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RESEARCH ARTICLE

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Retinal microvasculature and incident dementia over 10 years: The Three-City-Alienor cohort

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Abstract

Introduction: We explored the longitudinal relationship between retinal vascular features and dementia incidence over 10 years.

Methods: Among 584 participants from the Three-City-Alienor (3C-Alienor) population-based cohort, quantitative retinal vascular features (caliber, tortuosity, fractal dimension) were measured using semi-automated software. Dementia was actively diagnosed over the follow-up period.

Results: One hundred twenty-eight participants (21.9%) developed dementia over a median of 7.1 years. In Cox proportional hazards models adjusted for sociodemographic characteristics, apolipoprotein E (*APOE*) ε4, and vascular factors, increased retinal arteriolar tortuosity was associated with all-cause dementia (hazard ratio per standard deviation increase, 1.21; 95% confidence interval: 1.02–1.44). Wider retinal calibers and a higher venular tortuosity were associated with mixed/vascular dementia, but not Alzheimer's disease. Fractal dimensions were not associated with dementia.

Discussion: Changes in the retinal microvasculature were associated with dementia risk. More studies are needed to replicate these findings and determine which features might help identify persons at risk at an early stage.

KEYWORDS
dementia, fundus, retina, retinal imaging, retinal microvasculature

HIGHLIGHTS

- The retinal microvasculature might reflect the brain microvasculature
- We explored the association between retinal vascular features and incident dementia

- 584 participants from the Three-City-Alienor cohort were followed-up over 10 years
- Increased arteriolar tortuosity and venular calibers were associated with dementia risk
- Retinal imaging might help identify persons at risk of future dementia

1 | INTRODUCTION

Among the many neuropathological drivers of dementia, vascular brain injury appears to be a main contributor, and most dementias result from a combination of both neurodegenerative and vascular pathologies.[1,2] However, vascular brain injury is most often covert. In particular, cerebral small vessel disease (cSVD) is highly prevalent in older persons yet often missed, as its detection requires brain imaging, which is time-consuming and costly.

The retinal and cerebral microvasculatures share many anatomic and physiologic similarities, given their common embryologic origin; thus the retinal vasculature might reflect the brain vasculature.[3] The retinal vasculature can be easily visualized using fundus photography, a rapid, noninvasive, and inexpensive optical imaging technique that is now available in primary care. Thus, the use of retinal imaging is of increasing interest in the study of cerebrovascular and neurodegenerative diseases.[4,5] Different types of retinal vascular changes can be observed on the images: qualitative retinopathy signs (e.g., microaneurysms, arteriolar narrowing) or quantitative retinal vessel calibers and retinal vascular network features; the latter two require semi- or fully automated software for quantification. Previous studies have found that qualitative or quantitative retinal vascular abnormalities might be related to a range of cerebrovascular abnormalities or diseases in brain imaging studies,[6–11] as well as cognitive impairment[6,12–14] and dementia,[6,12,15–21] although the results, particularly for dementia, remain inconclusive. Furthermore, most studies assessing dementia were cross-sectional, with only a few longitudinal analyses,[16–18,21] the latter of which sometimes fail to replicate the cross-sectional findings.[17] Retinopathy signs[6,12,17,18] and retinal vessel calibers[12,15,16,18–21] were the most frequently studied features. Few cross-sectional studies have examined the relationship between quantitative retinal vascular network features (e.g., vessel tortuosity and fractal dimension) and dementia subtypes, such as Alzheimer's disease (AD).[15,19,20] The latter is particularly important because new therapeutics are available, but these drugs seem to only work in patients with early AD.[22,23] Thus identifying persons at risk of AD, particularly in primary care and community settings, is an important strategy.

Longitudinal studies are warranted to further evaluate the potential utility of the retinal vascular network for the identification of persons at risk of future dementia and AD. In this study, we aimed to investigate the longitudinal association between retinal vascular network features and the incidence of dementia and its main etiologies over 10 years within a population-based cohort study.

2 | SUBJECTS AND METHODS

2.1 | Study population

This article is based on the Three-City (3C) study and its ancillary ophthalmological study, the Alienor (Antioxydants, Lipides Essentiels, Nutrition et maladies OculaiRes) study. The 3C study is a prospective population-based cohort that aims to estimate the risk of dementia attributable to vascular factors. At baseline (1999–2001), 9294 community-dwelling French adults ≥65 years of age residing in three French cities (Bordeaux, Dijon, Montpellier) were included, including 2104 from Bordeaux. The methodology has been described elsewhere.[24] Data on sociodemographic characteristics, lifestyle, physical and mental health, disability, and cognitive function were assessed at baseline and subsequently every 2 or 3 years for up to 17 years. Blood samples were collected at baseline.

