· Intelligent Ophthalmology ·

Fundus blood flow density changes in the smoking population by artificial intelligence-based optical coherence tomography angiography

Ling-Yu Zhang[1], Qing-Jian Li[2], Qiang Zhou[2], Yu Zhang[2], Yan Liu[2], Zhi-Liang Wang[2], Pei Zhang[3]

[1]Tianjin Key Laboratory of Retinal Functions and Diseases, Tianjin Branch of National Clinical Research Center for Ocular Disease, Eye Institute and School of Optometry, Tianjin Medical University Eye Hospital, Tianjin 300380, China
[2]Department of Ophthalmology, Huashan Hospital, Fudan University, Shanghai 200040, China
[3]Department of Ophthalmology, Shanghai Fourth Rehabilitation Hospital, Shanghai 200040, China
Co-first Authors: Ling-Yu Zhang and Qing-Jian Li
Correspondence to: Pei Zhang. Department of Ophthalmology, Shanghai Fourth Rehabilitation Hospital, Shanghai 200040, China. zhangpei7607@163.com
Received: 2024-05-20 Accepted: 2025-07-16

Abstract
● **AIM:** To determine whether chronic smoking affects fundus blood flow density using optical coherence tomography angiography (OCTA) based on artificial intelligence (AI).
● **METHODS:** All participants underwent a comprehensive ophthalmological examination in this study. The subjects were categorized into two groups: control and smoker. Fundus data obtained through the novel OCTA device were compared.
● **RESULTS:** Utilizing deep learning denoising techniques removed background noise and smoothed vessel surfaces. OCTA showed a significant decrease in fundus blood flow density after AI-based denoising on the right eyes of 36 smokers (36 males, average age 44.17±9.85y) and age- and sex-matched participants who never smoked. The thickness of the retina in both control and smoker groups failed to show any statistically significant differences. Smoking was associated with decreased blood flow density in the macula and the optic disk.
● **CONCLUSION:** Utilizing AI-based denoising to improve the sensitivity of OCTA images can be highly beneficial.
● **KEYWORDS:** smoking; artificial intelligence; optical coherence tomography angiography; blood flow density; retinal thickness

DOI:10.18240/ijo.2025.09.01

Citation: Zhang LY, Li QJ, Zhou Q, Zhang Y, Liu Y, Wang ZL, Zhang P. Fundus blood flow density changes in the smoking population by artificial intelligence-based optical coherence tomography angiography. *Int J Ophthalmol* 2025;18(9):1613-1618

INTRODUCTION

Cigarette smoking is the leading preventable cause of morbidity and mortality across the globe, responsible for 11.5% of global deaths annually[1]. Despite the well-known devastating health effects of cigarettes and ongoing efforts to reduce smoking prevalence, approximately 1.6 billion people over the age of 14 smoke cigarettes daily worldwide, representing one-fifth of the world's population[2]. In addition to contributing to systemic vascular diseases, cigarette smoking causes pathological effects on macrovascular and microvascular structures[3-4]. Fundus blood flow provides an excellent window into the human microvascular system, allowing indirect and non-invasive observations of smoking's effects on the microvascular system[5-6]. Microvascular damage to the fundus may be one of the first detectable changes in its onset and progression.

Furthermore, smoking increases the risk of developing various ocular vascular diseases, including diabetic retinopathy, ischemic optic neuropathy, hypertensive retinopathy, and age-related macular degeneration (AMD)[7-9], since the harmful components of cigarettes affect vascular function and structure, which leads to endothelial damage and thickening of the blood vessel wall[10]. Hence, it is essential to investigate the effects of smoking on fundus blood flow.

Optical coherence tomography angiography (OCTA) imaging, a non-invasive optical imaging modality for visualizing fundus circulation without dye injection, has recently gained popularity in ophthalmic imaging[11]. The technology uses motion contrast imaging of blood flow to produce volumetric cross-sectional angiographic images of the retina, which measure the microvasculature of the retina in different layers[12-13]. OCTA displays high accuracy and reproducibility[14], measuring fundus blood flow density across various anatomical layers[15-16]. Clinical studies have shown that OCTA is particularly useful in studying fundus vascular diseases[16-17]. Nevertheless, it is vital to note that OCTA artifacts resulting from heteronomous motion and retinal projection significantly compromise the quality of images, thereby hindering precise interpretation and quantitative analysis[18-19]. Consequently, developing techniques to enhance the quality of OCTA images becomes imperative.

