Am J of Geriatric Psychiatry 31:8 (2023) 570–582

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ajgponline.org

>Regular Research Article

Brain and Cognition Signature Fingerprinting Vascular Health in Diabetic Individuals: An International Multi-Cohort Study

Pingting Zhong, M.D.*[#], *Shaoying Tan, M.D., Ph.D.*[#], *Zhuoting Zhu, M.D., Ph.D.*[#], *Junyao Zhang, B.Biomed.Sc., Shida Chen, M.D., Ph.D., Wenyong Huang, M.D., Ph.D., Mingguang He, M.D., Ph.D., Wei Wang, M.D., Ph.D.

ARTICLE INFO

Article history:
Received March, 21 2023
Revised April, 16 2023
Accepted April, 17 2023

Key Words:
Cognition
diabetes
mortality
vascular complication
UK Biobank

ABSTRACT

Objective: *To evaluate the correlation between cognitive signatures and the risk of diabetic vascular complications and mortality, based on a multicountry prospective study.* ***Methods:*** *The participants comprised 27,773 diabetics from the UK Biobank (UKB) and 1307 diabetics from the Guangzhou Diabetic Eye Study (GDES) cohort. The exposures were brain volume and cognitive screening tests for UKB participants, whilst the global cognitive score (GCS) measuring orientation to time and attention, episodic memory, and visuospatial abilities were determined for GDES participants. The outcomes for the UKB group were mortality, as well as macrovascular (myocardial infarction [MI] and stroke), microvascular (end-stage renal disease [ESRD], and diabetic retinopathy [DR]) events. The outcomes for the GDES group were retinal and renal microvascular damage.* ***Results:*** *In the UKB group, a 1-SD reduction in brain gray matter volume was associated with 34%–77% higher risks of incident MI, ESRD, and DR. The presence of impaired memory was associated with 18%–73% higher risk of mortality and ESRD; impaired reaction was associated with 1.2–1.7-fold higher*
Editorial accompaniment, please see page 583.

List of abbreviations: ESRD, end-stage renal disease; DR, diabetic retinopathy; CVD, cardiovascular disease; UKB, UK Biobank; GDES, Guangzhou Diabetic Eye Study; BMI, body mass index; OCTA, optical coherence tomography angiography; GCS, global cognitive score; Egfr, estimated glomerular filtration rate

From the State Key Laboratory of Ophthalmology (PZ, SC, WH, MH, WW), Zhongshan Ophthalmic Center, Sun Yat-sen University, Guangdong Provincial Key Laboratory of Ophthalmology and Visual Science, Guangdong Provincial Clinical Research Center for Ocular Diseases, Guangzhou, China; School of Optometry (ST, MH), The Hong Kong Polytechnic University, Hong Kong, China; Research Centre for SHARP Vision (ST, MH), The Hong Kong Polytechnic University, Hong Kong, China; Centre for Eye and Vision Research (CEVR) (ST, MH), 17W Hong Kong Science Park, Hong Kong; and the Centre for Eye Research Australia (ZZ, JZ, MH), Royal Victorian Eye and Ear Hospital, Melbourne, Australia. Send correspondence and reprint requests to: Wei Wang, M.D., Ph.D., Zhongshan Ophthalmic Center, State Key Laboratory of Ophthalmology, Sun Yat-sen University, Guangzhou, China. e-mail: wangwei@gzzoc.com

[#] Co-first authors

https://doi.org/10.1016/j.jagp.2023.04.010

risks of mortality, stroke, ESRD, and DR. In the GDES group, the lowest GCS tertile exhibited 1.4−2.2-fold higher risk of developing referable DR and a twofold faster decline in renal function and retinal capillary density compared with the highest tertile. Restricting data analysis to individuals aged less than 65 years produced consistent results. ***Conclusion:*** *Cognitive decline significantly elevates the risk of diabetic vascular complications and is correlated with retinal and renal microcirculation damage. Cognitive screening tests are strongly recommended as routine tools for management of diabetes.* (Am J Geriatr Psychiatry 2023; 31:570−582)

Highlights

- **What is the primary question addressed by this study?**
  Is cognitive signature related to diabetic complications and mortality?
- **What is the main finding of this study?**
  Cognitive signatures from magnetic resonance imaging and tests are significantly associated with increased risks of mortality and vascular complications in both middle- and older-aged people with diabetes.
  A faster decline in retinal microcirculation was found in diabetic patients with poorer cognitive function, reflecting the corresponding worse systemic circulation.
- **What is the meaning of the finding?**
  Questionnaire or brain-imaging-based cognition serves as a potential indicator of mortality and systemic vascular complications in the diabetic population.

INTRODUCTION

Cognitive impairment and dementia are the leading causes of disability and death during old age. Recent reports from the Lancet Commission and the World Health Organization have called for timely intervention to address these concerns.[1,2] Globally, a quarter of people aged 65 years or older suffer from diabetes, and 60% of people with type 2 diabetes mellitus (T2DM) have mild cognitive impairment.[3] In addition, early onset type 2 diabetes (< 40 years old) has become increasing common, in subjects who have had longer exposure time to hyperglycemia.[4] The management of hyperglycemia has transferred from a glucose-control centered to a prognosis-focused approach, in line with the consensus of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD).[5,6]

Vascular events in the heart, brain, kidney, and retina have been found to be risk factors for cognitive impairment or dementia among people with diabetes.[7−9] Cognitive impairment also poses a challenge for T2DM patients in achieving their glucose, blood pressure, and lipid goals. In addition, cognitive decline hinders patients from performing complex self-care tasks, such as glucose monitoring and adjusting insulin doses, as well as the ability to adhere to appropriate meal times and meal recipes.[5,6] However, the Action to Control Cardiovascular Risk in Diabetes-Memory in Diabetes (ACCORD-MIND) study and the Diabetes Control and Complications Trial showed no correlation between strictly controlling glucose levels and brain structure or cognitive function.[10,11] To date, few studies have examined the effects of cognition on the risk of vascular outcomes among people with diabetes.

The ADA guidelines recommend screening for cognitive impairment or dementia among diabetic patients aged 65 years or older.[12] Apart from cognitive tests, brain magnetic resonance imaging (MRI) has revealed an increased presence of lacunes and lower volume in the total brain, white matter, and gray matter among people with diabetes.[13,14] However, whether these brain signatures have prognostic value for vascular health remains unclear. To help fill

this knowledge gap, this study aimed to prospectively assess the association of cognition with the risks of vascular complications and mortality among people with diabetes based on two large cohorts from the UK and China.

