Subfoveal Choroidal Thickness, Cardiovascular History, and Risk Factors in the Elderly: The Montrachet Study

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Purpose. To measure subfoveal choroidal thickness (SFCT) in the elderly and to determine the associations among SFCT, cardiovascular history, and the 10-year risk of fatal cardiovascular disease (CVD).

Methods. We conducted a population-based study, the Montrachet (Maculopathy Optic Nerve, nuTRition neurovAsCular, and HEarT disease) study, in subjects older than 75 years. SFCT was measured with spectral-domain optical coherence tomography (SD-OCT) with enhanced-depth mode imaging. Participants underwent a comprehensive eye examination. The history of CVD, CVD risk factors, and a score-based estimation of their 10-year risk of cardiovascular mortality (Heart Score) were collected.

Results. Overall, 764 participants were retained for analysis. The mean SFCT was 206.4 ± 83.0 µm. The mean age was 81.9 ± 3.6 years. After a multivariable analysis, older age ($\beta = -32.56$ µm, $P < 0.001$) and longer axial length ($\beta = -20.71$ µm, $P < 0.001$) were independently associated with thinner SFCT. SFCT was not significantly associated with sex, cardiovascular history, classical CVD risk factors, or prognostic risk score.

Conclusions. This study confirms that longer axial length and older age are associated with thinner SFCT. However, SFCT does not appear to be a biomarker for cardiovascular history in this study.

Keywords: elderly, population-based study, cardiovascular disease, subfoveal choroidal thickness, Heart Score, Montrachet study, choroid, retina

Since the landmark study by Spaide et al.,[1] choroidal imaging has been widely used to investigate various retinal diseases. By means of spectral-domain optical coherence tomography (SD-OCT), subfoveal choroidal thickness (SFCT) can be measured noninvasively. Studies have measured choroidal thickness in normal eyes as well as eyes with various retinochoroidal disorders and glaucoma.[2–7] SFCT has been described as being associated with age, axial length, and sex in numerous studies.[8,9] In the past decade, several studies have attempted to decipher the relationship between retinal features and cardiovascular outcomes.[10] Retinal caliber modification (narrower retinal arterioles and wider retinal venules) or a sparse retinal vascular network (decreased fractal dimension) could confer a long-term risk of cardiovascular mortality and could be correlated with cardiovascular risk factors.[11–13] In contrast, the association between SFCT and cardiovascular risk factors remains unclear. As the choroidal blood supply is one of the highest in the human body per unit of surface, SFCT could be affected by vascular degenerative processes such as arteriosclerotic and obstructive atherosclerosis. Several studies focused on SFCT as a biomarker for cardiovascular outcome and common cardiovascular disease (CVD) risk factors.[14,15]

The purpose of this study was, first, to measure SFCT in an elderly population-based study. Then we sought to determine the associations among SFCT, cardiovascular history, and the 10-year risk of cardiovascular mortality in this population.

Methods

Study Design

The Montrachet (Maculopathy Optic Nerve nuTRition neurovAsCular and HEarT diseases) study focused on participants older than 75 years. This population-based study has been previously described.[16] It was conducted to assess the associations among age-related eye diseases, neurologic diseases, and heart degenerative diseases. Overall, 9294 persons older than 65 years, selected from three French urban cities (Dijon, Bordeaux, and Montpellier), were included ($n = 4931$