The development of artificial intelligence (AI)-based denoising software solutions has enhanced image quality[20]. It has already been reported that several OCTA studies have examined the effects of smoking on fundus vascular diseases[21-24]. However, the impact of chronic smoking on fundus blood flow density has not yet been studied using AI-based OCTA. We hypothesized that OCTA image quality might benefit from AI denoising. The research aimed to apply a novel AI-based denoising technique to OCTA images to assess fundus blood flow density variations between chronic smokers and non-smokers.

PARTICIPANTS AND METHODS

Ethical Approval According to the principles of the Helsinki Declaration, this study utilized a cross-sectional observational design at Huashan Hospital affiliated with Fudan University from February 2023 to June 2023. The study received approval from the Institutional Review Board of Huashan Hospital (No. KY2016-274). The informed consent was obtained.

Study Design and Participants Thirty-six smokers with a smoking history of more than ten years and 36 age- and sex-matched non-smokers were included in the study. Basic information, such as gender, age, smoking history, and clinical characteristics, is involved. Moreover, all participants were provided detailed explanations of the study's objectives and procedures before receiving comprehensive eye examinations. For each participant, only the right eye was examined.

Exclusion Criteria There were several exclusion criteria in the study: 1) Individuals who were under the age of eighteen and over the age of sixty; 2) Individuals who were uncooperative and dependent during extended OCTA testing; 3) Individuals whose best-corrected visual acuity was less than 0.4 logMAR; 4) Individuals who had spherical equivalent refraction of over 4 D; 5) Individuals with an axial length greater than 26 mm; 6) Individuals who had ocular diseases, including epiretinal membrane, diabetic retinopathy, or retinoschisis history; 7) Individuals who had ocular surgery or trauma history; 8) Individuals with a history of diabetes, hypertension, or thyroid diseases.

AI-Based Optical Coherence Tomography Angiography OCTA images were obtained utilizing the OCT-HS100 device manufactured by Canon in Tokyo, Japan. This device produced high-resolution microvascular images of the retina and choroid by rapidly scanning at a central wavelength of 855 nm. Images with a signal strength below 5, denoted on a scale ranging from 1 to 10, were omitted from the analysis. After undergoing rigorous deep learning training, an algorithm in the OCT-HS100 efficiently removed noise from images, creating a composite image from a single scan and eliminating the necessity for multiple scans. This algorithm effectively reduced background noise caused by blood flow density and smoothed the surface of blood vessels post-denoising. The measurement of retinal thickness included determining the distance between the internal limiting membrane (ILM) and the retinal pigment epithelium (RPE). The measurement area of the scan was segmented into three concentric circles, with the outer two rings subdivided into four quadrant sectors: superior, inferior, nasal, and temporal[25-27]. The area was divided into five subfields, each comprising a central region and four quadrants (superior, inferior, nasal, and temporal) for the assessment of vessel density. The segmentation of the superficial capillary plexus (SCP), deep capillary plexus (DCP), and choriocapillaris (CC) in the macula was achieved automatically[28]. Moreover, the segmentation of the SCP, DCP, CC, and radial peripapillary capillary (RPC) plexus was performed automatically within the optic disk[28]. The zones were initially partitioned by the Canon OCT-HS100 Software (Version 4.5.1) and subsequently refined by the examiner following the actual picture conditions.

Statistical Analysis The statistical analysis was performed using SPSS software (IBM, IL, USA). Categorical data were represented as frequencies (percentages), and continuous data were reported as mean±standard deviation. Chi-square tests were used to compare the two groups' categorical data, while paired *t*-tests were employed for continuous data. Statistical significance was defined as $P<0.05$.