At the 7-year follow-up (in 2006–2008, baseline for the present study), 963 participants from Bordeaux agreed to participate in the Alienor study.[25] Eye examinations were performed in the Bordeaux University Hospital Department of Ophthalmology. They included a recording of the ophthalmic history; measurements of visual acuity, refraction, and intraocular pressure; and capturing two nonmydriatic 45° color fundus photographs of each eye using nonmydriatic retinography (TRC NW6S; Topcon)—one centered on the macula and one on the optic nerve head (ONH).

Ethics committee approvals were obtained from the ethics committee of the University Hospital of Kremlin-Bicêtre and Sud-Mediterranée III for 3C and from the ethics committee of Bordeaux for Alienor. All participants signed an informed consent form.

In the present study, we focused on participants with retinal photographs. Among the 963 participants from the 3C-Alienor study, 849 had an ONH-centered photograph. We excluded 31 participants (3.7%) with prevalent dementia and 81 without any follow-up after baseline. We also excluded 153 participants with fewer than five biggest arterioles and venules assessed, leaving a study sample of 584 participants for the caliber analysis (measured in zone B). For the tortuosity and fractal dimension analysis (measured in zone C), we further excluded 29 ungradable measures in this zone; and for the fractal dimension sample only, we also excluded 92 participants with fewer than six biggest vessels identified. The study sample was thus composed of 555 participants for tortuosity analyses and 463 participants for fractal dimension analyses (Figure 1).

Compared to the 584 included participants, the excluded participants ($n = 379$) were older (mean age: 80.5 years vs 79.4), less often female (55.9% vs 65.8%), more often current or past smokers (38.5% vs 34.8%), and more often had diabetes (16.1% vs 13.9%) or a history of stroke (4.2% vs 2.2%). They were also more often apolipoprotein E (*APOE*) ε4 carriers (21.0% vs 15.8%).

2.2 | Retinal image analysis

For each participant, the right ONH-centered photograph was analyzed with SIVA (Singapore I Vessel Assessment) software, version 4.0. In cases of missing or poor-quality photographs of the right eye, the left eye was analyzed.

Seven retinal vascular features were considered in this study (Supplementary Methods). (1) Features related to vessel calibers: central retinal arteriolar (CRAE) and venular (CRVE) equivalents in the biggest vessels in zone B and the arteriole/venular ratio (AVR) of these calibers. These caliber measures represent the equivalent single-vessel parent caliber (width) for the biggest vessels in zone B. (2) Features related to tortuosity: simple arteriole/venule tortuosity, which represents the general straightness/curliness of the vessels. A higher tortuosity value indicates more curved retinal vessels. (3) The fractal dimension of arterioles and venules, which represent a measure of retinal vascular network complexity and density. A higher fractal dimension value indicates greater complexity of the retinal vascular network.

2.3 | Diagnosis of dementia

Dementia was actively diagnosed at baseline and at each follow-up visit using a three-step procedure. Trained psychologists assessed participants' cognitive function using the Mini Mental State Examination,[26] the Isaacs Set Test,[27] the Free and Cued Selective Reminding Test,[28] and the Trail Making Test Parts A and B.[29] After the neuropsychological examination, participants suspected of having dementia based on their neuropsychological performances or having a relative cognitive decline from a previous examination were examined by a neurologist. Finally, an independent committee of neurologists reviewed all potential cases of dementia to obtain a consensus on the diagnosis and etiology. Dementia was diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for dementia.[30] Dementia subtypes were determined according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for AD[31] and the Neuroepidemiology Branch of the National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) criteria for vascular dementia.[32] For the analyses, mixed dementia (defined as AD with vascular lesions) and pure vascular dementia were pooled in a single category.

RESEARCH IN CONTEXT

1. **Systematic Review**: We searched medical literature databases (e.g., PubMed and EMBASE) for studies examining the association between retinal microvasculature and dementia from inception to November 17, 2022. We identified three cross-sectional studies, but no longitudinal studies, examining retinal vascular network features, such as tortuosity or fractal dimension.
2. **Interpretation**: This study examined the relationship between retinal vascular features and incident dementia over 10 years. Changes in the retinal microvasculature at baseline (increased arteriolar tortuosity and to a lesser extent, increased venular calibers) were associated with an increased risk of dementia. Our findings suggest that retinal vascular features are useful for identifying individuals at risk of dementia.
3. **Future Directions**: The potential use of retinal vascular features deserves further research, including the examination of specific processes related to dementia etiology that might be involved. The use of retinal imaging in identifying persons at risk of future dementia should be evaluated.