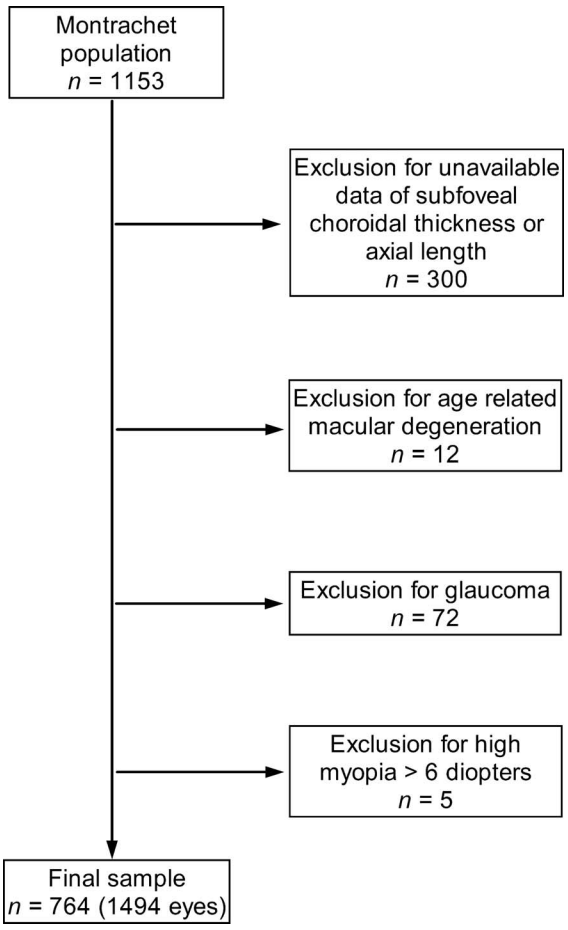

FIGURE 1. Flow chart for selection of participants in the Montrachet study (SFCT and cardiovascular risk factors).

participants in Dijon). Ten years later, a subgroup of participants from Dijon was invited to participate in the Montrachet study. All participants gave their written consent, and the study followed the tenets of the Declaration of Helsinki. The study was approved by the Dijon University Hospital ethics committee and was registered as 2009-A00448-49. We followed the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement according to the EQUATOR (Enhancing the QUAlity and Transparency Of health Research) Guidelines.[17]

Main Parameter Measurements

Participants underwent a comprehensive eye examination in the Department of Ophthalmology of the Dijon University Hospital, France. This examination included best-corrected visual acuity measurement (BCVA), IOP, lens status, and axial length measurement. Concerning chorioretinal imaging, an SD-OCT with enhanced-depth mode imaging (Spectralis; Heidelberg Engineering Co., Heidelberg, Germany) was performed after pupil dilation with tropicamide 0.5% (Théa, Clermont-Ferrand, France). The high-speed resolution mode and the eye-tracking system was activated to acquire the images. For the macula, an OCT image was obtained with a $20° \times 15°$ pattern size, 19 B-scans spaced 0.82° apart and the automatic real-time tracking mode on. The SFCT was measured independently by two trained ophthalmologists (LA, YE). It was defined as the vertical distance from the hyperreflective line of the Bruch membrane to the hyperreflective line of the inner surface of the sclera. This measurement was taken once below the fovea.

At baseline and every 2 years for 10 years, the participants in the three cities study filled in a complete questionnaire on their cardiovascular (myocardial infarction, angina, coronary artery dilatation, coronary bypass, and cardiovascular morbidity) and neurological history (ischemic and hemorrhagic stroke), as well as their medications (hypoglycemic treatment for diabetes mellitus, hypotensive treatment for hypertension, and cholesterol-lowering treatment for dyslipidemia) and lifestyle (smoking habit). During inclusion and follow-up, blood pressure was measured twice for each participant after 5 minutes in a seated position using a standard cuff placed around the right arm and an electronic monitor validated by the British Hypertension Society and the French Health Product Safety Agency. Concerning the associations between SFCT and CVD history, patients with high myopia (spherical equivalent >6 diopters), AMD, or glaucoma were excluded. Cardiovascular and ischemic stroke histories were summarized in a single variable: major adverse cardiovascular or cerebrovascular events (MACCE). Blood pressure, weight, and height were measured, and a blood sample (lipid, blood glucose tests, and creatinine values) was collected after fasting.

Statistical Analysis

Baseline characteristics were presented as *n* (%) for categorical variables and mean (± SD) or median (interquartile range) for continuous variables as appropriate. For comparison between participants and nonparticipants, a χ^2 or Fisher exact test for categorical data and Student's *t*-test or Kruskal-Wallis test for continuous data were used when appropriate. A missing data class for the education level variable was created before multivariable analysis to keep all eyes in multivariable analysis. To identify sociodemographic and CVD history factors associated with SFCT, a multivariable mixed linear regression model with the individual eye as the unit of analysis was used to take into account data for both eyes and their intraindividual correlation. All variables associated with SFCT with *P* values less than 0.20 in bivariate analysis were included in the multivariable model. Then a final model was built with age, education level, BCVA, and axial length. A manual backward procedure was applied with all variables associated with SFCT (*P* values < 0.10). Associations were expressed as β (SE). For all analyses, the tests were two-sided and the results were considered significant when *P* values were less than 0.05. Analyses were performed using SAS software (version 9.4; SAS institute, Inc., Cary, NC, USA).