RESULTS

This research involved 36 smokers and 36 age- and gender-matched controls. Both groups' demographic and clinical characteristics were outlined in Table 1. The average age of participants in both groups was 44.17±9.85y, ranging from 27 to 59y, with a male-to-female ratio of 36 to 0. The smokers in the study reported an average consumption of 18.33±10.14 cigarettes per day and had a smoking history of 23.86±8.10y.

All participants had access to data on blood flow density both pre- and post-implementation of denoising techniques employing AI. The corresponding measurements for blood flow density in the macula and optic disk were displayed in Tables 2 and 3, respectively. Significantly, all regions following the denoising procedure statistically observed a decrease in fundus blood flow density ($P<0.05$ for all comparisons).

Table 1 Demographic and clinical characteristics

Parameters	Control group	Smoker group	*P*
Participant, *n*	36	36	-
Eye, *n*	36	36	-
Sex, *n* (%)			1.000[a]
Male	36 (100.0)	36 (100.0)	
Female	0	0	
Age, y	44.17±9.85	44.17±9.85	1.000[b]
Range	27–59	27–59	
Daily amount of smoking, cigarettes	0	18.33±10.14	-
Years of smoking	0	23.86±8.10	-

[a]Chi-square test; [b]Paired *t*-test.

Table 2 Blood flow density in the macula between the original image and the denoised image

Flow density	Original image *n*=72	Denoised image *n*=72	*P*
SCP, %			
Center	33.15±7.84	21.61±6.62	<0.001[b]
Superior	43.79±7.22	38.40±7.00	<0.001[b]
Nasal	43.88±7.81	38.93±7.80	<0.001[b]
Inferior	43.83±7.85	39.27±7.79	<0.001[b]
Temporal	44.57±7.95	39.81±8.20	<0.001[b]
DCP, %			
Center	27.51±6.09	17.29±6.73	<0.001[b]
Superior	40.12±9.28	34.60±9.63	<0.001[b]
Nasal	44.12±7.28	39.27±7.44	<0.001[b]
Inferior	40.65±7.89	35.77±8.02	<0.001[b]
Temporal	42.97±7.59	37.98±7.40	<0.001[b]
CC, %			
Center	50.00±5.35	42.41±3.92	<0.001[b]
Superior	49.87±5.34	41.80±4.09	<0.001[b]
Nasal	49.57±4.93	42.28±3.65	<0.001[b]
Inferior	49.81±5.89	42.08±5.05	<0.001[b]
Temporal	49.66±7.72	43.02±4.26	<0.001[b]

SCP: Superficial capillary plexus; DCP: Deep capillary plexus; CC: Choriocapillaris. [b]Paired *t*-test.

Table 4 detailed the retinal thickness observed in the two groups. The analysis revealed no statistically significant differences in retinal thickness across all regions between the control and smoker groups.

Table 5 displayed the macular blood flow density for both groups. A decreasing trend in blood flow density within the macula was observed across all regions of the smoker group compared to the control. There were statistically significant differences in the center, superior, and nasal regions of DCP. Except for the inferior region, the SCP noted statistically significant differences. Regarding blood flow density in the CC, only the superior and temporal areas showed statistically significant variances.

Table 6 displayed the blood flow density in the optic disk. The smoker group noted a declining trend in blood flow density of the optic disk, albeit not as prominently as in the macula. Statistical differences were observed in the center (42.65±7.31 *vs* 38.11±8.57, *P*=0.030), nasal (50.52±5.22 *vs* 47.33±6.88, *P*=0.031), and inferior (50.21±4.43 *vs* 46.88±6.13, *P*=0.026) regions in the SCP. Additionally, statistically significant changes were observed in the temporal region of the CC (40.19±5.52 *vs* 37.72±4.98, *P*=0.046). All regions except for the superior and temporal areas noted significant alterations in RCP blood flow.

