhanced depth imaging SD-OCT horizontal lines and a calipers tool (Heidelberg Eye Explorer; Heidelberg Engineering), from the outer portion of the hyperreflective line corresponding to RPE in the foveal center to the inner surface of the sclera.[34]

Blood Samples

Blood samples were drawn from fasting subjects in our department and stored at –80°C before analysis, as reported previously.[35] Briefly, vitamin E, lutein, and zeaxanthin (L/Z) plasma levels were measured using high-performance liquid chromatography (HPLC). After extraction with absolute ethanol and hexane, we used two HPLC columns in tandem (Nucleosil C18, 25 × 4.6 mm ID, 5 µm; Thermo Finnigan, Villebon-sur-Yvette, France, and VIDAK C18, 25 × 4.6 mm ID, 5 µm; Altech France, Epernon, France) for measurements. The analytes were identified by their absorption spectra and their retention times.

Statistical Analysis

Categorical variables are expressed as n (%) and continuous variables as mean and standard deviation (SD) or median and

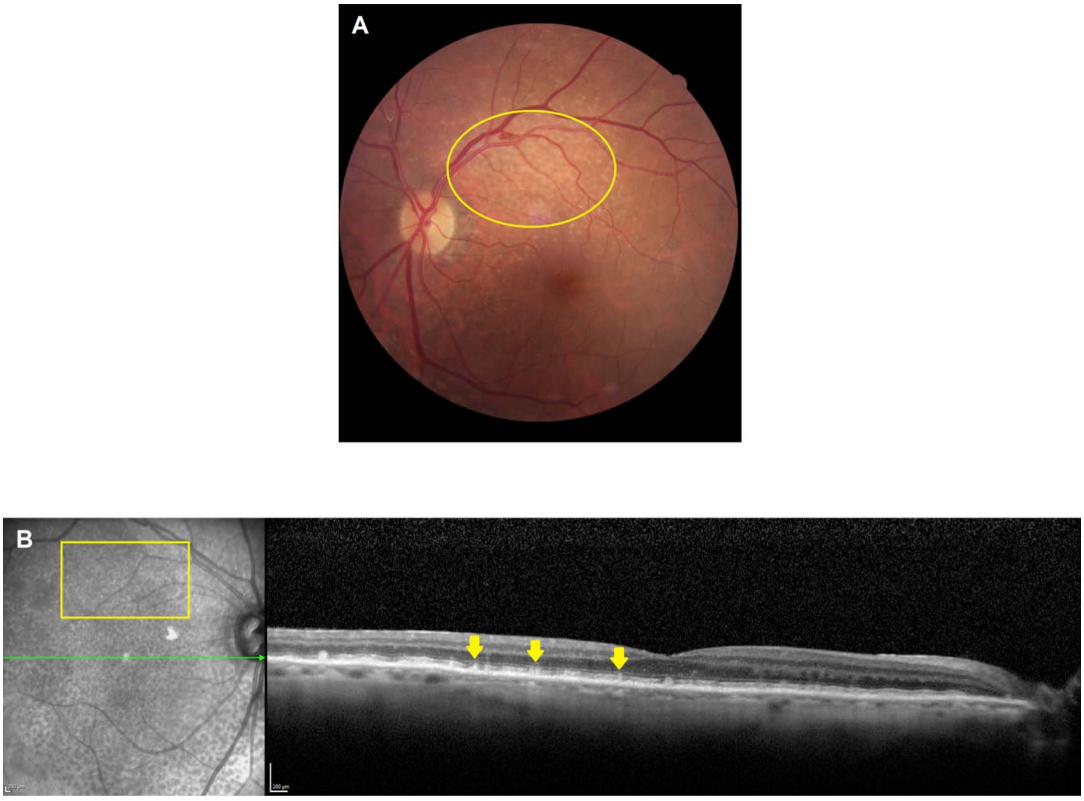

FIGURE 1. Color retinal photograph (**A**) of a first subject presenting subretinal drusenoid deposit in the upper part of the macula in the right eye and macular SD-OCT coupled with infrared reflectance image (**B**) of a second subject presenting subretinal drusenoid deposits in the macular region of the right eye. The *yellow circle*, *square*, and *arrows* indicate subretinal drusenoid deposits.

interquartile range (IQR) as appropriate. The prevalence of SDD in the participants was calculated. Associations of clinical and demographic characteristics, AMD stages, ellipsoid zone integrity, and other AMD characteristics detected with SD-OCT were estimated after adjustment for age and sex using generalized estimating equation (GEE) regression models to take into account intraindividual correlations between both eyes. Three multivariate models were used order to estimate demographics, clinical characteristics, and plasma carotenoid level associated with SDD as dependent variable. First, model 1a included age, sex, smoking history, educational level, and medical treatment. Second, model 1b included model 1a and subfoveal choroidal thickness and axial length. Third, model 1c included model 1a, L/Z supplementation, and plasma L/Z level. Factors associated with SDD in age- and sex-adjusted models with a value of $P < 0.20$ were then included in the final multivariate GEE regression models for SDD. Then final models were run with factors associated with SDD with a value of $P < 0.10$, except for smoking status and axial length, which were forced. Results are presented as odds ratios (ORs) with their 95% confidence intervals (95% CIs). For all tests, values of $P < 0.05$ were considered as statistically significant and the tests were two-tailed. All statistical analyses were performed using the statistical software SAS (version 9.4; SAS Institute, Inc., Cary, NC, USA).