RESULTS

Among the 1153 subjects included in the Montrachet study, 764 participants were retained for analysis (Fig. 1). The mean age was 81.9 ± 3.6 years with 34.3% men. The mean SFCT was 206.4 ± 83.0 μm.

Regarding the reproducibility of SFCT measurement, 50 examinations from randomly selected participants were assessed by two investigators (LA, YE) to determine interobserver reproducibility. To determine intraobserver reproducibility, SFCT was assessed twice by the principal investigator (LA) in 100 randomly selected participants. The intraclass correlation coefficient (ICC) showed substantial reproducibility (interobserver ICC = 0.97; 95% confidence interval [CI] 0.89–0.99) (intraobserver ICC = 0.83; 95% CI 0.79–0.87). Compared with the group of participants with SFCT measurements, the group of subjects without SFCT measurements was significantly older ($P = 0.004$) with more men ($P = 0.003$), and

Table 1. Baseline Characteristics Between Participants and Nonparticipants in the Montrachet Study

Baseline Characteristics	Total, $n = 1153$	Participants, $n = 764$	Nonparticipants, $n = 389$	P
Demographic				
Age, y				
<80	400 (34.69)	289 (37.83)	111 (28.53)	**0.004**
80–85	486 (42.15)	486 (42.15)	173 (44.47)	
>85	267 (23.16)	267 (23.16)	105 (26.99)	
Sex				
Male	430 (37.29)	262 (34.29)	168 (43.19)	**0.003**
Female	723 (62.71)	502 (65.71)	221(56.81)	
Education level ($n = 1064$)				
Primary education	142 (13.45)	93 (13.14)	49 (13.76)	0.512
Lower secondary education	467 (43.89)	322 (45.58)	145 (40.73)	
Upper secondary education	214 (20.11)	137 (19.35)	77 (21.63)	
Tertiary education	241 (22.65)	156 (22.03)	85 (23.88)	
Ophthalmic examination				
Lens status ($n = 1150$)				
Phakic	583 (50.70)	410 (53.74)	173 (44.70)	**0.004**
Pseudophakic	567 (49.30)	353 (46.26)	214 (55.30)	
Diabetic retinopathy				
No	1144 (99.22)	759 (99.35)	385 (98.97)	0.495
Yes	9 (0.78)	5 (0.65)	4 (1.03)	
Ocular hypertension, mm Hg				
No	1069 (92.71)	717 (93.85)	352 (90.49)	**0.038**
Yes	84 (7.29)	47 (6.15)	37 (9.51)	
BCVA, ETDRS				
≥20/60	1123 (97.40)	750 (98.17)	373 (95.89)	**0.021**
<20/60	30 (2.60)	14 (1.83)	16 (4.11)	
Iris color, $n = 1066$				
Blue/gray	428 (40.15)	279 (39.30)	149 (41.85)	0.192
Green/hazel	334 (31.33)	216 (30.42)	118 (33.15)	
Dark brown/black	304 (30.28)	215 (30.28)	89 (25.00)	
Cardiovascular risk factors				
Blood pressure, mm Hg, $n = 1014$				
Systolic	141.11 ± 19.34	140.68 ± 19.89	142.00 ± 18.16	0.325
Diastolic	74.05 ± 9.80	74.02 ± 9.73	74.11 ± 9.96	0.897
Plasma lipid, mM, $n = 1139$				
LDL cholesterol	3.60 ± 0.83	3.58 ± 0.82	3.64 ± 0.86	0.256
HDL cholesterol	1.66 ± 0.40	1.67 ± 0.40	1.64 ± 0.40	0.143
Diabetes, self-declared, $n = 938$				
No	817 (87.10)	547 (87.10)	270 (87.10)	0.998
Yes	121 (12.90)	81 (12.90)	40 (12.90)	
Treatment for systemic hypertension, $n = 1014$				
No	346 (34.12)	239 (35.10)	107 (32.13)	0.415
Yes <10 y	382 (37.67)	195 (28.63)	135 (40.54)	
Yes ≥10 y	286 (28.21)	247 (36.27)	91 (27.33)	
Hypoglycemic treatment, $n = 957$				
No	836 (87.36)	560 (87.36)	276 (87.34)	0.980
Yes <10 y	65 (6.79)	43 (6.71)	22 (6.96)	
Yes ≥10 y	56 (5.85)	38 (5.93)	18 (5.70)	
Cholesterol-lowering drug use, $n = 1021$				
No	321 (31.44)	204 (29.96)	117 (34.41)	0.255
Yes <10 y	187 (13.32)	123 (18.06)	64 (18.82)	
Yes ≥10 y	513 (50.24)	354 (51.98)	159 (46.76)	
Medical history				
CVD, $n = 1018$				
No	943 (92.63)	624 (92.17)	319 (93.55)	0.233
Yes <10 y	51 (5.01)	39 (5.76)	12 (3.52)	
Yes ≥10 y	24 (2.36)	14 (2.07)	10 (2.93)	
Stroke (ischemic and hemorrhagic), $n = 1052$				
No	1006 (95.63)	667 (95.01)	339 (96.86)	0.158
Yes <10 y	12 (1.14)	11 (1.57)	1 (0.29)	
Yes ≥10 y	34 (3.23)	24 (3.42)	10 (2.86)	
MACCE, $n = 1004$				
No	893 (89.94)	588 (82.82)	305 (91.04)	0.133
Yes	111 (11.06)	81 (11.42)	30 (8.96)	