Table 3 Blood flow density in the optic disk between the original image and the denoised image

Flow density	Original image *n*=72	Denoised image *n*=72	*P*
SCP, %			
Center	45.61±8.49	40.38±8.23	<0.001[b]
Superior	52.98±6.74	48.14±6.25	<0.001[b]
Nasal	53.76±6.09	48.93±6.27	<0.001[b]
Inferior	54.30±6.26	48.54±5.57	<0.001[b]
Temporal	52.05±6.35	45.72±5.97	<0.001[b]
DCP, %			
Center	34.08±9.34	27.98±8.94	<0.001[b]
Superior	34.73±7.98	28.34±7.53	<0.001[b]
Nasal	35.63±8.45	29.81±8.28	<0.001[b]
Inferior	35.74±8.08	30.38±8.24	<0.001[b]
Temporal	47.25±7.86	41.67±7.37	<0.001[b]
CC, %			
Center	25.82±8.69	18.35±7.40	<0.001[b]
Superior	35.58±8.42	27.70±6.87	<0.001[b]
Nasal	41.04±7.18	33.08±6.93	<0.001[b]
Inferior	39.27±7.06	30.85±6.32	<0.001[b]
Temporal	49.10±7.57	38.95±5.37	<0.001[b]
RPC, %			
Center	45.04±6.47	41.20±6.16	<0.001[b]
Superior	50.86±6.71	46.37±6.45	<0.001[b]
Nasal	49.99±6.47	46.13±7.05	<0.001[b]
Inferior	51.60±6.28	47.63±6.36	<0.001[b]
Temporal	50.15±6.74	45.21±6.47	<0.001[b]

SCP: Superficial capillary plexus; DCP: Deep capillary plexus; CC: Choriocapillaris; RPC: Radial peripapillary capillaries. [b]Paired *t*-test.

Table 4 Retinal thickness μm

Retinal thickness	Control group *n*=36	Smoker group *n*=36	*P*
Center	278.69±22.54	274.42±21.10	0.432[b]
Inner superior	347.25±20.66	347.19±17.92	0.991[b]
Inner nasal	349.39±20.23	348.83±21.78	0.917[b]
Inner inferior	345.83 ±19.94	344.06±20.01	0.732[b]
Inner temporal	336.78±18.52	336.28±14.99	0.899[b]
Outer superior	308.56±15.67	308.72±15.52	0.964[b]
Outer nasal	322.78±16.31	321.22±16.29	0.684[b]
Outer inferior	291.06±18.26	290.11±15.73	0.816[b]
Outer temporal	293.92±17.11	292.31±15.27	0.659[b]

[b]Paired *t*-test.

Table 5 Blood flow density in the macula

Flow density	Control group n=36	Smoker group n=36	P
SCP, %			
Center	23.58±6.50	19.64±6.22	0.006[b]
Superior	40.30±5.93	36.49±7.53	0.027[b]
Nasal	40.76±6.21	37.11±8.83	0.017[b]
Inferior	40.73±6.90	37.81±8.44	0.080[b]
Temporal	41.72±6.47	37.91±9.33	0.026[b]
DCP, %			
Center	19.15±7.30	15.42±5.62	0.025[b]
Superior	36.94±8.90	32.27±9.88	0.030[b]
Nasal	40.98±5.74	37.55±8.57	0.042[b]
Inferior	37.36±7.44	34.18±8.36	0.072[b]
Temporal	39.23±6.58	36.74±8.05	0.084[b]
CC, %			
Center	43.34±2.86	41.49±4.61	0.056[b]
Superior	42.85±2.94	40.75±4.80	0.033[b]
Nasal	42.90±3.62	41.66±3.63	0.171[b]
Inferior	42.50±5.29	41.66±4.83	0.468[b]
Temporal	44.08±3.26	41.97±4.89	0.033[b]

SCP: Superficial capillary plexus; DCP: Deep capillary plexus; CC: Choriocapillaris. [b]Paired *t*-test.