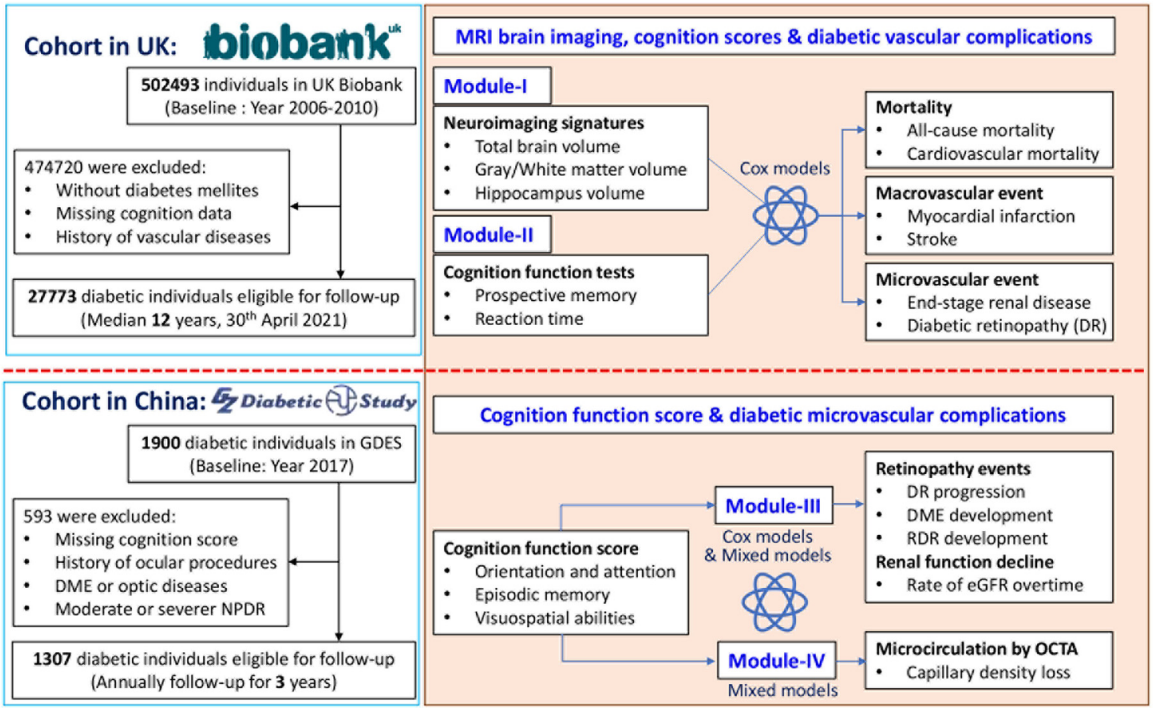
METHODS

Study Design and Population

Figure 1 shows the study design and analytic workflow. To enhance the robustness of the findings and clarify the relationship between cognitive decline and vascular events from both macroscopic and microscopic perspectives, the study utilized multiethnic populations and cohorts. The data was accessed from the UK Biobank (UKB), with a median follow-up of 12 years, and the Guangzhou Diabetic Eye Study (GDES) cohort in China, with a median follow-up of 2.2 years. The UKB Research Ethics Committee approved the UKB study (Research ID 62443), while the Ethics Committee of Zhongshan Ophthalmic Center approved the GDES study (Ref. No. 2017KYPJ094).

The UKB group comprised 502,493 participants aged 37−73 years, who were recruited from 22 centers across the UK between 2007 and 2010.[15] This study included individuals with diabetes and cognition assessments (brain MRI and cognitive tests). The association between brain volume and the risk of diabetic events was assessed for the participants who had undergone brain MRI (Module-I). The effects of cognitive function impairment on the risk of future vascular complications were also analyzed (Module-II). For the GDES, individuals with diabetes were recruited from Guangzhou communities for cognitive function and comprehensive examinations between November 2017 and December 2018.[16] This study included diabetic participants without diabetic retinopathy (DR) or with mild non-proliferative DR (NPDR). Participants with a history of ophthalmic

FIGURE 1. Overall structure of the whole study.



DR: diabetic retinopathy; CVD; cardiovascular disease; eGFR: estimated glomerular filtration rate.

treatment or diabetic macular edema (DME) were excluded. The associations between cognitive function scores and the risks of DR progression, incident DME, and referable DR were analyzed (Module-III). Optical coherence tomography angiography (OCTA) was used to assess the association of cognitive scores with the longitudinal rates of retinal capillary density loss (Module-IV).

Brain MRI Measures and Cognitive Function Tests

A subset of the UKB participants underwent brain imaging using a standard Siemens Skyra 3T MRI scanner with a standard 32-channel radio frequency receiver head coil. The neuroimaging data were already processed using a wide variety of tools and was made available for the study. T1- and T2-weighted scans were analyzed with the Functional MRI of the Brain Software Library. Adequate automatic quality control was developed and concentrated for the T1 images. The volumes of the total brain, gray matter, white matter, and hippocampus were assessed. The total brain volume was calculated by adding the gray matter and white matter volumes (excluding the cerebrospinal fluid). The brain volumes were normalized for head size based on the external surface of the skull using the ratio-corrected method.[17]

For UKB participants, cognitive function tests included prospective memory and reaction time. During the games, prospective memory was considered impaired if the participant forgot the instructions, skipped the question, or answered incorrectly after two attempts. The participant was considered to have reaction impairment if he/she had a mean reaction time greater than 770 ms (Supplementary method).

For GDES participants, the interview-based cognitive assessments were performed according to the China Health and Retirement Longitudinal Study, including measures of orientation to time and attention, episodic memory, and visuospatial abilities, through a word recall test (0−10 points), a telephone interview cognitive status test (0−10 points), and a pentagon drawing test (0−1 point).[18] The total score was defined as the global cognitive score (GCS), with a higher GCS representing better cognitive function. The participants were evenly divided into three groups according to their GCS tertiles: highest, middle, and lowest GCS.

Outcome Assessments

The outcomes of the UKB participants included incident all-cause and cardiovascular (CVD)-cause mortality, macrovascular events of myocardial infarction and stroke, and microvascular events of end-stage renal disease (ESRD) and DR among the diabetic participants during follow-up. The ICD-10 and OPCS4 codes for each outcome are listed in eTable 1 in the Supplement.