RESULTS

Among the 1153 participants of the Montrachet study, 1135 subjects (2241 eyes) with at least one OCT scan available and of sufficient quality were included in the study (Fig. 2). There was no difference between participants and nonparticipants regarding demographic and clinical characteristics (Table 1). The age of the participants was 82.3 ± 3.8 years, ranging from 75 to 96 years and 62.7% were female.

Table 2 presents the prevalence of SDD evaluated using fundus color photography, NIR and SD-OCT according to the sex and age of the participants, the bilaterality of cases and the lens status. The prevalence of SDD was 2.2% (23 patients), 17.4% (197 patients) and 18.1% (205 patients) using fundus color photography, NIR and SD-OCT, respectively. Using

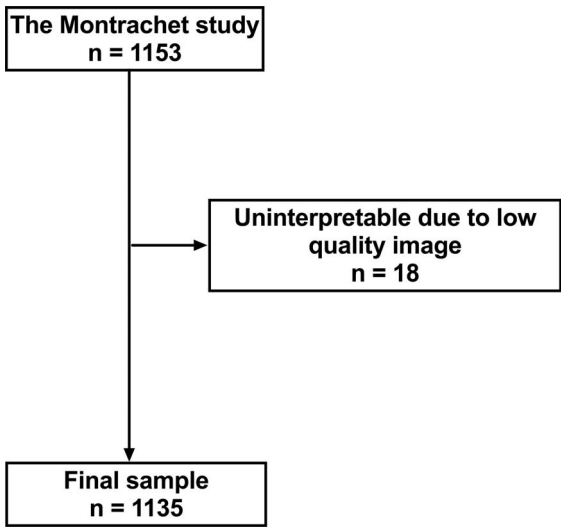

FIGURE 2. Flowchart of the Montrachet study and the subretinal drusenoid deposits study.

Table 1. Demographic and Clinical Characteristics of Participants and Nonparticipants in the Montrachet Subretinal Drusenoid Deposits Study

	Total (n = 1153)	Participants (n = 1135)	Nonparticipants (n = 18)	P Value
Age, y				
75–80	400 (34.7)	395 (34.8)	5 (27.8)	0.62
80–85	486 (42.2)	476 (41.9)	10 (55.6)	
>85	267 (23.2)	264 (23.3)	3 (16.7)	
Sex, female	723 (62.7)	712 (62.7)	11 (61.1)	0.89
Smoking history,* current or former	390 (34.4)	384 (34.4)	6 (33.3)	0.92
Alcohol consumption,* yes	64 (6.3)	53 (6.3)	1 (7.7)	0.57
Education level*				
No education or primary school	324 (28.1)	322 (28.4)	2 (11.1)	0.29
Short secondary school	160 (13.9)	158 (13.9)	2 (11.1)	
Long secondary school	207 (18.0)	202 (17.8)	5 (27.8)	
Post-secondary or university	461 (40.0)	452 (39.9)	9 (50.0)	
Cardiovascular risk factors				
BMI,* kg/m^2	26.1 ± 3.9	26.1 ± 3.8	28.0 ± 4.4	0.10
Blood pressure,* mm Hg				
Systolic	141.1 ± 19.3	141.1 ± 19.4	139.0 ± 11.7	0.69
Diastolic	74.0 ± 9.8	74.0 ± 9.8	76.0 ± 3.6	0.07
Plasma lipid,* mM				
LDL cholesterol	3.6 ± 0.8	3.6 ± 0.8	3.9 ± 0.9	0.15
HDL cholesterol	1.7 ± 0.4	1.7 ± 0.4	1.7 ± 0.4	0.39
Systemic hypertension	674 (58.5)	667 (58.8)	7 (38.9)	0.09
Diabetes*	121 (12.9)	121 (12.9)	0 (0.0)	0.63
Medical treatment*				
Hypoglycemic drugs	121 (12.6)	121 (12.8)	0 (0.0)	1.00
Antihypertensive drugs	615 (60.5)	608 (60.6)	7 (53.9)	0.62
Lipid-lowering drugs	425 (41.7)	419 (41.7)	6 (42.9)	0.74
Statins	275 (23.9)	272 (24.0)	3 (16.7)	0.58
Fibrates	115 (10.0)	112 (9.9)	3 (16.7)	0.41
Other lipid-lowering drugs†	35 (3.0)	35 (3.1)	0 (0.0)	1.00
Medical history*				
CVD				
No	943 (92.6)	930 (92.6)	13 (92.9)	0.66
Yes <10 y	51 (5.0)	50 (4.5)	1 (7.1)	
Yes >10 y	24 (2.4)	24 (2.4)	0 (0.0)	
Stroke (ischemic and hemorrhagic)				
No	1006 (95.6)	992 (95.6)	14 (100.0)	1.00
Yes <10 y	12 (1.1)	12 (1.2)	0 (0.0)	
Yes >10 y	34 (3.2)	34 (3.3)	0 (0.0)	
MACCE				
No	893 (88.9)	880 (88.9)	13 (92.9)	0.64
Yes	111 (11.1)	110 (11.1)	1 (7.1)	
Subfoveal choroidal thickness,* μm	222.5 ± 84.4	222.7 ± 84.3	151.7 ± 89.3	0.15
Lens status				
Phakic	582 (50.5)	576 (50.7)	6 (25.0)	0.14
Pseudophakic	515 (44.7)	505 (44.5)	10 (55.6)	
Aphakic	56 (4.9)	54 (4.8)	2 (11.1)	
Axial length,* mm	23.4 ± 1.3	23.4 ± 1.3	24.8 ± 1.9	0.92
Plasma vitamin E level,* μg/L	11.9 ± 3.6	11.9 ± 3.6	13.5 ± 3.8	0.13
Plasma carotenoids level,* μg/L				
Lutein	271.4 (178.1–453.9)	271.7 (178.1–453.4)	263.8 (193.5–479.4)	0.75
Zeaxanthin	17.8 (11.3–26.0)	17.7 (11.3–26.0)	19.8 (15.7–25.6)	0.58
Lutein + zeaxanthin	293.8 (191.6–473.3)	293.8 (191.6–471.1)	289.3 (199.7–497.9)	0.76
L/Z supplementation	65 (5.6)	62 (5.5)	3 (16.7)	0.08