Table 6 Blood flow density in the optic disk

Flow density	Control group n=36	Smoker group n=36	P
SCP, %			
Center	42.65±7.31	38.11±8.57	0.030[b]
Superior	49.11±6.05	47.17±6.38	0.189[b]
Nasal	50.52±5.22	47.33±6.88	0.031[b]
Inferior	50.21±4.43	46.88±6.13	0.026[b]
Temporal	46.54±4.93	44.89±6.83	0.246[b]
DCP, %			
Center	30.09±9.48	25.87±7.95	0.061[b]
Superior	29.95±6.43	26.74±8.27	0.109[b]
Nasal	31.19±8.40	28.42±8.05	0.159[b]
Inferior	32.04±8.98	28.72±7.16	0.083[b]
Temporal	43.44±5.44	39.89±8.61	0.053[b]
CC, %			
Center	20.09±7.42	16.61±7.06	0.056[b]
Superior	28.90±6.63	26.51±6.99	0.107[b]
Nasal	33.95±8.04	32.21±5.59	0.354[b]
Inferior	31.40±6.98	30.29±5.63	0.507[b]
Temporal	40.19±5.52	37.72±4.98	0.046[b]
RPC, %			
Center	42.95±4.94	39.45±6.80	0.011[b]
Superior	47.60±6.39	45.13±6.35	0.121[b]
Nasal	47.96±5.82	44.31±7.75	0.032[b]
Inferior	49.66±4.29	45.60±7.43	0.012[b]
Temporal	46.33±5.00	44.09±7.57	0.152[b]

SCP: Superficial capillary plexus; DCP: Deep capillary plexus; CC: Choriocapillaris; RPC: Radial peripapillary capillaries. [b]Paired *t*-test.

DISCUSSION

AI advances open new avenues for solving the complicated noise problem on OCTA images. There were 72 healthy subjects in our study, divided into groups of smokers and non-smokers. Both groups were matched based on age and sex. While conducting the current research, implementing deep learning denoising techniques effectively reduced background noise. Additionally, microvascular density parameters exhibited notable changes throughout the denoising process, indicating enhanced image quality. Using the novel OCTA, we compared fundus blood flow density and retinal thickness in smokers and non-smokers. According to the study, the smoker and non-smoker groups showed variable degrees of differences in blood flow density in the macula and optic disk, except for the retinal thickness. Moreover, the degree and range of the reduction in blood flow density were more marked in the macula than in the optic disk. The results indicated that AI-based OCTA could offer non-invasive diagnostic benefits for patients with fundus vascular diseases, enhancing diagnostic efficiency, especially for smokers. Fundus blood flow is evaluated by the AI-based OCTA, including retinal vasculature, CC, and RPC. The retinal vasculature is divided into SCP and DCP. Vertical vessels connect the capillary plexus, which provides oxygen and nutrients, removes retinal metabolic byproducts, and is affected by retinal vascular disease[29]. According to our study, smokers had lower fundus blood flow density than non-smokers. This finding is similar to previous studies on smokers[9,24,30]. It may be due to chronic smoking causing irreversible damage to the vasculature, which increases resistance to blood flow[31-32]. Several mechanisms are involved, including direct damage to the endothelium of fundus vasculature, structural damage, and vasculature dysfunction[31,33]. Smoking is a risky environmental factor in diseases of the fundus, such as AMD and polypoidal choroidal vasculopathy (PCV)[34-36]. Lois *et al*[37] have demonstrated that smoking poses a two to four times greater risk of developing AMD than non-smokers. Myers *et al*[38] have observed an association between smoking and the development of AMD. Cackett *et al*[39] have found that PCV is more prevalent among smokers. We speculate that our study's abnormal fundus blood flow could help elucidate why smokers are more susceptible to these ocular conditions and offer early diagnostic indicators. Nevertheless, some research holds contradictory conclusions that smoking affects fundus vascular without statistical significance compared with non-smokers[40-41]. The differences in sample size and participants' gender could explain these inconsistencies. We need to conduct further research to validate our findings. In addition, we found that the macula showed a more tremendous change in blood flow than the optic disk, which is the same as other researches[42-43]. There is a discrepancy in the autoregulation systems of the macula and optic disk vessels, which could account for the varying blood flow responses.