Each participant in the GDES cohort underwent a fundus examination. After pupil dilation, seven standardized 45° fundus photographs (Canon CX-1, Tokyo, Japan) were taken of each eye, and DR grading performed according to the Early Treatment Diabetic Retinopathy Study (ETDRS) scale.[19] Only the eye with the higher DR grade was included. A swept-source SS-OCTA device (DRI OCT Triton, Topcon, Tokyo, Japan) was used for the 3D visualization and quantification of the peripapillary microvasculature. Angio Disc 6×6 mm^2 scan modes were used to obtain optical nerve head-centered blood flow images and vessel density in the radial parapapillary capillary (RPC) was measured. The outcomes of the GDES participants include retinopathy events, estimated glomerular filtration rate (eGFR) decline, and OCTA-derived retinal capillary loss. Retinal events included 1) DR progression, 2) incident DME, and 3) incident referable diabetic retinopathy (RDR). DR progression refers to DR presence at baseline that increased by at least two steps; DME refers to central retinal thickness greater than or equal to 290 μm in females or greater than or equal to 305 μm in males; and RDR includes moderate NPDR, moderate PDR, or clinically significant DME. All eGFR and OCTA indicators were measured by the longitudinal rate, with years as the time unit.

Covariates

The covariates of age, sex, ethnicity, educational attainment, income, smoking status, physical activity, and medication history were obtained from the questionnaires. Height, weight, blood pressure (BP), and levels of glycosylated hemoglobin (HbA1c) and serum lipids from fasting venous blood samples were measured. The dementia gene ApoEε4 (carrier/non-carrier) and visual impairment status (yes/no) were also included. ApoEε4 carriage was detected using an Applied Biosystems (Waltham, MA) UK BiLEVE

Axiom array by Affymetrix (Santa Clara, CA) and an Applied Biosystems UKB Axiom Array. Visual impairment was defined as visual acuity below 0.3 logMAR units (Snellen 20/40) in the eye with better vision.[20]

Statistical Analysis

The demographic and clinical characteristics of the included participants were compared by chi-square test among the participants by the cognition performance in the UKB; or by ANOVA test among the participants by tertiles of the cognition performance in the GDES. Cox models were used to assess the associations between cognitive signatures and outcomes, with hazard ratios (HRs) and their 95% confidence intervals (95% CIs) used for quantifying the degree of risk.

For the UKB participants, two Cox models were constructed to analyze the brain imaging phenotypes and risks of outcome events: Model 1 was adjusted for age, sex, and ethnicity, while Model 2 was further adjusted for: educational attainment; income; smoking status; physical activity; body mass index (BMI); levels of systolic BP, HbA1c, total cholesterol, and serum creatinine; use of antihypertensive, lipid-lowering, and hypoglycemic medications; ApoEε4 carriers; and visual impairment status. Similar Cox models were also utilized to explore the association of the simple tests-based memory and reaction impairment with the risks of incident vascular events. Since there is no specific guideline pertaining to the necessity of cognition assessment for individuals with diabetes younger than 65 years, it was explored whether cognitive impairment is associated with a higher risk of incident outcome events specifically targeted at participants younger than 65 years. Furthermore, a subgroup analysis by sex (female/male) and a further sensitivity analysis, after excluding participants with baseline diseases that could impair cognitive function or outcome factors, were performed.

For the GDES participants, four Cox models were constructed to assess the effect of GCS levels on retinopathy events: Model 1 was unadjusted; Model 2 was adjusted for age and sex; Model 3 was further corrected for systolic BP, MAP, HbA1c, and diabetes duration; and Model 4 was additionally corrected for baseline DR. In addition, subgroups by sex (female/male) and age (<65 years/≥65 years) were analyzed. Mixed effect model was used to analyze the association between cognition status and the annual changes rates in eGFR and retinal microvascular density. The annual rate of eGFR decline according to the GCS tertile was adjusted for sex, systolic BP, HbA1c, and baseline eGFR. The annual rate of retinal capillary density loss among the GCS groups was compared with a crude model (Model 1), with a model adjusted for age, sex, and educational attainment (Model 2), and with a model further adjusted for BMI, HbA1c, and diabetes duration (Model 3). All statistical analyses were performed using Stata software (version 17.0, StataCorp, College Station, TX). A 2-tailed test with $p < 0.05$ was considered statistically significant.

RESULTS

Table 1 summarizes the baseline characteristics of the participants. The UKB group included 27,773 participants with diabetes, with a mean age of 59.3 years and comprising 11,246 (40.5%) females. Among these participants, 1168 had undergone a brain MRI, and 10,481 and 27,641 had completed prospective memory and reaction time tests, respectively (eTable 2−3 in the Supplement). The GDES group included 1,307 participants with diabetes, with a mean age of 64.5 years, of whom 755 (57.8%) were females (eTable 4 in the Supplement). The UKB participants suffered 4081 (14.7%) mortalities, which were attributable to cardiovascular mortality (1,529, 5.5%), myocardial infarction (2430, 8.8%), stroke (856, 3.1%), and ESRD (411, 1.5%), and 2508 (9.0%) cases of DR during a median follow-up period of 12 years (eTable 5 in the Supplement). During the median of 2.2-year follow-up, 288 (22.0%) GDES participants experienced DR progression, 69 (5.3%) developed new-onset DME, and 169 (12.9%) developed RDR.

Module-I: Brain Volume and Diabetic Complications in the UK Biobank

Individuals with cognition impairment on memory and reaction showed decrease in brain volume, compared to those without cognition impairment (eTable 6 in the Supplement). Besides, a decrease in brain volume revealed by MRI scans was associated with a higher risk of incident vascular events, but

TABLE 1. Characteristics of the Participants Included in the UKB and GDES Cohorts