Categorical variables are given as n (%) and continuous variables as mean ± standard deviation or median (IQR) as appropriate. CVD, cardiovascular diseases; HDL, high density lipoprotein; LDL, low density lipoprotein; L/Z, lutein/zeaxanthin; MACCE, major adverse cardiac and cerebrovascular events.

* Missing data for: smoking history (n = 20), alcohol consumption (n = 136), education level (n = 1), BMI (n = 286), systolic blood pressure (n = 139), diastolic blood pressure (n = 139), plasma lipid (n = 14), diabetes (n = 215), hypoglycemic drugs (n = 196), antihypertensive drugs (n = 136), lipid-lowering drugs use (n = 135), CVD (n = 135), Stroke (n = 101), MACCE (n = 149), subfoveal choroidal thickness (n = 70), axial length (n = 199), plasma vitamin E level (n = 358), and plasma carotenoids level (n = 358).

† Other lipid-modifying agents included: Bil acid sequestrants and dextrothyroxine, probucol, tiadenol, meglutol, omega-3-triglycerides including other esters and acids, magnesium pyridoxal 5-phosphate glutamate, policosanol, alipogene tiparvovec, mipomersen, lomitapide, evolocumab, alirocumab.

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Table 2. Prevalence of Subretinal Drusenoid Deposits in the Montrachet Study

	Spectral Domain-Optical Coherence Tomography					Near-Infrared Reflectance Imaging					Color Fundus Photography				
	Sample Size		SDD			Sample Size		SDD			Sample Size		SDD		
	n (%)	Eyes, *n* (%)	*n* (%)	Eyes, *n* (%)	*P* Value	*n* (%)	Eyes, *n* (%)	*N* (%)	Eyes, *n* (%)	*P* Value	*N* (%)	Eyes, *N* (%)	*N* (%)	Eyes, *N* (%)	*P* Value
All	1135 (100.0)	2241 (100.0)	205 (18.1)	342 (15.3)		1135 (100.0)	2241 (100.0)	197 (17.4)	326 (14.5)		1055 (100.0)	2024 (100.0)	23 (2.2)	35 (1.7)	
Sex					0.014					0.027					0.12
Men	423 (37.3)		61 (29.8)					59 (29.9)					5 (21.7)		
Women	712 (62.7)		144 (70.2)					138 (70.1)					18 (78.3)		
Age, y					<0.001					<0.001					0.68
<80	395 (34.8)		38 (18.5)					38 (19.3)					7 (30.4)		
80–84	476 (41.9)		83 (40.5)					79 (40.1)					12 (52.2)		
≥85	240 (19.4)		84 (41.0)					80 (40.6)					4 (17.4)		
Bilaterality					<0.001					<0.001					0.27
Unilateral			68 (33.2)					68 (34.5)					11 (47.8)		
Bilateral			137 (66.8)					129 (65.5)					12 (52.2)		
Lens status					0.21					0.13					1.00
Phakic	576 (50.7)		87 (42.4)					89 (43.1)					12 (52.2)		
Pseudophakic	505 (44.5)		109 (53.2)					99 (52.3)					10 (43.5)		
Aphakic	54 (4.8)		9 (4.4)					9 (4.6)					1 (4.3)		

Categorical variables are expressed as *n* (%).

fundus color photography, we did not find any association with age and sex. Using SD-OCT and NIR, SDD were more likely to be observed in female ($P < 0.014$ and 0.027, respectively) and in older patients ($P < 0.001$ and < 0.001, respectively). The SDD were bilateral in 52.2%, 65.5%, and 66.8% of cases using color fundus photography, NIR and SD-OCT, respectively.