The current investigation revealed no statistically significant disparities in retinal thickness between smokers and non-smokers. Differently, in a study conducted on the Greek population who had smoked for more than 25y, it was found that chronic smoking resulted in thinner retinal thickness than non-smokers[44]. An additional study of elderly Chinese found that smoking cigarettes was associated with a lower macular fovea thickness compared with non-smokers[45]. Our distinctive result may be due to the relatively short smoking history and the focus of the sample on young and middle-aged people. Moreover, the retinal layer (SCP and DCP) showed more significant and extensive blood flow density decreases than the choroidal layer. Changes in the choroidal vasculature may occur later than in the retinal vasculature[46-48], which may interpret our results.

Our study applied AI-based noise reduction techniques to improve the quality of OCTA images, focusing on changes in fundus blood flow in smokers, which may provide early indications of fundus vascular disease. Despite this, it is essential to acknowledge the limitations of our research. First, since the study was cross-sectional, causal relationships between variables are impossible to establish. Addressing this question could conduct a longitudinal study over an extended period, providing more convincing evidence of the association between smoking and blood flow density. Second, our study only included participants from Huashan Hospital affiliated with Fudan University, which limits their generalizability. Other populations should also be studied to determine the effects of smoking on fundus blood flow. Finally, changes in fundus blood flow with a longer smoking history should be studied to comprehensively observe the impact of tobacco on fundus blood flow and retinal thickness.

The present study revealed a decline in fundus blood flow density among smokers. These findings strongly suggest that OCTA examination with AI denoising holds promise as an efficient and non-invasive diagnostic tool for fundus vascular diseases.

ACKNOWLEDGEMENTS

Foundation: Supported by the Shanghai Health Commission (No.202240097).

Conflicts of Interest: Zhang LY, None; **Li QJ,** None; **Zhou Q,** None; **Zhang Y,** None; **Liu Y,** None; **Wang ZL,** None; **Zhang P,** None.

REFERENCES

1 Yang Y, Peng N, Chen G, *et al.* Interaction between smoking and diabetes in relation to subsequent risk of cardiovascular events. *Cardiovasc Diabetol* 2022;21(1):14.

2 Ethier AR, McKinney TL, Tottenham LS, *et al.* The effect of reproductive hormones on women's daily smoking across the menstrual cycle. *Biol Sex Differ* 2021;12(1):41.

3 Kondo T, Nakano Y, Adachi S, *et al.* Effects of tobacco smoking on cardiovascular disease. *Circ J* 2019;83(10):1980-1985.

4 Duong M, Rangarajan S, Zhang XH, *et al.* Effects of bidi smoking on all-cause mortality and cardiorespiratory outcomes in men from south Asia: an observational community-based substudy of the Prospective Urban Rural Epidemiology Study (PURE). *Lancet Glob Health* 2017;5(2):e168-e176.

5 Li LJ, Ikram MK, Broekman L, *et al.* Antenatal mental health and retinal vascular caliber in pregnant women. *Transl Vis Sci Technol* 2013;2(2):2.

6 Korsiak J, Perepeluk KL, Peterson NG, *et al.* Air pollution and retinal vessel diameter and blood pressure in school-aged children in a region impacted by residential biomass burning. *Sci Rep* 2021;11(1):12790.

7 Garhöfer G, Resch H, Sacu S, *et al.* Effect of regular smoking on flicker induced retinal vasodilatation in healthy subjects. *Microvasc Res* 2011;82(3):351-355.

8 Gao JY, Cui JZ, Wang AK, *et al.* The reduction of XIAP is associated with inflammasome activation in RPE: implications for AMD pathogenesis. *J Neuroinflammation* 2019;16(1):171.

9 Ting DSW, Tan GSW, Agrawal R, *et al.* Optical coherence tomographic angiography in type 2 diabetes and diabetic retinopathy. *JAMA Ophthalmol* 2017;135(4):306-312.

10 Cai C, Wu F, He J, *et al.* Mitochondrial quality control in diabetic cardiomyopathy: from molecular mechanisms to therapeutic strategies. *Int J Biol Sci* 2022;18(14):5276-5290.

11 de Carlo TE, Romano A, Waheed NK, *et al.* A review of optical coherence tomography angiography (OCTA). *Int J Retina Vitreous* 2015;1:5.