Characteristics	Cohort in UK UKB (n = 27,773)	Cohort in China GDES (n = 1,307)
Age, years	59.3 ± 7.3	64.5 ± 7.6
Female	11246 (40.5%)	755 (57.8%)
Ethnicity	White (86.9%)	Chinese (100%)
Current smoker	3190 (11.5%)	179 (13.7%)
Systolic blood pressure, mm Hg	141.5 ± 17.7	133.4 ± 18.5
Diastolic blood pressure, mm Hg	82.1 ± 10.0	70.5 ±10.3
Mean arterial pressure, mm Hg	101.9 ± 11.1	91.5 ±11.4
Body mass index, kg/m^2	31.4 ± 5.9	24.6 ± 3.2
Waist to hip ratio	0.9 ± 0.1	0.9 ± 0.1
Current drinker	23,372 (84.2%)	115 (8.8%)
Below college/university	21,093 (76.0%)	990 (75.7%)
HbA1c, (%)	7.0 ± 1.3	6.9 ± 1.3
Total cholesterol, mmol/L	4.7 ± 1.1	4.8 ± 1.1
Triglycerides, mmol/L	2.2 ± 1.3	2.4 ± 1.7
High density lipoprotein, mmol/L	1.2 ± 0.3	1.3 ± 0.4
Low density lipoprotein, mmol/L	2.8 ± 0.9	3.0 ± 1.0
Serum creatinine, mg/Dl	0.8 ± 0.2	1.1 ± 0.2
Microalbuminuria, mg/dL	1.6 (1.0−3.4)	0.9 (0.3−2.5)
C-reactive protein, mg/L	2.0 (0.9−4.1)	1.5 (0.7−2.7)
Spherical equivalent, diopter	NA	0.6 (-0.4 to 1.5)
Axial length, mm	NA	23.6 ± 1.3
Intraocular pressure, mm Hg	NA	16.2 ± 2.7
Presence of diabetic retinopathy	0 (0%)	78 (6.0%)
eGFR, mL/min/1.73 m^2	90.1 ± 16.0	97.7 ± 18.8
Diabetes duration, years	NA	7.0 (3.0−12.0)
Follow-up, years	12.0 (11.1−12.8)	2.8 (2.1−3.1)
ApoEε4 carrier	5,939 (22.0%)	NA
Moderate to severe visual impairment	262 (1.0%)	0 (0%)
Anti-hypertension medications	6,101 (22.0%)	459 (35.1%)
Lipid-lowering medications	18,581 (66.9%)	384 (29.4%)
Use of insulin	1,923 (6.9%)	246 (18.8%)

Data are presented as mean ± SD, No. (%), or median (IQR).

UKB: United Kingdom Biobank; GDES: Guangzhou Diabetic Eye Study; NA: not available; BMI: body mass index; SBP: systolic blood pressure; MAP: mean arterial pressure; HbA1c: hemoglobin A1c; eGFR: estimated glomerular filtration rate.

not of mortality, among people with diabetes (Table 2). Increased risk of developing myocardial infarction was associated with a decrease in the brain volume of the gray matter (HR, 1.63, 95% CI, 1.13, 2.36) and the hippocampus (HR, 1.57, 95% CI, 1.12, 2.21). For microvascular complications, more than fourfold higher risks of new-onset ESRD were found per 1-SD decrease in both total brain volume (HR, 4.45, 95% CI, 1.07, 18.53) and gray matter (HR, 4.21, 95% CI, 1.34, 13.02). Approximately 1.5-fold greater risks were demonstrated for incident DR per 1-SD decrease in total brain volume (HR, 1.58, 95% CI, 1.13, 2.22), gray matter (HR, 1.51, 95% CI, 1.11, 2.06), and white matter (HR, 1.51, 95% CI, 1.06, 2.12). Brain atrophy in MRI scans was significantly associated with a higher risk of diabetic complications, even in those younger than 65 years (eTable 7 in the Supplement).

Module-II: Cognitive Tests and Diabetic Complications in the UK Biobank

Impairments in both prospective memory and reaction were associated with an increased risk of mortality and vascular complications (Fig. 2). After fully adjusting for other factors, prospective memory impairment was associated with 18% (95% CI: 1.02, 1.37), 37% (1.07, 1.77), and 73% (1.11, 2.70) increased risks of all-cause mortality, cardiovascular mortality, and ESRD, respectively. Similarly, impairment in reaction speed was associated with 43% (1.25, 1.64), 38% (1.11, 1.73), 73% (1.11, 2.71), 40% (1.04, 2.41), and 31% (1.11, 1.57) higher risks of all-cause mortality, cardiovascular mortality, stroke, ESRD, and DR, respectively. The subgroup analysis by sex and age, and the sensitivity analysis obtained consistent results with the primary analyses (eFigs. 1−4 in the Supplement).

TABLE 2. Hazard Ratios (95% Confidence Intervals) of Incident Diabetic Complications With per 1-SD Decrease in Brain Volume in the UKB

	Total Brain Volume (mL)	Grey Matter (mL)	White Matter (mL)	Hippocampus (μL)
All-cause mortality				
Model 1 [a]	1.32 (0.80, 2.20)	1.44 (0.90, 2.31)	1.13 (0.69, 1.85)	1.21 (0.79, 1.85)
Model 2 [b]	1.26 (0.67, 2.36)	1.27 (0.72, 2.24)	1.16 (0.62, 2.18)	1.29 (0.74, 2.24)
CVD mortality				
Model 1 [a]	1.46 (0.35, 6.07)	1.29 (0.33, 5.01)	1.53 (0.37, 6.30)	0.87 (0.25, 3.05)
Model 2 [b]	1.26 (0.24, 6.64)	1.157 (0.22, 6.01)	1.30 (0.25, 6.68)	0.76 (0.17, 3.31)
Myocardial infarction				
Model 1 [a]	1.27 (0.89, 1.81)	**1.56 (1.11, 2.18)**[c]	0.99 (0.71, 1.39)	**1.43 (1.05, 1.94)**[c]
Model 2 [b]	1.27 (0.87, 1.86)	**1.63 (1.13, 2.36)**[c]	0.96 (0.67, 1.38)	**1.57 (1.12, 2.21)**[c]
Stroke				
Model 1 [a]	0.77 (0.37, 1.56)	0.92 (0.47, 1.81)	0.69 (0.34, 1.37)	0.60 (0.33, 1.06)
Model 2 [b]	0.55 (0.23, 1.30)	0.74 (0.36, 1.53)	0.44 (0.17, 1.13)	0.56 (0.29, 1.08)
End-stage renal disease				
Model 1 [a]	**3.17 (1.00, 10.01)**[c]	**3.79 (1.31, 10.96)**[c]	2.03 (0.66, 6.26)	2.02 (0.75, 5.42)
Model 2 [b]	**4.45 (1.07, 18.53)** [c]	**4.20 (1.35, 13.02)**[c]	2.92 (0.61, 13.87)	2.41 (0.73, 7.97)
Diabetic retinopathy				
Model 1 [a]	**1.47 (1.09, 1.97)**[c]	**1.49 (1.13, 1.96)**[c]	1.32 (0.99, 1.77)	0.98 (0.76, 1.26)
Model 2 [b]	**1.58 (1.13, 2.22)**[c]	**1.51 (1.11, 2.06)**[c]	**1.51 (1.06, 2.12)**[c]	1.13 (0.85, 1.51)

[a] Model 1: adjusted for age, sex (female/male), and ethnicity (White/non-White).
[b] Model 2: further adjusted (from Model 1) for educational attainment (college/university or above, below college/university), income, smoking status (never/former or current smoker), physical activity (low/moderate/high), body mass index, systolic blood pressure, hemoglobin A1c, total cholesterol, serum creatinine, use of antihypertensive, lipid-lowering, and glucose-lowering medications (yes/no), ApoEε4 status (carrier/non-carrier), and visual impairment (yes/no).
[c] Bold indicates statistical significance.