2.4 | Other variables

The following covariates were considered: age, sex, education (elementary school without diploma, short secondary school vs higher level), the presence of at least one *APOE* ε4 allele, and vascular risk factors: smoking (past and current smokers vs. no smokers), hypertension (blood pressure ≥140/90 mmHg and/or antihypertensive treatment), pulse pressure (calculated as the difference between systolic and diastolic blood pressures), hypercholesterolemia (fasting cholesterol level ≥6.2 mmol/L and/or lipid-lowering treatment), diabetes (fasting glucose level ≥7 mmol/L or non-fasting level ≥11 mmol/L, and/or antidiabetic treatment), body mass index (BMI, self-reported weight/height^2), history of coronary heart disease, and history of stroke.

2.5 | Statistical analysis

Characteristics of the study sample are presented according to incident dementia with means (standard deviations, SDs) for quantitative variables and numbers (percentages) for qualitative variables. We used Cox proportional hazards models to estimate the risk of incident dementia and its main etiologies (i.e., probable or possible AD and mixed or vascular dementia) associated with retinal vascular features, and we provided hazard ratios (HRs) and 95% confidence intervals (CIs). Participants were censored either at the last follow-up visit, for those who did not develop dementia, or in the middle of the interval

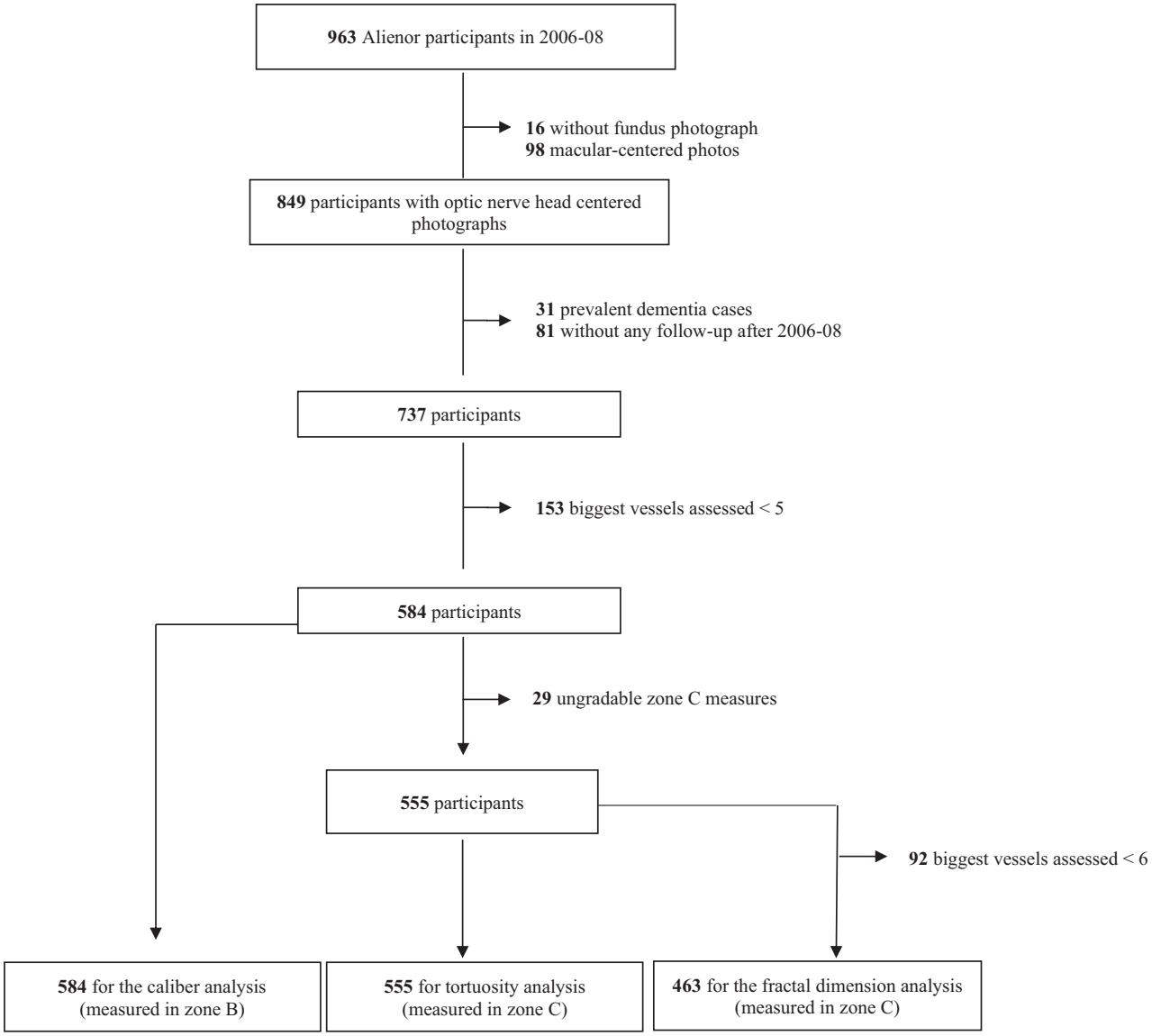

FIGURE 1 Flow chart of the participants. The Three-City-Alienor study.

between the last visit prior to the dementia diagnosis and the visit when dementia was diagnosed, for those who developed dementia. The different retinal vascular features were analyzed separately. Model 1 was adjusted for sociodemographic variables (age, sex, and education), and Model 2 was additionally adjusted for vascular risk factors (smoking, pulse pressure, hypercholesterolemia, diabetes, BMI, coronary heart disease, and stroke) and the *APOE* ε4 genotype. Based on preliminary analyses, we retained pulse pressure rather than hypertension due to better Akaike criteria. All retinal features were considered as mean-centered variables; thus, HRs are reported per SD increase in the considered variable, except for CRAE, which is reported per SD decrease. The linearity of the quantitative independent variables was verified by penalized splines with four knots, and the proportional hazard assumption check was based on Schoenfeld residual testing. When linearity was violated, the continuous variable was divided into tertiles. When the proportional hazard assumption was violated, HRs were presented for different follow-up periods.