12 Camino A, Guo YK, You QS, *et al.* Detecting and measuring areas of choriocapillaris low perfusion in intermediate, non-neovascular age-related macular degeneration. *Neurophotonics* 2019;6(4):041108.

13 Ong SS, Patel TP, Singh MS. Optical coherence tomography angiography imaging in inherited retinal diseases. *J Clin Med* 2019;8(12):2078.

14 Czakó C, Sándor G, Ecsedy M, *et al.* Intrasession and between-visit variability of retinal vessel density values measured with OCT angiography in diabetic patients. *Sci Rep* 2018;8(1):10598.

15 Sato R, Kunikata H, Asano T, *et al.* Quantitative analysis of the macula with optical coherence tomography angiography in normal Japanese subjects: The Taiwa Study. *Sci Rep* 2019;9(1):8875.

16 Zhu ZH, Zhao YY, Zou R, *et al.* Evaluation of optic nerve head vessels density changes after phacoemulsification cataract surgery using optical coherence tomography angiography. *Int J Ophthalmol* 2023;16(6):884-890.

17 Matet A, Daruich A, Dirani A, *et al.* Macular telangiectasia type 1: capillary density and microvascular abnormalities assessed by optical coherence tomography angiography. *Am J Ophthalmol* 2016;167:18-30.

18 Rabiolo A, Gelormini F, Marchese A, *et al.* Macular perfusion parameters in different angiocube sizes: does the size matter in quantitative optical coherence tomography angiography? *Invest Ophthalmol Vis Sci* 2018;59(1):231-237.

19 Lei J, Durbin MK, Shi Y, *et al.* Repeatability and reproducibility of superficial macular retinal vessel density measurements using optical coherence tomography angiography en face images. *JAMA Ophthalmol* 2017;135(10):1092-1098.

20 Brendlin AS, Plajer D, Chaika M, *et al.* AI denoising significantly improves image quality in whole-body low-dose computed tomography staging. *Diagnostics* (*Basel*) 2022;12(1):225.

21 Sigler EJ, Randolph JC, Calzada JI, *et al.* Smoking and choroidal thickness in patients over 65 with early-atrophic age-related macular degeneration and normals. *Eye* (*Lond*) 2014;28(7):838-846.

22 Yang WZ, Song CY, Gao M, *et al.* Effects of smoking on the retina of patients with dry age-related macular degeneration by optical coherence tomography angiography. *BMC Ophthalmol* 2022;22(1):315.

23 Liu DW, Haq Z, Yang D, *et al.* Association between smoking history and optical coherence tomography angiography findings in diabetic patients without diabetic retinopathy. *PLoS One* 2021;16(7):e0253928.

24 Aboud SA, Hammouda LM, Saif MYS, *et al.* Effect of smoking on the macula and optic nerve integrity using optical coherence tomography angiography. *Eur J Ophthalmol* 2022;32(1):436-442.

25 Li QJ, Qian YW, Xu SN, *et al.* Relationships of rheumatoid factor with thickness of retina and choroid in subjects without ocular symptoms using swept-source optical coherence tomography. *J Immunol Res* 2021;2021:5547533.

26 Li QJ, Zhou SM, Zhang LY, *et al.* Evaluation of retinal and choroidal thickness changes in overweight and obese adults without ocular symptoms by swept-source optical coherence tomography. *Int J Ophthalmol* 2024;17(4):707-712.

27 Wang J, Ji QL, Lin SJ, *et al.* Determining gender-based differences in retinal and choroidal thickness in underweight individuals *via* swept-source optical coherence tomography. *J Vis Exp* 2023;(202).

28 Wang J, Wang YC, Zhang P, *et al.* Retinal thickness and fundus blood flow density changes in chest pain subjects with dyslipidemia. *Int J Ophthalmol* 2023;16(11):1860-1866.

29 Liu GD, Keyal K, Wang F. Interocular symmetry of vascular density and association with central macular thickness of healthy adults by optical coherence tomography angiography. *Sci Rep* 2017;7(1):16297.

30 Kalayci M, Cetinkaya E, Suren E, *et al.* The effect of electronic cigarette smoking on retinal microcirculation: Enlargement of the foveal avascular zone. *Photodiagnosis Photodyn Ther* 2020;32:102068.

