Ganglion Cell-Inner Plexiform Layer Thickness is Associated with Persistently Cognitive Decline -The Rugao Longevity and Aging Study

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Research

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Abstract

Background: The simple, convenient and well-validated biomarkers are imperative for detection of cognitive decline (CD). The powerful evidence is lacked for verifying the reliability and clinical utility of retinal biomarkers for detection of CD with repeated assessments. To investigate the association of retinal thickness with CD using repeated assessments.

Methods: This study included 446 older adults with three-time repeated assessments of cognitive function during 5-years follow-up. Retinal thickness measured on spectral-domain optical coherence tomography. Logistic regression models were conducted to analyze the association of retinal thickness with cognitive function.

Results: According to cognitive status in three assessments, individuals were categorized into consistently normal cognition groups (N = 159), persistently CD groups (N = 134), progressed to CD groups (N = 70), and reverting or fluctuating CD groups (N = 83). Thinner ganglion cell-inner plexiform layer (GC-IPL) was associated with persistently CD (odds ratio [OR] per 1-μm decrease: 1.09, 95% confidence interval [CI], 1.02-1.18; per standard deviation [SD] decrease: 1.78, 95%CI, 1.04-3.19) rather than progressed to CD, reverting or fluctuating CD. No significant relationship was found between retinal nerve fiber layer and any CD subgroups ($p > 0.05$).

Conclusions: Thinner GC-IPL was associated with persistently CD, suggesting retinal neurodegeneration may be a promising biomarker for persistently CD. Further studies, including both longitudinal and repeated measurements of retinal layer thickness and cognitive function, are needed to assess the possibility of retinal thickness as a biomarker for persistent CD.

Background

Dementia is neurodegenerative disease that characterized by cognitive decline (CD). Due to expanding population numbers and ageing, it ranks as the leading cause group of disability-adjusted life-years, and the burden of the disease has increased substantially over the past 25 years [1]. Fortunately, if interventions could just delay disease onset by modest 1 year, the number of patients would reduce by as many as 11.8 million [2]. Therefore, the preclinical detection of CD is crucial for reducing the global burden of the disease. More importantly, the simple, convenient and well-validated biomarkers of neurological disease processes are imperative for detection of CD in community.

Spectral-domain optical coherence tomography (SD-OCT) is a simple, convenient and noninvasive optical imaging technique for facilitating retinal thickness measurements. It provides an excellent opportunity to visualize retinal nerve tissue in vivo and to detect neuro-axonal degeneration [3–5]. Overwhelmingly case-control studies demonstrated retinal thickness might be a diagnostic biomarker for MCI and AD. Patients with mild cognitive impairment (MCI) and early Alzheimer's disease (AD) had thinner retinal thickness compared with controls [6–8]. Thinning of retina was also associated with cerebral gray and white matter atrophy [9, 10], as well as worse white matter microstructure of the brain [10–12]. Additionally,

prospective longitudinal studies found that thinner retina was a risk factor for incidence of AD and future cognitive impairments, suggesting the possibly predictive role of retinal thickness [13, 14]. Hence, overwhelming studies demonstrated the possible role of retinal thickness in diagnosis and detection of MCI and AD. However, it was still lacking powerful evidences to draw conclusions with respect to the reliability or clinical utility of any potential retinal biomarkers with CD in repeated assessments [15, 16]. Therefore, we aimed to investigate the association of retinal thickness with CD using repeated assessments among 5-years follow-up.

Methods

Study population

The Rugao Longevity and Ageing Study (RuLAS) is an observational, prospective and community-based cohort study [17]. The baseline survey was conducted from November to December 2014 (Wave 1). A total of 1788 adults aged 70–84 years were recruited. Then, three follow-up surveys were conducted in April 2016 (Wave 2), November 2017 (Wave 3) and December 2019 (Wave 4). This study was approved by the Human Ethics Committee of the School of Life Sciences of Fudan University. Informed consent was obtained from each participant.

In December 2019, SD-OCT was added to perform at wave 4 of the cohort. A total of 2200 older adults were recruited in wave 4. SD-OCT was available for 1721 subjects (78.22%). Subjects who did not undergo SD-OCT (n = 479) or had upgradable OCT due to poor quality scans (n = 538) were excluded. A total of 1183 subjects who had complete retinal thickness data were recruited in wave 4. Among the 1183 subjects, 480 subjects completed both three visits (December 2014, November 2017 and December 2019) and had cognitive information. In addition, subjects with retinal related disease were excluded, including glaucoma (n = 4), age-related macular degeneration (n = 4), diabetic retinopathy (n = 3), pathological myopia (n = 16) and other retinal disease (n = 7). At last, 446 participants with three repeated measurements of cognitive function were included and analyzed in our study (Fig. 1).

Outcomes

In our study, cognitive function was evaluated by the revised Hasegawa's dementia scale (HDS-R) [17], which comprising of orientation, memory, attention/calculation and verbal fluency [18]. HDS-R has been widely accepted in Asian populations in clinical and epidemiological surveys for the assessment of cognitive impairment [19]. Previous studies observed that HDS-R was similar to Mini-Mental State Examination and had better diagnostic accuracy for screening AD [20]. In addition, the HDS-R was more robust to demographic influence (such as level of education, age and gender) than MMSE [20, 21]. In conclusion, it was a brief and reliable tool to assess global cognitive function in Asian [22, 23]. In our study, individuals who scored higher than 21.5 were defined as normal cognition, while who scored 21.5

or below were defined as CD [17, 24, 25]. Cognitive function was assessed in November 2014, November 2017 and December 2019.