Because diabetes and hypertension are two main cardiovascular and cerebrovascular risk factors that potentially affect the retinal microvasculature in different ways (e.g., diabetes is associated with widening of retinal arterioles,[33–35] whereas hypertension is associated with narrowing of retinal arterioles[36]), we tested if the associations between retinal vascular features and dementia differed according to the diabetes or hypertensive status in supplementary analyses by adding an interaction term in the models. When a significant interaction was observed (p-value for the interaction < 0.05), stratified analyses are presented. Finally, in sensitivity analyses, we excluded subjects with severe ocular diseases (age-related macular degeneration and epiretinal membranes).

Statistical analyses were performed with R (version 3.6.2; R Core Team).

TABLE 1 Characteristics of the study population according to incident dementia over the 10-year follow-up period. The Three-City-Alienor study, *N* = 584.

	Total (*N* = 584)		Non-demented (*N* = 456)		Incident dementia (*N* = 128)	
	Mean or *n*	SD or %	Mean or *n*	SD or %	Mean or *n*	SD or %
Sociodemographic and medical characteristics						
Age: mean (SD)	79.4	4.4	79.0	4.2	81.1	4.6
Sex, female	384	65.8	294	64.5	90	70.3
Education						
Elementary school	60	10.3	39	8.5	21	16.4
Short secondary school	287	49.1	226	49.6	61	47.7
Higher level	237	40.6	191	41.9	46	35.9
APOE ε4[a]	85	15.8	66	15.7	19	16.1
Pulse pressure (mm Hg): mean (SD)	67.5	16.1	67.2	15.4	68.6	18.3
Hypertension	478	81.8	373	81.8	105	82.0
Tobacco consumption						
Non-smoker	381	65.2	301	66.0	80	62.5
Past smoker	175	30.0	134	29.4	41	32.0
Current smoker	28	4.8	21	4.6	7	5.5
Hypercholesterolemia	379	64.9	296	64.9	83	64.8
Body mass index (kg/m^2): mean (SD)[a]	26.1	3.9	26.2	4.0	25.5	3.6
Diabetes	81	13.9	61	13.4	20	15.6
History of coronary heart disease	33	5.7	24	5.3	9	7.0
History of stroke	13	2.2	10	2.2	3	2.3
Retinal vascular measures						
AVR	0.71	0.07	0.71	0.07	0.70	0.07
CRAE (μm)	135.6	14.2	135.5	13.7	136.1	15.8
CRVE (μm)	192.6	20.3	192.1	20.3	194.4	20.0
Arteriolar tortuosity[a]	1.10	0.03	1.10	0.03	1.11	0.04
Venular tortuosity[a]	1.10	0.02	1.10	0.02	1.09	0.02
Arteriolar fractal dimension[a]	1.148	0.057	1.148	0.056	1.145	0.064
Venular fractal dimension[a]	1.139	0.050	1.139	0.049	1.137	0.054

Note: Values are numbers and percentages unless otherwise indicated.
Abbreviations: *APOE*, apolipoprotein E gene; AVR, arteriole-venular ratio in the biggest vessels in zone B; CRAE, central retinal arteriolar equivalent in the biggest vessels in zone B; CRVE, central retinal venular equivalent in the biggest vessels in zone B; SD, standard deviation.
[a]Missing value: *APOE* ε4 (*n* = 46), body mass index (*n* = 2), arteriolar tortuosity (*n* = 29), venular tortuosity (*n* = 29), arteriolar and fractal dimension (*n* = 121).