31 Zimmerman M, McGeachie J. The effect of nicotine on aortic endothelium. A quantitative ultrastructural study. *Atherosclerosis* 1987;63(1):33-41.

32 Quillen JE, Rossen JD, Oskarsson HJ, *et al.* Acute effect of cigarette smoking on the coronary circulation: constriction of epicardial and resistance vessels. *J Am Coll Cardiol* 1993;22(3):642-647.

33 Booyse FM, Osikowicz G, Quarfoot AJ. Effects of chronic oral consumption of nicotine on the rabbit aortic endothelium. *Am J Pathol* 1981;102(2):229-238.

34 Liu K, Lai TY, Chiang SW, *et al.* Gender specific association of a complement component 3 polymorphism with polypoidal choroidal vasculopathy. *Sci Rep* 2014;4:7018.

35 Yang DL, Elner SG, Lin LR, *et al.* Association of superoxide anions with retinal pigment epithelial cell apoptosis induced by mononuclear phagocytes. *Invest Ophthalmol Vis Sci* 2009;50(10):4998-5005.

36 Schnabolk G, Rohrer B, Simpson KN. Increased nonexudative age-related macular degeneration diagnosis among medicare beneficiaries with rheumatoid arthritis. *Invest Ophthalmol Vis Sci* 2019;60(10):3520-3526.

37 Lois N, Abdelkader E, Reglitz K, *et al.* Environmental tobacco smoke exposure and eye disease. *Br J Ophthalmol* 2008;92(10):1304-1310.

38 Myers CE, Klein BE, Gangnon R, *et al.* Cigarette smoking and the natural history of age-related macular degeneration: the Beaver Dam Eye Study. *Ophthalmology* 2014;121(10):1949-1955.

39 Cackett P, Yeo I, Cheung CM, *et al.* Relationship of smoking and cardiovascular risk factors with polypoidal choroidal vasculopathy and age-related macular degeneration in Chinese persons. *Ophthalmology* 2011;118(5):846-852.

40 Ayhan Z, Kaya M, Ozturk T, *et al.* Evaluation of macular perfusion in healthy smokers by using optical coherence tomography angiography. *Ophthalmic Surg Lasers Imaging Retina* 2017;48(8):617-622.

41 Eriş E, Aydin E, Özçift SG. The effect of the smoking on choroidal thickness, central macular vascular and optic disc perfusion. *Photodiagnosis Photodyn Ther* 2019;28:142-145.

42 Shoeibi N, Rajaei P, Ghobadi M, *et al.* Acute effects of coffee consumption on the microcirculation of macula and optic nerve head. *Nutr Health* 2022:2601060221130424.

43 Dastiridou A, Kassos I, Samouilidou M, *et al.* Age and signal strength-related changes in vessel density in the choroid and the retina: an OCT angiography study of the macula and optic disc. *Acta Ophthalmol* 2022;100(5):e1095-e1102.

44 Moschos MM, Nitoda E, Laios K, *et al.* The impact of chronic tobacco smoking on retinal and choroidal thickness in Greek population. *Oxid Med Cell Longev* 2016;2016:2905789.

45 Cui BH, He K, Zhang XD, *et al.* Association of cigarette smoking with retinal thickness and vascular structure in an elderly Chinese population. *Photodiagnosis Photodyn Ther* 2021;36:102481.

46 Battaglia Parodi M, Cicinelli MV, Rabiolo A, *et al.* Vessel density analysis in patients with retinitis pigmentosa by means of optical coherence tomography angiography. *Br J Ophthalmol* 2017;101(4):428-432.

47 Sugahara M, Miyata M, Ishihara K, *et al.* Optical coherence tomography angiography to estimate retinal blood flow in eyes with retinitis pigmentosa. *Sci Rep* 2017;7:46396.

48 Jauregui R, Park KS, Duong JK, *et al.* Quantitative progression of retinitis pigmentosa by optical coherence tomography angiography. *Sci Rep* 2018;8(1):13130.