Table 3 presents the associations between the clinical and demographic characteristics and the prevalence of SDD. After adjustment for age and sex, subjects with SDD were more likely to be older (age >85 years, OR, 4.1; 95% 95% CI, 2.7–6.2; $P < 0.001$), female (OR, 1.6; 95% CI, 1.1–2.2; $P = 0.006$), with higher plasma L/Z levels (OR, 1.3; 95% CI, 1.2–1.6, $P < 0.001$), and using L/Z supplementation (OR, 3.2; 95% CI, 1.9–5.7; $P < 0.001$). Subjects with SDD were less likely to use lipid-lowering drugs, notably statin medications (OR, 0.7; 95% CI, 0.5–0.9; $P = 0.019$ and OR, 0.6; 95% CI, 0.4–0.9; $P = 0.045$, respectively, for lipid-lowering drug and statin medications use) and to have a thicker subfoveal choroidal thickness (OR, 0.8; 95% CI, 0.7–0.9; $P < 0.001$).

Table 4 presents the associations between SDD and different stages of early AMD, late AMD, ellipsoid zone integrity, and other AMD characteristics detected on SD-OCT. After adjustment for age and sex, SDD were more likely to be noted with higher stages of early AMD (OR, 2.1; 95% CI, 1.5–3.1; $P < 0.0001$ and OR, 3.2; 95% CI, 1.5–6.8; $P < 0.003$, for early AMD 2 and 3, respectively). Moreover, subjects with SDD were more likely to have a disruption of the ellipsoid zone (OR, 2.7; 95% CI, 1.9–3.9; $P < 0.001$), notably near the fovea (OR, 9.0; 95% CI, 6.3–12.7; $P < 0.001$). Eyes with SDD were also more likely to have drusen (OR, 1.9; 95% CI, 1.5–2.5; $P < 0.001$), particularly if the drusen were subfoveal (OR, 2.2; 95% CI, 1.4–3.4; $P < 0.001$) and confluent (OR, 2.3; 95% CI, 1.6–3.3; $P < 0.001$). Other AMD characteristics were not significantly associated with SDD. The prevalence of AMD lesions and ellipsoid zone disruption in the Montrachet study is presented in Supplementary Table S1.

In multivariate analysis, SDD were more likely to be observed with increasing age (OR, 2.4; 95% CI, 1.5–3.9; $P < 0.001$ and OR, 4.6; 95% CI, 2.8–7.7; $P < 0.001$, respectively, for subjects aged 80–85 years and those aged >85 years), in females (OR, 1.7; 95% CI, 1.2–2.4; $P = 0.005$) and in individuals with higher plasma L/Z level (OR, 1.2; 95% CI, 1.0–1.5; $P = 0.039$), and less likely in association with lipid-lowering drugs use such as statin and fibrate medications (OR, 0.5; 95% CI, 0.3–0.9; $P = 0.014$ and OR, 0.4; 95% CI, 0.2–0.8; $P = 0.012$, for statins and fibrates, respectively), and with thicker subfoveal choroidal thickness (OR, 0.8; 95% CI, 0.7–0.9; $P = 0.002$) (Table 5). SDD were positively associated with a history of smoking in the model incorporating clinical, demographic, and axial length characteristics of subjects (OR, 1.6; 95% CI, 1.01–2.37; $P = 0.04$), but the association was not significant after adjustment for L/Z supplementation and plasma L/Z levels (OR, 1.3; 95% CI, 0.8–2.00; $P = 0.36$; Table 5). SDD were negatively associated with a lower education level in the model incorporating clinical, demographic, and L/Z supplementation and plasma L/Z levels (OR, 0.4; 95% CI, 0.2–0.93; $P = 0.033$, for subjects with shorter secondary school education level; Table 5).

Discussion

The aim of our study was to estimate the prevalence and associated factors of SDD in the elderly. We found a high prevalence of SDD in patients aged over 75. Age, sex, early AMD stages, ellipsoid zone integrity, subfoveal choroidal thickness, lipid-lowering drugs use, plasma L/Z level, smoking history, and level of education were associated with SDD.

Our final prevalence rate is based on SDD detected using SD-OCT imaging, which is considered the most accurate method for diagnosing SDD with both good sensitivity and specificity.[13,16] The prevalence of SDD in our study was 18.1%, 17.4%, and 2.2% using SD-OCT, NIR and color fundus photography, respectively. These rates are in line with those of the Alienor study (17.4% and 18.1% using SD-OCT and NIR, accordingly), another French population-based study of participants aged older than 77 years in which they documented SDD prevalence using different multimodal imaging (color fundus photography, autofluorescence, SD-OCT, and NIR imaging).[25] However, we found a lower prevalence of SDD compared with Zarubina et al.[26] study (32%). The differences of population type (primary care clinic-based study), definition of SDD (one or more dome-shaped or oval hyperreflective material of ≥25 μm in size internal to and adjacent to the RPE with or without disturbance of the ellipsoid zone) and imaging protocol (multimodal imaging with color fundus photography, NIR, autofluorescence and combine macular and optic nerve head SD-OCT) may explain the variation of the results.