3 | RESULTS

The descriptive characteristics of the 584 participants are shown in Table 1. The mean age was 79.4 years, and 65.8% were women. A total of 10.3% had a very low educational level (i.e., no education or primary school without a diploma), and 15.8% were *APOE* ε4 carriers. Regarding vascular risk factors, 81.8% had hypertension, 34.8% were past or current smokers, 13.9% had diabetes, 64.9% had hypercholesterolemia, and the mean BMI was 26.1 kg/m^2.

Over the 10-year follow-up period, 128 participants (21.9%) developed dementia (incidence rate: 30.7 per 1000 person-years), including 85 (66.4%) probable or possible AD and 36 (28.1%) mixed or vascular dementia (19 mixed and 17 vascular, Table S1). Participants with future incident dementia were older, less educated, and were more likely to have diabetes and a history of coronary heart disease than participants without dementia. Regarding retinal features, they also had wider calibers and lower fractal dimension values, but their tortuosity values were similar (Table 1). The cognitive performance of participants with dementia at the time of their diagnosis is presented in Table S2.

In the fully adjusted Cox proportional hazard model, higher arteriolar tortuosity was associated with an increased risk of incident dementia over the 10-year follow-up period (HR per SD increase = 1.21, 95% CI = 1.02–1.44, Table 2, Model 2). Regarding venular tortuosity, the proportional hazard assumption was violated,

TABLE 2 Association between retinal microvascular features and incident dementia over the 10-year follow-up period. The Three-City-Alienor study, *N* = 584.

	Model 1[a]			Model 2[b]		
Retinal microvascular features	**HR**	**95% CI**	***p***	**HR**	**95% CI**	***p***
Calibers	*N* = 584 (128 cases)			*N* = 538 (118 cases)		
AVR (per SD increase)	0.90	0.75; 1.08	0.254	0.86	0.71; 1.05	0.143
CRAE (μm) (per SD decrease)	0.97	0.81; 1.16	0.736	0.95	0.78; 1.15	0.587
CRVE (μm) (per SD increase)	1.11	0.94; 1.32	0.233	1.18	0.98; 1.42	0.080
Tortuosity	*N* = 555 (119 cases)			*N* = 511 (110 cases)		
Arteriole (per SD increase)	1.20	1.03; 1.41	0.022	1.21	1.02; 1.44	0.026
Venule (per SD increase)			0.033[c]			0.032[c]
5 years of follow-up	0.99	0.55; 1.43		1.02	0.55; 1.49	
7 years of follow-up	1.16	0.72; 1.60		1.20	0.73; 1.67	
10 years of follow-up	1.46	1.02; 1.90		1.53	1.06; 2.00	
Fractal dimension	*N* = 463 (94 cases)			*N* = 426 (86 cases)		
Arteriole[d]						
<1.127	0.92	0.56; 1.51	0.744	0.89	0.52; 1.52	0.661
1.127–1.172	0.79	0.48; 1.30	0.358	0.82	0.49; 1.37	0.451
≥1.172	Ref	Ref	Ref	Ref	Ref	Ref
Venule (per SD increase)	0.96	0.78; 1.18	0.704	0.98	0.79; 1.22	0.851

Abbreviations: *APOE*, apolipoprotein E gene; AVR, arteriole-venular ratio; CI, confidence interval; CRAE, central retinal arteriolar equivalent; CRVE, central retinal venular equivalent; HR, hazard ratio.

[a]Model 1: Cox model adjusted for age, sex, and education.

[b]Model 2: Model 1 + *APOE* ε4, tobacco consumption, diabetes, pulse pressure, hypercholesterolemia, body mass index, history of coronary heart disease, history of stroke. Forty-six subjects with missing data for at least one of the adjustment factors were excluded in the Model 2 for the calibers, 44 for tortuosity, and 37 for fractal dimension.

[c]Interaction *p*-value tortuosity*time.