P value was calculated between participants and nonparticipants. The results are displayed as n (%) for categorical variables and mean ± SD or median (interquartile range) for continuous variables depending on their distribution. Bold values indicate P values <0.05. ETDRS, Early Treatment Diabetic Retinopathy Study; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

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Table 2. Univariate Analysis and Subfoveal Central Thickness in the Montrachet Study ($n = 1494$)

Baseline Characteristics	Total	SFCT, µm	β (SE)*	P
Demographic				
Age, y				
<80	289 (37.98)	218.46 ± 81.43	Ref	
80–85	313 (40.97)	207.06 ± 83.80	−12.19 (6.33)	0.055
>85	162 (21.20)	183.70 ± 79.98	−30.88 (7.64)	**<0.001**
Sex				
Male	262 (34.29)	204.40 ± 82.81	−4.20 (5.98)	0.483
Female	502 (65.71)	207.50 ± 83.16	Ref	
Education level				
Primary education	93 (13.14)	197.36 ± 76.35	Ref	
Lower secondary education	322 (45.58)	215.61 ± 86.94	14.79 (9.14)	0.106
Upper secondary education	137 (19.35)	204.37 ± 82.68	−6.67 (10.18)	0.513
Tertiary education	156 (22.03)	196.12 ± 76.45	2.23 (10.43)	0.830
Ophthalmic examination				
Lens status				
Phakic	410 (53.74)	213.60 ± 79.22	Ref	
Pseudophakic	353 (46.26)	198.00 ± 86.62	−15.68 (5.67)	**0.006**
Ocular hypertension, mm Hg				
≤21	717 (93.85)	206.90 ± 82.81	Ref	
>21	47 (6.15)	199.70 ± 86.45	−11.50 (11.84)	0.332
Diabetic retinopathy				
No	759 (99.35)	206 ± 83.06	Ref	
Yes	5 (0.65)	258 ± 57.39	30.87 (31.38)	0.325
BCVA, ETDRS				
≥20/60	750 (98.17)	207.20 ± 82.87	Ref	
<20/60	14 (1.83)	164.80 ± 82.05	−41.16 (21.25)	0.053
Iris color				
Blue/gray	279 (39.30)	211.11 ± 84.13	Ref	
Green/hazel	216 (30.42)	206.29 ± 87.57	−7.41 (7.09)	0.297
Dark brown/black	215 (30.28)	202.09 ± 77.66	−8.18 (7.11)	0.250
Axial length, mm	23.37 ± 1.23		−20.42 (2.20)	**<0.001**
Cardiovascular risk factors				
Blood pressure, mm Hg				
Systolic	140.68 ± 19.89		−0.01 (0.15)	0.973
Diastolic	74.02 ± 9.73		0.19 (0.32)	0.549
Plasma lipid, mM				
LDL cholesterol	3.58 ± 0.82		1.38 (3.45)	0.689
HDL cholesterol	1.67 ± 0.40		9.58 (7.06)	0.175
Body mass index, kg/m^2				
≤25	353 (46.20)	205.70 ± 88.85	Ref	
>25	357 (46.73)	208.10 ± 77.48	2.57 (5.88)	0.663
Diabetes, self-declared				
No	547 (87.10)	209.00 ± 83.59	Ref	
Yes	81 (12.90)	196.00 ± 85.16	−10.35 (9.40)	0.271
Treatment for systemic hypertension				
No	239 (35.10)	212.29 ± 83.26	Ref	
Yes <10 y	195 (28.63)	202.22 ± 83.56	−6.21 (7.63)	0.416
Yes ≥10 y	247 (36.27)	205.98 ± 85.59	−4.98 (7.18)	0.488
Hypoglycemic treatment				
No	560 (87.36)	210.05 ± 84.12	Ref	
Yes <10 y	43 (6.71)	192.91 ± 90.49	−15.21 (12.53)	0.225
Yes ≥10 y	38 (5.93)	199.60 ± 79.75	−7.18 (13.28)	0.589
Cholesterol-lowering drug use				
No	204 (29.96)	211.31 ± 82.85	Ref	
Yes <10 y	123 (18.06)	204.90 ± 86.61	−5.97 (9.03)	0.508
Yes ≥10 y	354 (51.98)	207.11 ± 83.78	−5.77 (6.95)	0.406
Medical history				
CVD				
No	624 (92.17)	205.33 ± 82.51	Ref	
Yes <10 y	39 (5.76)	206.38 ± 85.99	−4.50 (12.83)	0.726
Yes ≥10 y	14 (2.07)	196.28 ± 78.36	−12.61 (20.94)	0.547
Stroke, ischemic and hemorrhagic				
No	667 (95.01)	206.69 ± 83.69	Ref	
Yes <10 y	11 (1.57)	202.36 ± 60.59	0.01 (23.79)	0.999
Yes ≥10 y	24 (3.42)	206.00 ± 83.69	7.96 (16.27)	0.625
MACCE				
No	588 (82.82)	205.20 ± 82.82	Ref	0.784
Yes	81 (11.42)	202.50 ± 80.94	−1.34 (9.20)	0.884