Moreover, we found a low prevalence similar to that of other studies where the imaging protocol was based on color fundus photography analysis (0.7% in the Beaver Dam Eye Study,[24] 0.4% in the Melbourne Collaborative Cohort Study,[36] and 1.95% in the Blue Mountains Eye Study[23]) or on combined color and near-infrared fundus imaging in the Rotterdam Eye Study with a prevalence of 4.9%.[37]

The association of SDD with older age and female sex has already been described in other studies.[24,25,36–38] We also found a significant association between smoking and SDD, which is consistent with other results[23,24,36] and the current knowledge that smoking is a risk factor of early AMD and its progression.[39] By contrast with the Beaver Dam Eye study, a lower level of education was negatively associated with SDD in our study.[24]

Our study showed that SDD were less likely to be noted in subjects using lipid-lowering drugs. This observation may emphasize the role of outer retina lipid homeostasis in the formation of SDD. Curcio et al.[22] proposed that alterations in lipid transport mechanisms between the RPE and outer segments of photoreceptors, based on lipoprotein-mediated transfer or lipoprotein interphotoreceptor binding protein (IRBP) implicated in the retinoid cycle, might be involved in the formation of SDD.[40,41] Our hypothesis is that lipid-lowering drugs might prevent the formation of SDD through the reduction of cholesterol within lipoproteins in the blood.[42,43]

Surprisingly, we also noted that SDD were more likely to be observed with high plasma levels of carotenoids. Carotenoid macular bioavailability is influenced by various factors, but studies showed that carotenoid incorporation in the macula is mainly based on lipoprotein transport mechanisms such as IRBP, requires a minimal diet intake of fat and that polyunsaturated fatty acid-rich diet improves absorption of carotenoids.[44–46] Curcio[47] suggested a link between macular pigment delivery system through Müller glial cells and the formation of drusen. We may hypothesize that, despite the established benefit of L/Z supplementation to the foveal vision, there may be a price to be paid for the delivery of L/Z to the fovea, namely a higher lipid uptake in the RPE and the retina, which then must be discarded as drusen or SDD.

We found a significant association of SDD with higher stage of early AMD and soft drusen, especially if soft drusen were subfoveal and confluent. This is consistent with previous studies. In the Beaver Dam study, drusen type was associated with an increased risk of incident SDD (soft indistinct drusen being the most at risk, OR 1.4).[24] In the Blue Mountains Eye study, a central location of drusen and soft drusen type were significantly associated with a greater risk of SDD.[38] The