[d]Nonlinear effects.

with higher venular tortuosity associated only with a long-term risk of dementia (Model 2, HR at 10 years per SD increase = 1.53, 95% CI = 1.06–2.00). Regarding vessel calibers, although the result was not significant, a trend toward an increased risk of dementia was observed for a larger CRVE (Model 2, HR per SD increase = 1.18, 95% CI = 0.98–1.42). No association was observed for CRAE.

The association between the arteriolar fractal dimension and dementia was not linear, thus we divided the fractal dimension into tertiles; no association with dementia was observed. Notably, in this fractal dimension sample (including 463 participants), the results for the arteriolar tortuosity and caliber were similar to those obtained for the main sample, with even a significant association between a wider CRVE and higher dementia risk (Table S3, Model 2). In sensitivity analyses, the results were unchanged after excluding participants presenting severe ocular diseases.

When considering the different etiologies of dementia (Table 3), no significant associations were identified between retinal vascular features and AD. In contrast, a reduced CRAE (HR per SD decrease = 1.49, 95% CI = 1.01–2.19) and increased CRVE (HR per SD increase = 1.52, 95% CI = 1.04–2.22) were significantly associated with a higher risk of mixed and vascular dementia, with a higher HR observed than for all-cause dementia for CRVE. Consequently, a higher AVR was associated with a lower risk of mixed and vascular dementia (HR per SD increase = 0.41, 95% CI = 0.28–0.61). Moreover, higher venular tortuosity was associated with an increased risk of mixed and vascular dementia (HR per SD increase = 1.45, 95% CI = 1.05–2.02), whereas no significant association was identified for arteriolar tortuosity. No associations were observed for the fractal dimension.

In supplementary analyses, two associations between retinal vascular features and dementia differed by the diabetes (CRAE) or hypertensive status (arteriolar tortuosity) (*p* for the interaction < 0.05) (Table S4). According to the diabetes status, a decreased arteriolar caliber was associated with a reduced dementia risk in participants with diabetes (HR per SD decrease = 0.45, 95% CI = 0.23–0.89), but not in those without (HR per SD decrease = 1.04, 95% CI = 0.84–1.28). Regarding the hypertensive status, a higher arteriolar tortuosity was significantly associated with dementia risk in participants without hypertension (HR per SD increase = 2.10, 95% CI = 1.23–3.56), whereas the risk was lower and nonsignificant in participants with hypertension (HR per SD increase = 1.13, 95% CI = 0.93–1.37).

4 | DISCUSSION

In our large population-based study, we showed that more tortuous retinal arterioles were associated with an increased risk of incident

TABLE 3 Association between retinal microvascular features and incident dementia over the 10-year follow-up period according to the etiology of dementia. The Three-City-Alienor study.

	Alzheimer's dementia[a]			Mixed/vascular dementia[a]		
Retinal microvascular features	**HR[a]**	**95% CI**	***p***	**HR[a]**	**95% CI**	***p***
Calibers	*N* = 538 (78 cases)			*N* = 538 (33 cases)		
AVR (per SD increase)	1.12	0.88; 1.42	0.360	0.41	0.28; 0.61	$1.2e^{-05}$
CRAE (μm) (per SD decrease)	0.82	0.65; 1.03	0.083	1.49	1.01; 2.19	0.042
CRVE (μm) (per SD increase)	1.11	0.89; 1.40	0.350	1.52	1.04; 2.22	0.029
Tortuosity	*N* = 511 (71 cases)			*N* = 511 (33 cases)		
Arteriole (per SD increase)	1.13	0.90; 1.42	0.280	1.20	0.89; 1.62	0.222
Venule (per SD increase)	0.93	0.70; 1.22	0.590	1.45	1.05; 2.02	0.025
Fractal dimension	*N* = 426 (57 cases)			*N* = 426 (24 cases)		
Arteriole (per SD increase)	1.00	0.76; 1.33	0.980	0.95	0.60; 1.50	0.826
Venule (per SD increase)	1.06	0.81; 1.38	0.690	0.98	0.65; 1.48	0.931

Abbreviations: *APOE*, apolipoprotein E gene; AVR, arteriole-venular ratio; CI, confidence interval.; CRAE, central retinal arteriolar equivalent; CRVE, central retinal venular equivalent; HR, hazard ratio.

[a]Model 2: Cox model adjusted for age, sex and education, *APOE* ε4, tobacco consumption, diabetes, pulse pressure, hypercholesterolemia, body mass index, history of coronary heart disease, history of stroke.

dementia over a 10-year period; this association was even stronger in participants without hypertension. Although the association was nonsignificant in the main sample, wider retinal venular calibers were also associated with dementia risk in the smaller "fractal dimension" subsample. Moreover, although arteriolar calibers did not appear to be associated with all-cause dementia, an interaction with the diabetes status was observed: decreased arteriolar calibers were associated with a reduced dementia risk in participants with diabetes, but not in those without diabetes. According to the dementia subtype, we did not observe associations with AD. In contrast, wider calibers, both arteriolar and venular, and more tortuous retinal venules were significantly associated with a higher mixed and vascular dementia risk. No associations were identified for the fractal dimension.