The results are displayed as n (%) for categorical variables and mean ± SD or median (interquartile range) for continuous variables depending on their distribution. Bold values indicate P values <0.05.

* Estimated using linear regression mixed model taking into account correlation between eyes.

Table 3. Multivariate Analysis of Factors Associated With SFCT in the Montrachet Study, $n = 1494$

Baseline Characteristics	β (SE)*	P
Age, vs. <80 y		
80–85	−12.66 (5.97)	**0.034**
>85	−32.56 (7.24)	**<0.001**
Education level versus primary education		
Lower secondary education	16.93 (8.66)	0.051
Upper secondary education	8.14 (9.58)	0.408
Tertiary education	5.63 (9.71)	0.562
Missing	14.65 (12.49)	0.241
BCVA	−36.00 (20.07)	0.073
Axial length, mm	−20.71 (2.19)	**<0.001**

Bold values indicate P values <0.05.

* Estimated using linear regression mixed model taking into account correlation between eyes.

they had undergone more cataract extraction ($P = 0.04$) (Table 1).

In univariate analyses, older age was significantly associated with a thinner SFCT ($\beta = -30.88$, $P < 0.001$) (Fig. 2). Moreover, longer axial length was associated with a thinner SFCT ($\beta = -20.42$, $P < 0.001$) (Fig. 3). No association was found with sex ($\beta = -4.20$, $P = 0.483$). There was no significant association between SFCT and cardiovascular risk factors, past history of MACCE or Heart Score risk profile (Table 2). After a multivariable analysis including all variables with P value < 0.20 (age, axial length, education level, and BCVA), age older than 85 years ($\beta = -32.56$ µm, $P < 0.001$) and axial length ($\beta = -20.71$ µm, $P < 0.001$) were independently associated with a thinner SFCT (Table 3).

Discussion

In this elderly population-based study, we found that mean SFCT was 206.4 ± 83.0 µm. Older age and longer axial length were associated with thinner SFCT in a multivariable analysis. SFCT was not significantly associated with sex, cardiovascular history, common CVD risk factors, or prognostic risk score.