Table 3. Associations With SDD in the Montrachet Study*

	Subretinal Drusenoid Deposits				
	Total (n = 1135)	**Absent (n = 930)**	**Present (n = 205)**	**OR† (95% CI)**	***P* Value**
Age, y					
<80	395 (34.8)	357 (38.4)	38 (18.5)	Ref	
80–85	476 (41.9)	393 (42.3)	83 (40.5)	1.9 (1.3–2.9)	0.002
>85	240 (19.4)	180 (19.4)	84 (41.0)	4.1 (2.7–6.2)	<0.001
Sex, female	712 (62.7)	568 (61.1)	144 (70.2)	1.6 (1.1–2.2)	0.006
Smoking history,‡ former or current	384 (34.4)	318 (34.6)	66 (33.5)	1.3 (0.9–1.9)	0.16
Alcohol consumption,‡ yes	63 (6.4)	52 (6.4)	11 (6.6)	1.4 (0.7–2.9)	0.41
Education level‡					
No education or primary school	322 (28.4)	253 (27.2)	69 (33.7)	Ref	
Short secondary school	158 (13.9)	134 (14.4)	24 (11.7)	0.8 (0.4–1.3)	0.28
Long secondary school	202 (17.8)	162 (17.4)	40 (19.5)	1.0 (0.7–1.6)	0.92
Post-secondary or university	452 (39.9)	380 (40.9)	72 (35.1)	0.7 (0.5–1.1)	0.09
Cardiovascular risk factors					
BMI,‡ kg/m^2		26.12 ± 3.9	26.0 ± 3.8	1.0 (1.0–1.1)	0.31
Blood pressure,‡ mm Hg					
Systolic	141.1 ± 19.4	141.2 ± 19.4	140.7 ± 19.3	0.9 (0.8–1.1)	0.29
Diastolic	74.0 ± 9.8	74.1 ± 9.6	73.6 ± 9.9	1.0 (0.9–1.2)	0.75
Plasma lipid,‡ mM					
LDL cholesterol	3.6 ± 0.8	3.6 ± 0.8	3.5 ± 0.8	0.9 (0.8–1.1)	0.38
HDL cholesterol	1.7 ± 0.4	1.6 ± 0.4	1.7 ± 0.4	1.0 (0.9–1.2)	0.75
Systemic hypertension‡	667 (58.8)	550 (59.1)	117 (57.1)	0.9 (0.6–1.2)	0.41
Diabetes‡	121 (13.0)	98 (12.8)	23 (14.1)	1.2 (0.7–2.0)	0.52
Medical treatment‡					
Hypoglycemic drugs	121 (12.8)	98 (12.6)	23 (13.6)	1.1 (0.6–2.5)	0.64
Antihypertensive drugs	608 (60.6)	501 (60.4)	107 (61.1)	0.9 (0.6–1.3)	0.47
Lipid-lowering drugs	419 (41.7)	367 (44.3)	52 (29.7)	0.7 (0.5–0.9)	0.019
Statins	272 (24.0)	237 (25.5)	35 (17.1)	0.6 (0.4–0.9)	0.045
Fibrates	112 (9.9)	98 (10.5)	14 (6.8)	0.5 (0.3–1.0)	0.065
Other lipid-lowering drugs||	35 (3.08)	32 (3.44)	3 (1.46)	0.3 (0.1–1.6)	0.24
Medical history‡					
CVD					
No	930 (92.6)	759 (92.7)	171 (92.4)	Ref	
Yes <10 y	50 (4.5)	42 (5.1)	8 (4.3)	0.8 (0.4–1.8)	0.58
Yes >10 y	24 (2.4)	18 (2.2)	6 (3.2)	1.8 (0.7–5.1)	0.24
Stroke (ischemic and hemorrhagic)					
No	992 (95.6)	808 (95.4)	184 (96.3)	Ref	
Yes <10 y	12 (1.2)	10 (1.2)	2 (0.2)	0.6 (0.2–1.7)	0.34
Yes >10 y	34 (3.3)	29 (3.4)	5 (2.6)	0.7 (0.1–3.7)	0.63
MACCE					
No	880 (88.9)	718 (88.9)	162 (89.0)	Ref	
Yes	110 (11.1)	90 (11.1)	20 (11.0)	1.0 (0.6–1.7)	0.88
SFCT,‡ µm	222.5 ± 84.4	229.1 ± 82.9	193.7 ± 85.0	0.8 (0.7–0.9)	<0.001
Lens status					
Phakic	576 (50.7)	489 (52.6)	87 (42.4)	Ref	
Pseudophakic	505 (44.5)	396 (42.6)	109 (53.2)	1.0 (0.7–1.3)	0.76
Aphakic	54 (4.8)	45 (4.8)	9 (4.4)	0.8 (0.4–1.6)	0.47
Axial length,‡ mm	23.4 ± 1.4	23.4 ± 1.3	23.5 ± 1.3	1.0 (0.8–1.2)	0.83
Plasma vitamin E level,‡ µg/L	11.9 ± 3.6	11.8 ± 3.5	12.5 ± 4.1	1.1 (1.0–1.2)	0.06
Plasma carotenoid levels,‡ µg/L					
Lutein	271.4 (178.1–453.9)	262.2 (177.9–438.6)	322.4 (179.7–527.8)	1.3 (1.1–1.6)	<0.001
Zeaxanthin	11.8 (11.3–26.0)	17.7 (11.1–25.5)	17.8 (11.5–31.1)	1.2 (1.0–1.5)	0.033
Lutein + zeaxanthin	291.8 (191.6–473.3)	283.3 (191.4–461.9)	325.1 (196.3–554.6)	1.3 (1.2–1.6)	<0.001
L/Z supplementation‡	62 (5.5)	35 (3.8)	27 (13.2)	3.2 (1.9–5.7)	<0.001

Ref, reference; SFCT, subfoveal choroidal thickness.

* Categoric variables are given as n (%) and continuous variables as mean ± standard deviation or median (IQR) as appropriate.

† Odds ratio adjusted for age and sex estimated using generalized estimating equation regression model. Odds ratios for continuous variables are expressed as the odds ratio associated with a one-standard deviation unit increase in the variable.

‡ Missing data for participants: smoking history (n = 20), alcohol consumption (n = 131), education level (n = 1), BMI (n = 279), systolic blood pressure (n = 134), diastolic blood pressure (n = 134), plasma lipid (n = 14), diabetes (n = 207), hypoglycemic treatment (n = 188), antihypertensive drugs (n = 131), lipid-lowering drugs use (n = 131), CVD (n = 131), Stroke (n = 101), MACCE (n = 133), subfoveal choroidal thickness (n = 55), axial length (n = 195), plasma vitamin E level (n = 353) and plasma carotenoid levels (n = 353).

|| Other lipid-modifying agents included: Bil acid sequestrants and dextrothyroxine, probucol, tiadenol, meglutol, omega-3-triglycerides including other esters and acids, magnesium pyridoxal 5-phosphate glutamate, policosanol, alipogene tiparvovec, mipomersen, lomitapide, evolocumab, alirocumab.