Dementia begins years before any symptoms are manifested, and the subclinical phases may allow the early identification of at-risk individuals at a time when secondary prevention and new AD therapeutics might be effective.[22,23] Indeed, dementia is a multifactorial disease caused by a combination of neurodegeneration, neuroinflammation, and vascular lesions, and cSVD is one of the major mechanisms favoring cerebral vulnerability.[1,2,37] Abnormalities at the microvascular retinal level have been associated with low cognitive performance and brain imaging alterations[6–14] and may represent an early marker for cerebral microvascular abnormalities in the subclinical phase.

Although retinopathy signs have been consistently associated with dementia in previous studies,[6,12,17,18] the findings are less conclusive for quantitative retinal vascular features. Discrepancies in the findings may arise from differences in the included populations, either the general population or at-risk populations with high vascular profiles; different methods for the segmentation of retinal vascular features; or different study designs. In our study, venous widening was associated with mixed and vascular dementia, whereas the results for all-cause dementia were less strong, as the association was significant only in the smaller "fractal dimension" sample. One previous longitudinal population-based study also reported an association between venous widening and dementia,[16] including vascular dementia. In several retinal imaging studies, an increased venular caliber was also associated with several markers of cSVD,[8,9,11,38] reinforcing the potential involvement of this parameter in dementia occurrence. However, unlike some previous cross-sectional[12,15,19] and longitudinal[16,18,21] studies, we failed to observe any association between arteriolar narrowing and all-cause dementia and identified a significant association only with the mixed and vascular dementia risk. Of interest, the HRs were in opposite directions for mixed and vascular and AD dementia, with a narrower arteriolar caliber associated with an increased risk of mixed and vascular dementia, but a nonsignificant lower risk of AD. This result may be partially explained by the different involvement of risk factors in AD and mixed and vascular dementia, each of which leads to different retinal vessel abnormalities.

Indeed, metabolic factors, including diabetes, lead mainly to retinal venule abnormalities, including both higher tortuosity and wider retinal venules, whereas atherosclerotic factors are more related to arteriolar abnormalities.[39] In addition, hypertension has been consistently associated with retinal arteriolar narrowing,[36,39] whereas diabetes leads to wider retinal arterioles,[33–35] although some studies observed only venular widening.[40] The mechanisms underlying wider retinal arterioles in diabetes are unclear; several mechanisms have been proposed, including impaired autoregulation of small vessels driven by hyperglycemia and hypoxia.[41] In addition, diabetes-related factors (e.g., the disease duration and associated metabolic factors) may also influence vessel changes. Moreover, although diabetes is a risk factor for both AD and mixed and vascular dementia, its involvement in AD physiopathology far exceeds its vascular effect, including insulin dysregulation, inflammation, oxidative stress, and effects on amyloid beta (Aβ) deposits.[42] All of the preceding may explain why (1)

we did not observe consistent associations for arteriolar narrowing-associated risks, with risks identified in opposite directions for AD and mixed and vascular dementia; and (2) in stratified analyses, we observed that a decreased arteriolar caliber was associated with a lower risk of dementia in persons with diabetes.

The results for retinal tortuosity are inconsistent in many previous cross-sectional studies. Some studies reported increased arteriolar and venular tortuosity in AD,[15] whereas others detected associations with lower venular tortuosity[19] and/or arteriolar tortuosity.[20] Our results suggest that higher arteriolar tortuosity, and to a lesser extent, higher venular tortuosity are associated with increased risks of all-cause dementia and mixed and vascular dementia. However, surprisingly, although arteriolar tortuosity was associated with all-cause dementia, it was not associated significantly with mixed and vascular dementia in our study. This result may be due to a lack of power but also to the fact that the association between arteriolar tortuosity and dementia seems stronger among persons without hypertension, as shown in stratified analyses. Among persons with hypertension, arteriolar tortuosity may not reflect factors related to hypertension, such as the duration/severity of hypertension and/or the associated comorbidities; these factors are reflected mainly by arteriolar narrowing.[39]

The results from previous studies examining the relationship between the fractal dimension and brain health are far from conclusive. Reduced arteriolar and venular fractal dimensions were associated with poorer cognitive performance globally and in specific domains in one study,[43] whereas others failed to observe any significant associations.[44,45] Regarding brain imaging, a few studies have shown an association between a reduced arteriolar fractal dimension[8,10] or arteriolar and venular fractals[46] and cerebrovascular disease or brain imaging alterations, but others revealed that increased arteriolar[8] and venular[47] fractal dimensions were related to brain imaging alterations. Finally, some studies reported that reduced arteriolar[15,19] and/or venular[15,19,20] fractal dimensions were associated with dementia, but all of them were cross-sectional. Using a longitudinal design, we failed to observe any significant association between arteriolar or venular fractal dimensions and dementia.