The mean SFCT is in keeping with other published data, considering that our population consisted of an elderly group older than 75 years. In another population-based study, the Beijing Study,[18] SFCT was 253.8 ± 107.0 µm with a mean age of 64.3 ± 9.6 years. In fact, an age-related decline in SFCT was reported ranging from 3.3 to 5.4 µm per year. Independently, axial length was also a very consistent and influential parameter on SFCT in this study. The axial elongation-associated thinning of the subfoveal choroid combined with axial elongation-related thinning of the sclera have been addressed in animal studies and human cohorts.[19,20]

Until now, associations between retinal vessels' geometric features and general cardiovascular parameters have been well documented. For instance, software such as the SIVA analysis program with retinal fundus has provided promising results.[21] These results also could be consolidated with vessel density measurement with OCT angiography.[22] Therefore, it seems reasonable to find an association with the choroid. However, we did not find any association between SFCT and the cardiovascular pattern. Although retinal vascular network quantitative analyses can be used as a cardiovascular biomarker, the role of choroidal thickness as another risk factor remains unclear. The association among SFCT, the cardiovascular risk factor, and heart function has been studied in limited samples.[23,24] However, these studies focused on young subjects with heterogeneous CVDs such as angina, and abnormal stress test to coronary heart disease without any adjustment on axial length. In these studies, the severity of the CVD and the chronology with the ophthalmic examinations were not discussed. Furthermore, even if the choroid comprises blood vessels that could be affected by arteriosclerosis, blood flow, or microvasculature impairment, it is also composed of an extravascular structure that is less likely to be affected by the cardiovascular outcome. Indeed, the choroid presents stroma, collagen fibers, fibroblasts, nonvascular smooth muscle cells, large melanocytes, and a lymphatic system. Last, the possible relationship between systemic orthosympathetic activation in cardiovascular disease and choroid has not yet been elucidated.[25]

The results of our study differ from what was found in another population-based study regarding the association between choroidal thickness and cardiovascular status.[26] We

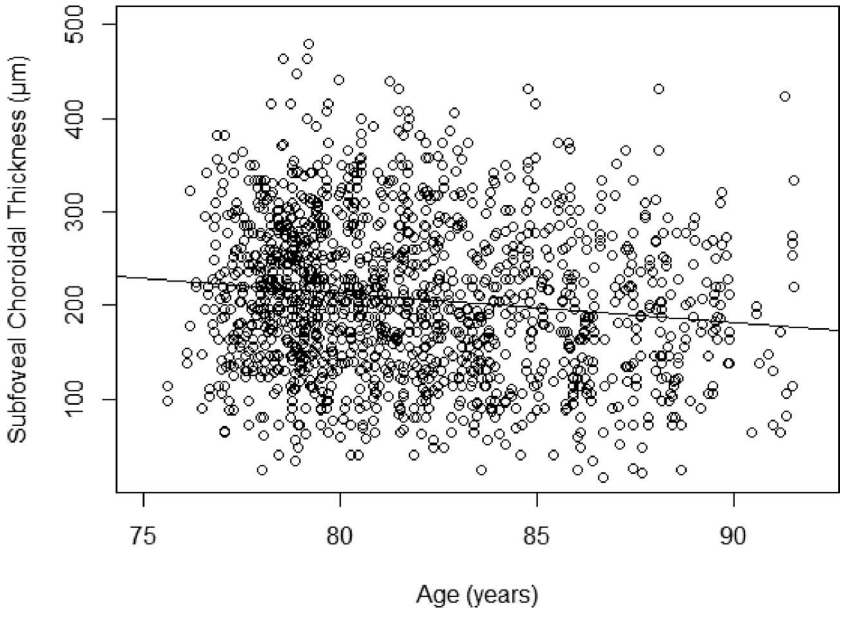

Figure 2. Association between age and SFCT in the Montrachet study.