Table 4. Associations of Different Stages of AMD, Ellipsoid Zone Integrity and Other AMD Characteristics Detected With OCT With Subretinal Drusenoid Deposits in the Montrachet Study

	Subretinal Drusenoid Deposits (n = 342 Eyes)		
	N (%)	OR* (95% CI)	P Value
Stages of AMD			
No AMD (n = 1277)	81 (6.3)	Ref	
Early AMD 1 (n = 541)	130 (24.0)	1.1 (0.9–1.4)	0.37
Early AMD 2 (n = 149)	70 (47.0)	2.1 (1.5–3.1)	<0.001
Early AMD 3 (n = 32)	17 (53.1)	3.2 (1.5–6.8)	0.003
Late AMD			
Atrophic AMD (n = 111)	42 (37.8)	0.8 (0.5–1.3)	0.35
Neovascular AMD (n = 189)	47 (24.9)	0.8 (0.4–1.4)	0.40
Ellipsoid zone integrity†			
Disruption of ellipsoid zone			
Absence (n = 1740)	70 (4.0)	Ref	
Presence (n = 501)	272 (54.3)	2.7 (1.9–3.9)	<0.001
Foveal disruption of ellipsoid zone			
Absence (n = 1989)	202 (10.2)	Ref	
Presence (n = 252)	140 (55.6)	9.0 (6.3–12.7)	<0.001
AMD lesions†			
Drusen			
Absence (n = 1694)	182 (10.7)	Ref	
Presence (n = 547)	160 (29.2)	1.9 (1.5–2.5)	<0.001
Subfoveal drusen			
Absence (n =197)	27 (13.7)	Ref	
Presence (n = 351)	133 (37.9)	2.2 (1.4–3.4)	<0.001
Confluent drusen			
Absence (n = 326)	60 (18.4)	Ref	
Presence (n = 222)	100 (45.0)	2.3 (1.6–3.3)	<0.001
Pigment epithelial detachment			
Absence (n = 2179)	321 (14.7)	Ref	
Presence (n = 62)	21 (33.9)	1.0 (0.4–2.3)	0.99
RPE atrophy			
Absence (n = 2113)	292 (13.8)	Ref	
Presence (n = 128)	50 (39.1)	1.3 (0.8–2.0)	0.36
Subfoveal RPE atrophy			
Absence (n = 54)	20 (37.0)	Ref	
Presence (n = 74)	30 (40.5)	1.0 (0.4–2.6)	0.98
Intraretinal tubular changes			
Absence (n = 2217)	333 (15.0)	Ref	
Presence (n = 24)	9 (37.5)	0.7 (0.1–4.8)	0.71
Intraretinal cystic spaces			
Absence (n = 2152)	328 (15.2)	Ref	
Presence (n = 89)	14 (15.7)	0.6 (0.3–1.3)	0.11
Subretinal fluid			
Absence (n = 2207)	332 (15.0)	Ref	
Presence (n = 34)	10 (29.4)	0.6 (0.1–2.2)	0.41
Subfoveal subretinal fluid			
Absence (n = 14)	5 (35.7)	Ref	
Presence (n = 20)	5 (25.0)	0.8 (0.1–5.5)	0.81
Subretinal material			
Absence (n = 2188)	325 (14.8)	Ref	
Presence (n = 53)	17 (32.1)	0.6 (0.1–1.8)	0.37
Subfoveal subretinal material			
Absence (n = 12)	6 (50.0)	Ref	
Presence (n = 42)	12 (28.6)	0.4 (0.1–1.8)	0.26

Categorical variables are expressed as n (%).

* Age- and sex-adjusted associations estimated using generalized estimating equation regression models.

† Defined according to the European Eye Epidemiology (E3) SD-OCT classification of macular diseases.[33]

Alienor study found also similar results with a significant association between SDD and an increasing stage of early AMD, as well as intermediate soft drusen at any location and central large drusen.[25] Contrary to other studies,[9,11,24] we did not find any significant association between late atrophic or neovascular AMD and SDD. These results could be due to the difficulty to detect SDD in late AMD because they usually fade in advanced neovascular disease or disappear with RPE atrophy and remain detectable only outside the macula, as already hypothesized in the Alienor study.[25] In our population, subjects with SDD were more likely to present with ellipsoid zone disruption, notably near the fovea. These results are consistent with the classification of SDD, where integrity of the ellipsoid zone was altered in stage 3 of 4.[14,15]

Our study also showed that a thinner choroid was associated with a significant increased risk of SDD lesions, which has already been described in other studies.[20,21,34,48–50] This emphasizes the need for prospective studies on SDD and choroidal changes in order to understand their interrelationship. Spaide[51] recently published a new classification system of AMD, which is partly based on choroidal thickness. Some drusen, namely pachydrusen and SDD, seem to be associated with choroidal thickness and topographical location in the macula; the former is associated with a thicker choroid and the latter with a thinner choroid. The relationship between SDD and choroidal thinning is probably more complex involving RPE dysfunction as a third factor impacting both SDD and the choroid. Indeed, the RPE plays a key role in maintaining the choriocapillaris by secreting vascular endothelial growth factor (VEGF). Gattousi et al.[52] recently showed that RPE alterations were associated with choroidal thinning and that use of lipid-lowering drugs was negatively associated with choroidal thinning. Our results showed that lipid-lowering drugs were protective against SDD. These results highlight the hypothesis of a primary RPE dysfunction, causing both choriocapillaris degeneration due to decreased VEGF secretion with choroidal thinning and accumulation of SDD due to defective lipid transport based on lipoproteins.