Module-III: Cognitive Score and Microvascular Events in the GDES Cohort

A lower GCS was associated with higher risks of developing DR and a faster eGFR decline (eTables 8 −9 in the Supplement). The participants in the lowest GCS tertile were 1.44 (1.06, 1.96) times more likely to experience DR progression, 2.25 (1.17, 4.37) times more likely to develop DME, and 1.78 (1.19, 2.68) times more likely to develop RDR than those in the highest GCS tertile (eTable 8 in the Supplement). The rate of eGFR decline was 1.63-fold faster in the middle GCS tertile (−2.54, −0.72) and almost twice as fast as in the lowest GCS tertile (β = −1.99, 95% CI, −3.13, −0.85) than those in the highest GCS tertile (eTable 9 in the Supplement). Subgroup analysis by age, whether older than or younger than 65 years, showed similar findings (eTable 10 in the Supplement).

Module-IV: Cognitive Score and Rate of Retinal Capillary Loss in the GDES Cohort

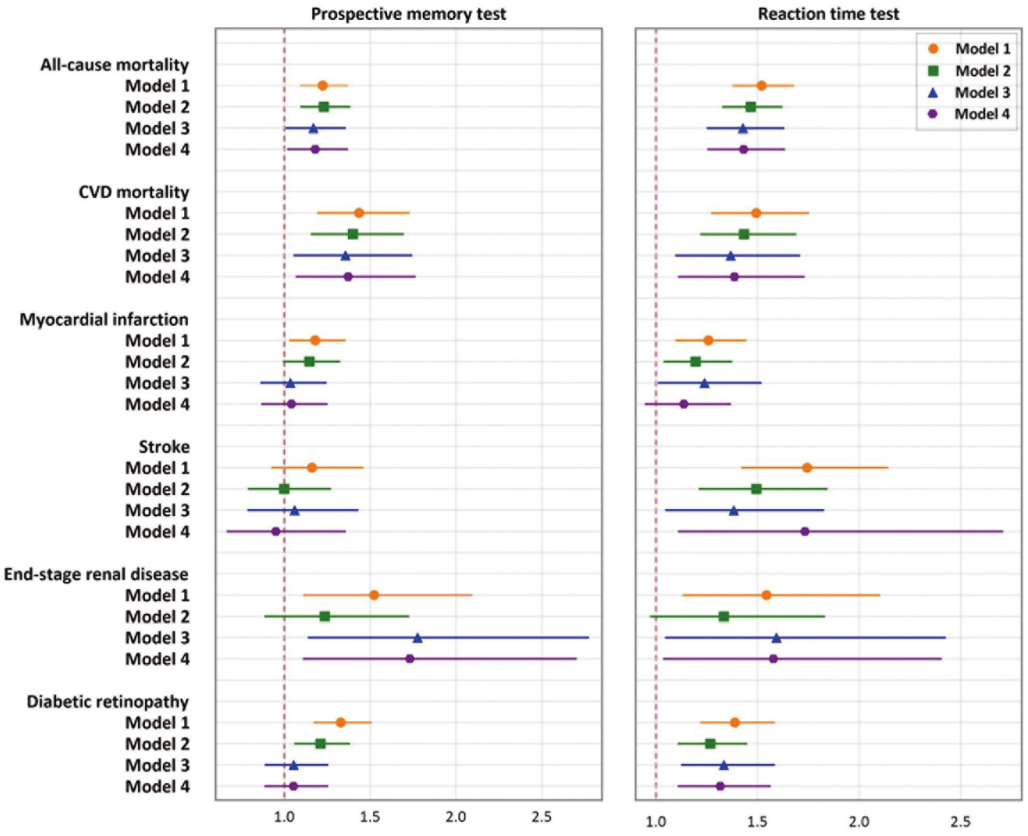
Figure 3 shows that the lowest GCS was associated with a faster decline of capillary loss in the optic nerve head obtained by OCTA (all p <0.05). After being fully adjusted, the highest GCS tertile presented a lower damage rate in the entire image (β = 0.09, 95% CI, 0.00, 0.18) and in the inner circles (β = 0.14, 95% CI, 0.00, 0.27) compared with the lowest GCS tertile (eTable 11 in the Supplement).

DISCUSSION

This study demonstrated that cognitive signatures were significantly associated with risks of mortality and vascular outcomes among people with diabetes. The diabetic patients younger than 65 years exhibited a greater probability of suffering from diabetic complications if they presented cognitive impairment. In addition, more rapid damage to retinal microcirculation was observed in diabetic participants with poorer cognitive function, which may reflect the corresponding poorer systemic circulation. These results indicate that cognition may be a potential indicator of mortality and systemic vascular complications in the diabetic population.

This study provides the first evidence of the relationship between MRI signs of cognition and diabetic vascular complications. Decreased volume in the gray matter and hippocampus was found to be associated with cognitive impairment or dementia, and

FIGURE 2. Hazard ratios (95% confidence intervals) of mortality and vascular events with baseline cognitive impairment in the UKB.