The main strength of our study is the longitudinal design, with up to 10 years of follow-up. In addition, dementia was actively screened for and diagnosed by neurologists, which prevented bias due to underdiagnosis. Fundus photographs were graded by semi-automatic SIVA software independently from clinical data. Moreover, we adjusted for numerous major potential confounding factors, in particular vascular risk factors and vascular diseases, to identify the independent association between retinal vascular features and dementia.

Our study has some limitations. Because the Alienor study is focused mainly on age-related macular degeneration, the first fundus image was centered on the macula, and the second image centered on the ONH was sometimes of lesser quality. This approach has led to the exclusion of images in which large vessels could not be identified, thereby limiting the power of the analysis. The number of dementia cases identified over the follow-up was quite high; however, analyses stratified according to dementia subtypes were less powerful, perhaps preventing us from identifying some associations, particularly associations with arteriolar tortuosity. Although potential confounders were adjusted in the analyses, residual confounding cannot be excluded. In the current study we excluded participants whose fundus images were of poor quality and those without follow-up visit. These excluded participants had a greater number of risk factors. Thus, our sample mainly included well-functioning and highly educated subjects who underwent ophthalmologic examinations, limiting the extrapolation of these results. However, the exclusion of participants in poorer health should rather have biased our results toward the null. Finally, the slight differences between the results obtained for the main sample and the "fractal dimension" sample that included better-quality images, along with greater accuracy of the estimated risk of dementia associated with venular calibers, may prompt questions regarding the effect of image selection on the quantification of retinal vascular features.

Our findings suggest that some changes in the retinal vascular network are associated with the risk of future dementia in a community-dwelling population. Changes in the retinal microvascular network probably represent early stages of vascular changes in the brain, and this network might represent a surrogate marker for diseased cerebral vessels. However, although previous brain imaging studies have found that retinal vascular abnormalities might be related to cerebrovascular abnormalities,[6–11] as detailed above, results from studies aiming to predict clinical outcomes such as cognitive decline or dementia are far from agreeing on which markers would be the best; and even further from defining a threshold that could be used in clinical settings. Future tools for detecting early stages of dementia could arise from artificial intelligence, with a few works in progress in this field.[4,21] Yet, understanding the most important lesions/parameters should continue through studies with extensive phenotyping of participants. Future tools could also arise from more precise techniques such as Optical Coherence Tomographie-Angiography (OCT-A).[48–50] However, to date previous studies using OCT-A had small sample sizes or were cross-sectional and employed different types of image analysis methods and metrics definition, making it difficult to compare their results. Whatever the technique, the way is long and more work is still needed to obtain accurate, reliable, and reproducible tools that could help identify persons at risk of future dementia at an early stage when monitoring vascular risk factors may help slow brain damage.

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CONFLICT OF INTEREST STATEMENT

Sara Cristina Lima Rebouças, Louis Arnould, Carol Y. Cheung, Tien Y. Wong, and Catherine Helmer have no conflicts of interest to disclose. Audrey Cougnard-Gregoire is consultant for Laboratoires Théa. Marie-Noëlle Delyfer is consultant for AbbVie, Bayer, Horama, Horus Pharma, Novartis, and Roche et Thea. Cédric Schweitzer is consultatnt for Abbvie, Alcon, Glaukos, Nicox, Théa, Horus, Johnson & Johnson, Santen, and Bausch & Lomb. Jean-François Korobelnik is consultant for Abbvie, Apellis, Bayer, Janssen, Nanoretina, Roche, Théa, and Carl Zeiss Meditec, and is member of the Data and Safety Monitoring Board (DSMB) for Alexion, Nonordisk. Alexandra Foubert-Samier received honoraria from Aguettant Laboratory; and grants from the French Rare Disease Foundation, from the French regional health agency (Agence Régionale de Santé de nouvelle Aquitaine), and from France Parkinson association. Cecile Delcourt is consultant for Allergan, Chauvin-Bausch+Lomb, Laboratoires Théa, and Novartis, and received speaker's honoraria from Apellis. Author disclosures are available in the supporting information.

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