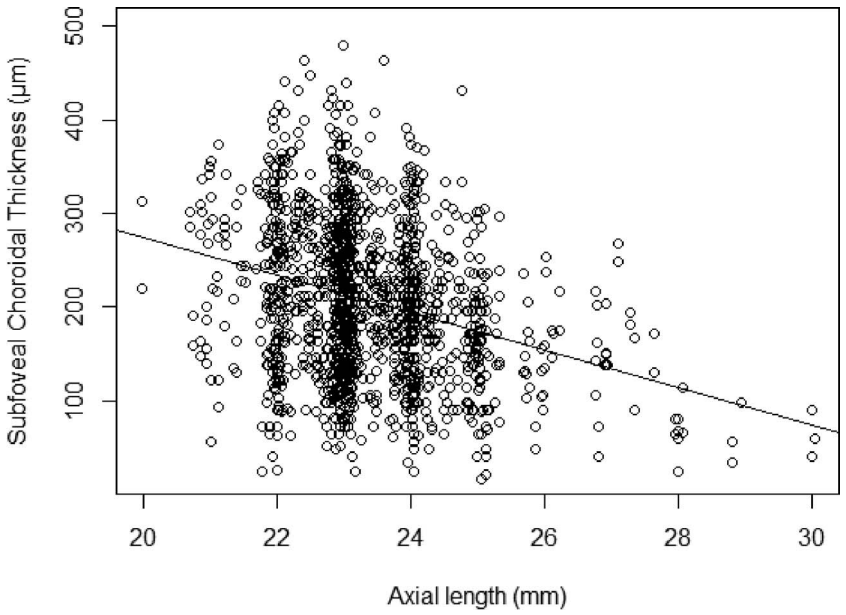

FIGURE 3. Association between axial length and SFCT in the Montrachet study.

found a similar choroidal thickness for elderly participants; we did not find an independent association among SFCT, heavy smoking, fasting blood glucose higher than 7 mM, and treatment of hyperlipidemia. Rather than a single isolated cardiovascular risk factor, we were interested in a more global one, such as MACCE and the Heart Score. Concerning the relationship between choroidal thickness and hypertensive medications, we acknowledge a limitation to this study, because of missing data on effective treatment status (arterial hypertension treated sufficiently, treated insufficiently, or untreated). We did not detect any difference between diabetic and nondiabetic participants concerning choroidal thickness in this study, which was not in accordance with the literature.[27–29] This difference might be explained by the lack of information on HbA1c level, treatment possibilities (insulin-dependent or non–insulin-dependent) and duration of diabetes. Moreover, we decided to exclude participants with AMD and glaucoma to avoid any interaction with ocular parameters.

In all these studies, manual SFCT measurements with calipers on SD-OCT were performed and provided a limited single dimension of the choroid. To consider these measurements as a surrogate marker of the choroidal blood flow seems questionable; however, imaging and quantification of choroidal flow remains challenging because of its heterogeneous vascular structure (choriocapillaris, anastomosed capillaries; Sattler's layer, medium-sized vessels; and Haller's layer, larger vessels).[29] The choroid is a three-dimensional vascular structure and it would probably be more accurate to study volume rather than SFCT with calipers to evaluate the potential cardiovascular biomarker of the choroid. SFCT is an imperfect biomarker of the physiology and choroidal blood flow and it could not be generalized to the entire choroid. This study would have benefited from measurement of a broader range of choroidal parameters.

Vupparaboina et al.[30] proposed a segmentation algorithm to estimate choroidal thickness distribution and volume. These techniques could be of great value to measure the choroid and its association with cardiovascular status. Furthermore, choroidal vascular flow would probably be better assessed through imaging examinations such as ultrasonography and Doppler flow imaging.[31,32]

The potential limitations of this study should be mentioned. First, the significant difference in the age and sex of nonparticipants compared with participants may have led to a selection bias. Second, Montrachet participants are urban volunteers, who usually follow a healthy lifestyle.[16] Therefore, cardiovascular risk factors could have been diagnosed and treated early, leading to a very low prevalence of further cardiovascular events. To consolidate our results, we could conduct a study with a design comparing cohorts of individuals with low and high cardiovascular risk status. Moreover past history and treatment were based on self-declaration. Third, these findings based on a Caucasian European population cannot be extrapolated to other parts of the world and other ethnicities.[33] Fourth, we performed only one manual SFCT measurement using built-in calipers with the potential impact of focal modification of the choroid and measurement errors[34]; however, intergrader reliability was high (interobserver reproducibility coefficient, 0.97) and we assume that measurement errors with enhanced-depth mode imaging are limited in our sample. Fifth, we excluded participants with high myopia. As a consequence, we studied only the association between SFCT and axial length in participants with less than 6 diopters of myopia.

This study is a large elderly population-based study, with data collected over a 10-year period based on the 3C study's medical records and the collection of a wide range of systemic medical features. In conclusion, in the Montrachet study, we confirmed that longer axial length and older age were associated with thinner SFCT. By contrast, SFCT did not appear to be a biomarker of the underlying cardiovascular outcomes.

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