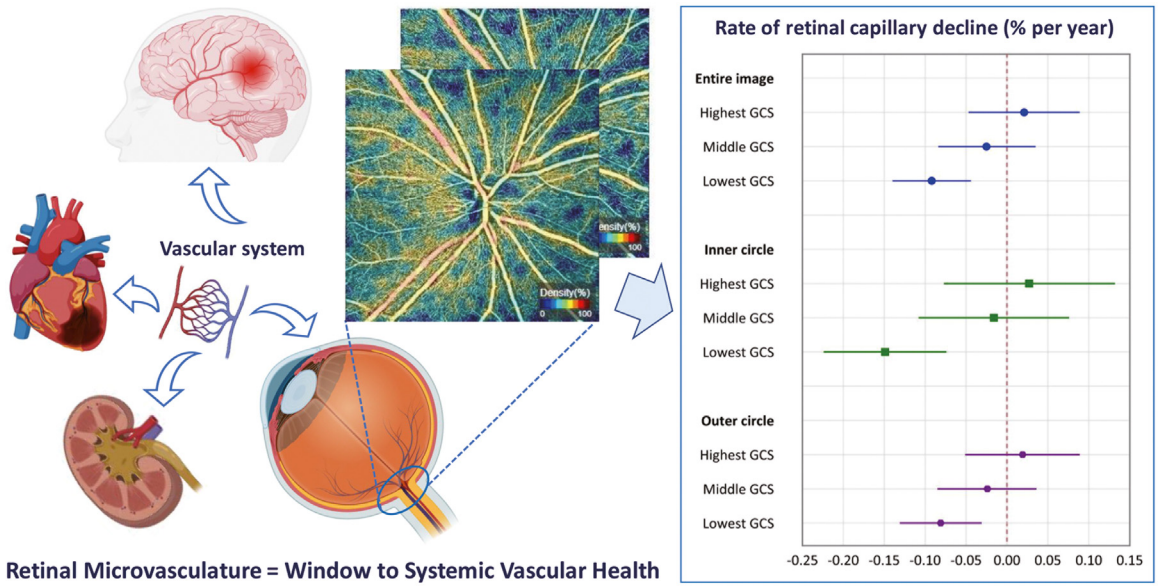


CVD: cardiovascular disease. Model 1: unadjusted; Model 2: adjusted for age, sex (female/male), and ethnicity (White/non-White); Model 3: further adjusted (from Model 2) for educational attainment (college/university or above, below college/university), income, smoking status (never/former or current smoker), physical activity (low/moderate/high), body mass index, systolic blood pressure, hemoglobin A1c, total cholesterol, serum creatinine, use of antihypertensive, lipid-lowering, and glucose-lowering medications (yes/no); Model 4: further adjusted (from Model 3) for ApoEε4 status (carrier/non-carrier) and visual impairment (yes/no). Cognitive test normal was considered as reference in all the analyses.

medial temporal decline was commonly associated with memory impairment both in people with cognitive decline and diabetes.[21,22] Most studies have found cardiovascular, cerebrovascular, renal, and retinal vessel disease to be risks for brain structure changes and damage.[8,9,23,24] However, the effects of brain volume on systemic vascular disease have not been fully explored. The current study has indicated that atrophies in the total brain, white matter, gray matter, and hippocampus, were associated with higher risks of myocardial infarction, ESRD, and DR among people with diabetes. However, brain MRI may not be a feasible and simple method for routine cognition assessment in diabetic patients. The limitations of time and low cost-effectiveness may hinder the patients' willingness to participate, leading to failure in the early detection of cognitive impairment.[25]

Cognitive function tests may serve as a simple and convenient replacement to assess cognition in the routine screening for diabetic patients.[1] Cognitive screening tests are well-established and have been used in many studies, such as CVD-related research, as a tool to evaluate cognition status.[26] In addition, cognitive tests based on cognitive impairment have been strongly proposed as a marker for a high risk of developing cardiovascular events. A 20-year follow-up

FIGURE 3. Baseline cognition status and longitudinal rate (% per year) of retinal capillary density in the Guangzhou Diabetic Eye Study (GDES) cohort.



GCS: global cognition score; VD; vessel density. Participants with diabetes in the lower GCS group exhibited accelerated decline in capillary density compared to higher GCS group.

study of 2,000 middle- and older-aged participants found that cognitive impairment was associated with a twofold to fourfold higher risk of all-cause and CVD mortality and a 34%–56% increase in risks of all-cause and CVD mortality for each five-point decrease in the mini-mental state examination (MMSE) score.[27] Similarly, a retrospective analysis of more than 2 million adolescents used general intelligence tests as indicators of cognitive function, demonstrating a strong relationship between cognitive decline in youth with 1–3 times higher risks of future all-cause and CVD-related mortality.[28] These studies confirmed the credibility of cognitive tests as a tool to assess cognition status, as well as the adverse effects of cognitive impairment on systemic vascular diseases. However, most of these studies were based on a single center or ethnicity and only a few have focused specifically on the population with diabetes. Based on a large population and multiple ethnicities, the current study has demonstrated that cognitive impairment in memory, reaction, orientation, and visuospatial abilities was associated with higher risks of mortality and vascular complications among diabetic patients.

Cognitive impairment has been identified as a key indicator of covert CVD in individuals with diabetes. In the Medalists cohort, elderly type-I diabetics with CVD and proliferative DR demonstrated cognitive decline in executive function and psychomotor speed, respectively.[7] Similarly, in the ONTARGET and TRANSCEND trials, which included a large sample of high-risk CVD patients (aged ≥55 years with established CVD or diabetes mellitus with end-organ damage), individuals with lower MMSE scores (score of 27–29, 24–26, and <24) were found to have a graded increased risk of major CVD events such as CVD mortality, stroke, and myocardial infarction.[29] Additionally, the ADVANCE trial, which focused on diabetic patients, also revealed a similar association between cognitive decline and CVD events, with severe cognitive dysfunction increasing the risk of severe hypoglycemia.[30] Our findings further supported the utility of simple cognitive screening tests for identifying patients at risk for CVD and CVD mortality. Consequently, individuals with impaired cognitive test results should receive aggressive vascular risk factor modification.

The ADA guidelines for the prevention and management of ASCVD and heart failure recommend that all patients with diabetes should be evaluated, at least annually, for cardiovascular risk factors, including obesity/overweight, hypertension, dyslipidemia, smoking, family history of premature coronary heart disease, chronic kidney disease, and albuminuria.[5,6] Risk score-based prediction models and other cardiovascular biomarkers have also been developed for secondary prevention for those already at high risk for ASCVD.[5,6] However, neither cognitive scores nor brain MRI parameters have been incorporated into the management strategy or prediction models. The current study suggests that screening tests covering memory, reaction, attention, recall, and executive ability are well-established, convenient, and simple methods to assess an individual's cognitive status and should be included in the screening and diagnosis of people with diabetes to detect and manage cognitive decline.[31] The ADA guidelines recommend that diabetic patients aged 65 or older should receive cognition screening (REF). However, the present study indicates that cognition screening should be expanded to all age groups, because of the significant associations between cognition/brain volumes and vascular events, even in patients younger than 65 years.