Lastly, we did not find any significant association between SDD and the cardiovascular risk factors and history in our cohort. Our findings do not support the hypothesis that SDD could be associated with choroidal vascular infarction and subsequent thinning due to systemic vascular process proposed by other workers.[53] Thus, the findings of the present study do not explain the poorer survival of persons with SDD described by Klein et al.[24]

We acknowledge several limitations to this study. First, we used a protocol of OCT imaging of $20° \times 15°$ with 19 horizontal B-scans. Thereby, we probably did not detect some SDD outside of the cube, since they are frequently located near the superior temporal vascular arcades.[9,16] Second, we recruited 1153 subjects of the 3901 participants of the fifth run of the 3C study in Dijon, which can induce selection bias and underestimate the prevalence of the SDD. Third, this study only investigated a white, urban, and generally healthy population with high economic status in a European country[28]; therefore, the results cannot be extrapolated to other regions of the world. Fourth, the association with systemic diseases was based only on self-report, which may lead to bias. Finally, the cross-sectional design of our study did not allow us to investigate the temporality of the interrelationships of SDD with other factors. The strengths of this study include its large population sample as well as the use of SD-OCT and IR imaging to detect SDD and the concurrent analysis of potential ocular and systemic risk factors.

In conclusion, our study provides epidemiological data on SDD confirming their high prevalence in an elderly European cohort, as described in other population in the United States or

Table 5. Multivariate Analysis of Factors Associated With SDD in the Montrachet Study

	Model 1a (n = 2200 Eyes)		Model 1b (n = 1662 Eyes)		Model 1c (n = 1519 Eyes)	
	OR* (95%CI)	*P* Value	OR* (95%CI)	*P* Value	OR* (95%CI)	*P* Value
Age, y						
<80	Ref		Ref		Ref	
80–85	1.9 (1.3–3.0)	0.003	2.4 (1.5–3.9)	<0.001	1.8 (1.1–9.0)	0.026
>85	3.9 (2.5–6.1)	<0.001	4.6 (2.8–7.7)	<0.001	4.0 (2.3–6.8)	<0.001
Sex, female	1.7 (1.2–2.4)	0.005	1.5 (0.9–2.3)	0.12	1.6 (1.0–2.6)	0.048
Smoking history, former or current	1.4 (1.0–2.0)	0.07	1.6 (1.0–2.4)	0.04	1.3 (0.8–2.0)	0.36
Education level						
No education or primary school	Ref		Ref		Ref	
Short secondary school	0.7 (0.4–1.2)	0.16	0.8 (0.4–1.4)	0.35	0.4 (0.2–0.93)	0.033
Long secondary school	1.0 (0.6–1.6)	0.94	1.0 (0.6–1.8)	0.87	1.0 (0.6–1.8)	0.91
Post-secondary or university	0.7 (0.5–1.1)	0.05	0.7 (0.4–1.0)	0.06	0.7 (0.4–1.1)	0.093
Medical treatment						
Lipid-lowering drugs						
Statins	0.6 (0.4–0.9)	0.018	0.5 (0.3–0.9)	0.014	0.6 (0.4–0.9)	0.041
Fibrates	0.5 (0.3–0.9)	0.044	0.4 (0.2–0.8)	0.012	0.5 (0.3–1.1)	0.09
Subfoveal choroidal thickness, μm	N/I		0.8 (0.7–0.9)	0.002	N/I	
Axial length, mm	N/I		0.9 (0.7–1.2)	0.62	N/I	
Lutein/zeaxanthin supplementation					1.9 (0.8–4.3)	0.14
Plasma lutein + zeaxanthin level, μg/mL	N/I		N/I		1.2 (1.0–1.5)	0.039

Model 1a included sociodemographic characteristics and medical treatment. Model 1b = model 1a + subfoveal choroidal thickness + axial length. Model 1c = model 1a + lutein/zeaxanthin supplementation + plasma lutein + zeaxanthin level. N/I, not included in the multivariate analysis.

* Odds ratio estimated using generalized estimating equation regression models. Odds ratios for continuous variable are expressed as the odds ratio associated with a one-standard deviation unit increase in the exposure.

Japan.[26,54,55] We found several factors associated with SDD, such as increasing age, female gender, higher stage of early AMD, subfoveal confluent soft drusen, disruption of ellipsoid zone, and thinner subfoveal choroidal thickness. The association with other factors such as lipid-lowering drugs deserves further investigation.

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