The development and progression of cardiovascular diseases and stroke had a unifying feature, i.e alterations in the microvessel (lumen diameter <300 μm), which can be evaluated in vivo by eye eamination.[31] Retinal imaging is a unique tool for the early detection of microvascular alterations and the identification of high-risk patients.[32,33] The past decades have witnessed impressive achievements in retinal imaging technology, among which the advent of OCTA has unprecedently revolutionized ocular imaging.[34] It combines structural imaging and functional imaging at the capillary level to assess the details of the retinal and choroidal microvascular system and serves as a potent alternative for microvascular perfusion, providing added value for the current risk stratification algorithm of CVD. Reduced retinal vascular density has been noted in individuals with CVD. Emerging evidence has also demonstrated that retinal capillary perfusion can predict the risks of hypertension, renal impairment, coronary heart disease, cerebrovascular disease, and diabetes mellitus.[35,36] The current study revealed that cognitive function significantly influenced the OCTA-derived perfusion metrics, implying that a decline in cognitive function had significantly impaired vascular health before the appearance of macrovascular pathology. Considering that sight is ranked as the most important sense, simultaneous evaluation of cognition performance and non-invasive OCTA to assess systemic vascular health is necessary and significant for public vascular health.[34]

This study also has public health implications for DR screening. National population-based DR screening programs have been implemented in Iceland, the UK, and Ireland. Annual large-scale, population-based DR screening has also progressed substantially in parts of Africa (especially Botswana) and Asia (especially China, Singapore, Indonesia, and Bangladesh).[37] Given that the retina is embryologically a brain-derived tissue, the eye can provide an effective window into the brain, supporting easy, non-invasive studies of neurodegenerative similarities between the retina and the brain.[38] The current study suggests that cognitive function can be determined at the time of DR screening at the population level, which helps enhance the implementation of self-care and adjustment of clinical decision-making. This opens up new perspectives on DR screening strategies for those over 60 years of age, as DR screening may not be limited to the prevention of visual impairment, but also provides an excellent screening setting for identifying individuals at risk of cognitive decompensation. According to the ADA guidelines, early diagnosis of cognitive impairment allows physicians to consider a more individualized approach to treatment. During DR screening, simultaneously helping patients determine whether they are at risk for cardiovascular disease and cognitive impairment may change attitudes to DR screening, with benefits beyond the prevention of vision loss.[37]

This study has several strengths. First, the large sample size and long-term follow-up allowed for testing the correlation between cognitive impairment and the risk of diabetic complications with powerful statistical validity. Data from two different large-scale populations allowed for high generalizability and credibility. Second, standardized brain MRI imaging was used as a complementary method to study the pathophysiology of cognitive impairment. Third, alterations in microvascular indicators (OCTA-based retinal capillary density and eGFR), connecting macroscopic cognitive impairment with microvascular dysfunction were evaluated, which fostered a better understanding of the association between cognitive impairment and diabetic complications. Fourth, the

relationship between cognitive function and multiple complications were comprehensively explored, all of which were found to be significantly correlated. These findings underscore the robustness of cognitive function as a potential screening indicator.

However, the study has some limitations. First, only a small percentage of participants underwent brain MRIs, meaning that the effects of brain volume on diabetic events should be interpreted cautiously. Second, data on diet and treatment adherence were not collected. Poor adherence caused by cognitive impairment may be associated with misuse of medications and impaired quality of life, both of which are risk factors for diabetic complications. Third, dynamic data of cognition assessment were unavailable, which may limit further exploration of the relationship between the changes in cognitive status and the risk of diabetic complications.

CONCLUSIONS

Based on the findings from two large cohort studies in the UK and China, cognitive impairment is significantly associated with an increased risk of mortality and vascular complications in people with diabetes, both in individuals older than or younger than 65 years. Cognitive impairment may be a potential indicator of mortality and systemic vascular complications in the population with diabetes. Cognition assessments, especially brief cognitive screening tests, are strongly recommended for routine use by endocrinologists and diabetologists, as they would facilitate early detection of and timely intervention for cognitive impairment and may improve the quality of life of diabetic patients.

Ethics Approval and Consent to Participate

This research was conducted by the UK Biobank resource (application number: 62443) and Guangzhou Diabetic Eye study (ID: 2017KYPJ094). All authors are grateful to the participants of the UK Biobank and Guangzhou Diabetic Eye study. All participants signed the informed consent before entering the study. All authors are grateful to the participants of the UK Biobank and Guangzhou Diabetic Eye study.

Consent for Publication

Not applicable.

Availability of Data and Material

Data and materials are available via UK Biobank at http://www.ukbiobank.ac.uk/.

AUTHOR CONTRIBUTIONS

WW designed the study and performed the statistical analysis. WW, ZZ, SC, and MH interpreted data. PZ, ST and WW interpreted the findings and drafted the manuscript. ZZ, WW, and MH designed and supervised the study. All authors reviewed the manuscript, edited it for intellectual content, and gave final approval for this version to be published. MH, ZZ, and WW are the guarantors of this work and, as such, had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

DISCLOSURES

This study was funded by the National Natural Science Foundation of China (82000901, 82171084) and InnoHK initiative and the Hong Kong Special Administrative Region Government. All authors declare no conflicts of interest related to this study.

ACKNOWLEDGEMENTS

The authors express their sincere gratitude to Dr. Maureen Boost in the School of Optometry, The Hong Kong Polytechnic University, for editing the language in this paper.

DATA STATEMENT

The data has not been previously presented orally or by poster at scientific meetings.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.jagp.2023.04.010.

References

1. Livingston G, Huntley J, Sommerlad A, et al: Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. Lancet 2020; 396(10248):413–446
2. The Lancet Neurology: WHO has a dementia plan, now we need action. Lancet Neurol 2017; 16(8):571
3. Rawlings AM, Sharrett AR, Albert MS, et al: The association of late-life diabetes status and hyperglycemia with incident mild cognitive impairment and dementia: the ARIC study. Diabetes Care 2019; 42(7):1248–1254
4. Xie J, Wang M, Long Z, et al: Global burden of type 2 diabetes in adolescents and young adults, 1990-2019: systematic analysis of the Global Burden of Disease Study 2019. BMJ 2022; 379:e72385
5. Davies MJ, Aroda VR, Collins BS, et al: Management of hyperglycaemia in type 2 diabetes, 2022. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia 2022; 65 (12):1925–1966
6. Davies MJ, Aroda VR, Collins BS, et al: Management of Hyperglycemia in Type 2 Diabetes, 2022. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2022; 45 (11):2753–2786
7. Musen G, Tinsley LJ, Marcinkowski KA, et al: Cognitive function deficits associated with long-duration type 1 diabetes and vascular complications. Diabetes Care 2018; 41(8):1749–1756
8. Hugenschmidt CE, Lovato JF, Ambrosius WT, et al: The cross-sectional and longitudinal associations of diabetic retinopathy with cognitive function and brain MRI findings: the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. Diabetes Care 2014; 37(12):3244–3252
9. Freedman BI, Sink KM, Hugenschmidt CE, et al: Associations of early kidney disease with brain magnetic resonance imaging and cognitive function in African Americans with type 2 diabetes mellitus. Am J Kidney Dis 2017; 70(5):627–637
10. Cukierman-Yaffe T, Gerstein HC, Williamson JD, et al: Relationship between baseline glycemic control and cognitive function in individuals with type 2 diabetes and other cardiovascular risk factors: the action to control cardiovascular risk in diabetes-memory in diabetes (ACCORD-MIND) trial. Diabetes Care 2009; 32(2):221–226
11. Jacobson AM, Ryan CM, Braffett BH, et al: Cognitive performance declines in older adults with type 1 diabetes: results from 32 years of follow-up in the DCCT and EDIC Study. Lancet Diabetes Endocrinol 2021; 9(7):436–445
12. American Diabetes Association: Older adults: standards of medical care in diabetes-2020. Diabetes Care 2020; 43(1):S152–S162, Suppl
13. Moran C, Beare R, Phan T, et al: Neuroimaging and its relevance to understanding pathways linking diabetes and cognitive dysfunction. J Alzheimers Dis 2017; 59(2):405–419
14. Bryan RN, Bilello M, Davatzikos C, et al: Effect of diabetes on brain structure: the action to control cardiovascular risk in diabetes MR imaging baseline data. Radiology 2014; 272 (1):210–216
15. Sudlow C, Gallacher J, Allen N, et al: UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. PLoS Med 2015; 12 (3):e1001779
16. Guo X, Chen Y, Bulloch G, et al: Parapapillary choroidal microvasculature predicts diabetic retinopathy progression and diabetic macular edema development: a three-year prospective study. Am J Ophthalmol 2022; 245:164–173
17. Alfaro-Almagro F, Jenkinson M, Bangerter NK, et al: Image processing and quality control for the first 10,000 brain imaging datasets from UK Biobank. Neuroimage 2018; 166:400–424
18. Rong H, Lai X, Jing R, et al: Association of sensory impairments with cognitive decline and depression among older adults in China. JAMA Netw Open 2020; 3(9):e2014186
19. Early Treatment Diabetic Retinopathy Study Research Group: Grading diabetic retinopathy from stereoscopic color fundus photographs - an extension of the modified airlie house classification: ETDRS report number 10. Ophthalmology 2020; 127(4S): S99–S119
20. Chua S, Thomas D, Allen N, et al: Cohort profile: design and methods in the eye and vision consortium of UK Biobank. BMJ Open 2019; 9(2):e25077
21. Buckner RL: Memory and executive function in aging and AD: multiple factors that cause decline and reserve factors that compensate. Neuron 2004; 44(1):195–208
22. Suzuki H, Venkataraman AV, Bai W, et al: Associations of regional brain structural differences with aging, modifiable risk factors for dementia, and cognitive performance. JAMA Netw Open 2019; 2 (12):e1917257
23. Kurella TM, Gaussoin S, Pajewski NM, et al: Kidney disease, hypertension treatment, and cerebral perfusion and structure. Am J Kidney Dis 2022; 79(5):677–687
24. van der Veen PH, Muller M, Vincken KL, et al: Brain volumes and risk of cardiovascular events and mortality. The SMART-MR study. Neurobiol Aging 2014; 35(7):1624–1631
25. Biessels GJ, Nobili F, Teunissen CE, et al: Understanding multifactorial brain changes in type 2 diabetes: a biomarker perspective. Lancet Neurol 2020; 19(8):699–710
26. Paradise MB, Shepherd CE, Wen W, et al: Neuroimaging and neuropathology indices of cerebrovascular disease burden: a systematic review. Neurology 2018; 91(7):310–320
27. An J, Li H, Tang Z, et al: Cognitive impairment and risk of all-cause and cardiovascular disease mortality over 20-year follow-up: results from the BLSA. J Am Heart Assoc 2018; 7(15):e8252
28. Twig G, Tirosh A, Derazne E, et al: Cognitive function in adolescence and the risk for premature diabetes and cardiovascular mortality in adulthood. Cardiovasc Diabetol 2018; 17(1):154
29. O'Donnell M, Teo K, Gao P, et al: Cognitive impairment and risk of cardiovascular events and mortality. Eur Heart J 2012; 33 (14):1777–1786
30. de Galan BE, Zoungas S, Chalmers J, et al: Cognitive function and risks of cardiovascular disease and hypoglycaemia in patients with type 2 diabetes: the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial. Diabetologia 2009; 52(11):2328–2336
31. Sinclair AJ, Hillson R, Bayer AJ: Diabetes and dementia in older people: a best clinical practice statement by a multidisciplinary National Expert Working Group. Diabet Med 2014; 31(9):1024–1031
32. Farrah TE, Webb DJ, Dhaun N: Retinal fingerprints for precision profiling of cardiovascular risk. Nat Rev Cardiol 2019; 16 (7):379–381

33. Zekavat SM, Raghu VK, Trinder M, et al: Deep learning of the retina enables phenome- and genome-wide analyses of the microvasculature. Circulation 2022; 145(2):134–150
34. Wagner SK, Fu DJ, Faes L, et al: Insights into systemic disease through retinal imaging-based oculomics. Transl Vis Sci Technol 2020; 9(2):6
35. Drinkwater JJ, Chen FK, Brooks AM, et al: Carotid disease and retinal optical coherence tomography angiography parameters in type 2 diabetes: the Fremantle Diabetes Study Phase II. Diabetes Care 2020; 43(12):3034–3041
36. Kannenkeril D, Nolde JM, Kiuchi MG, et al: Retinal Capillary damage is already evident in patients with hypertension and prediabetes and associated with HbA1c levels in the nondiabetic range. Diabetes Care 2022; 45(6):1472–1475
37. Vujosevic S, Aldington SJ, Silva P, et al: Screening for diabetic retinopathy: new perspectives and challenges. Lancet Diabetes Endocrinol 2020; 8(4):337–347
38. Little K, Llorian-Salvador M, Scullion S, et al: Common pathways in dementia and diabetic retinopathy: understanding the mechanisms of diabetes-related cognitive decline. Trends Endocrinol Metab 2022; 33(1):50–71