Individuals were categorized into four subgroups according to cognitive function in three repeated assessments among 5-years follow-up [26]. Individuals with consistently normal cognition (Normal-Normal-Normal) in both three visits were categorized into consistently normal cognition group (N = 159); Individuals with consistently CD in both three visits (CD-CD-CD) were categorized into persistently CD group (N = 134); Individuals who progressed to CD from normal cognition within three visits (Normal-Normal-CD or Normal-CD-CD) were categorized into progressed to CD group (N = 70). Individuals who returned to CD from normal cognitive (Normal-CD-Normal, or CD-Normal-CD), or returned to normal cognitive from CD in any two visits (CD-Normal-Normal, or CD-CD-Normal) were categorized into reverting or fluctuating CD group (N = 83).

SD-OCT scan

SD-OCT scanning was performed without pupil dilation using the spectral domain OCT-HS100 (Canon Inc, Tokyo, Japan) with a macular 3D scans over a 10 × 10 mm area (1024 A-Scan × 128 B-Scan). The Early Treatment Diabetic Retinopathy Study (ETDRS) grid focused on the macular was used for OCT measurements (Fig. 2). The ETDRS grid consisted of three concentric circles of 1, 3, and 6 mm diameters. The 3- and 6-mm circles were each divided into superior, inferior, nasal and temporal quadrants. Macular retinal nerve fiber layer (mRNFL) and ganglion cell layer-inner plexiform layer (GC-IPL) were segmented.

The right eye was used for measurements if the Signal Strength Index was ≥ 5. Otherwise, the left eye was used. The exclusion criteria included: (1) with signal strength index of both eyes < 5; (2) any ocular disorders, including pathological myopia, age-related macular degeneration, diabetic retinopathy, glaucoma, vitreoretinal interface abnormalities (e.g. epiretinal membrane, macular hole), and other eye pathology; (3) a history of clinical stoke, uncontrolled diabetes and hypertension. The thickness were automatically segmented, and manually corrected was conducted by two masked examiners (Shen H and Gong W) if necessary. The mean thickness was calculated.

Covariates

Demographic, physiologic and clinical data were collected from the RuLAS. Demographic data included age, gender, married status, educational status, smoking and alcohol consumption. Physiologic variables, including body mass index (BMI), high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglyceride, serum creatinine, fasting blood glucose (FBG) and High-sensitivity C-reactive protein (Hs-CRP) were also measured. Clinical variables, including, major cardiovascular disease (CVD), diabetes mellitus, depressive status (assessed by the 15-item Geriatric Depression Scale [27]), hypertension were collected. Major CVD included cerebral infarction, stroke, cerebral hemorrhage, coronary heart disease,

myocardial infarction and heart failure. In addition, mobility (measured by time up and go test [28]) and grip strength was also assessed in our study.

Statistical Analyses

Firstly, we described the characteristics of participants in our study. Continuous and categorical variables were presented as mean with standard deviation (SD) and frequency (%), respectively. Group differences between the four groups were analyzed by chi-square or t test. The differences between consistently normal cognition and CD subgroups were also analyzed. Secondly, we fitted logistic regression models, treating memberships in all four group as outcome variables, with the consistently normal cognition group as reference, to assess the effect of mRNFL and GC-IPL in four models. Model 1: unadjusted; Model 2: adjusted for age, body mass index, sex, smoking, alcohol accumulation, married status and education; Model 3: adjusted for model 2 + serum fasting glucose, triglyceride, HDL, LDL, creatinine and Hs-CRP; Model 4: adjusted for model 3 + CVD, hypertension, diabetes mellitus, mobility, grip strength and depressive status. Lastly, sensitivity analyses using logistic regression models were conducted to validate the relationship in participants without CVD and/or diabetes. A p-value (two-tailed) less than 0.05 determined as statistical significant. All analyses were conducted by SPSS 22.0 or R (Version 3.6.1: www.r-project.org/).

Results

Characteristics of included population

In our study, a total of 446 participants were analyzed. Table 1 summarized demographic, physiologic and clinical data of the participants according to different CD subgroups. One hundred and fifty-nine (35.65%), 70 (15.70%), 83 (18.61%) and 134 (30.04%) individuals were categorized into consistently normal cognition group, progressed to CD group, reverting or fluctuating CD group and persistent CD group, respectively. Difference was observed in the four subgroups. The mean age were 78.96 (3.05), 80.16 (3.81), 80.00 (3.24) and 80.37 (3.52) years, respectively. The detail information was showed in Table 1.

Table 1
Demographic and clinical characteristics in study population

	Consistently normal cognition (N = 159)	Progressed to CD (N = 70) §	Reverting or fluctuating CD (N = 83) §	Persistently CD (N = 134) §	P-value ▯
Age, Mean (SD), years	78.96 (3.05)	80.16 (3.81) *	80.00 (3.24) *	80.37 (3.52) ***	0.002
Males, No. (%)	135 (84.91%)	26 (37.14%) ***	40 (48.19%)	15 (11.19%) ***	< 0.001
Body mass index, Mean (SD), kg/m^2	23.75 (3.48)	24.31 (3.60)	23.56 (4.04)	23.63 (3.75)	0.591
Smoking, No. (%)	66 (41.51%)	16 (22.86%) **	24 (28.92%)	10 (7.46%) ***	< 0.001
Alcohol accumulation, No. (%)	69 (43.40%)	26 (37.14%)	27 (32.53%)	28 (20.90%) ***	0.001
Married and living together, No. (%)	114 (71.70%)	35 (50.00%) **	49 (36.57%) *	67 (50.00%) ***	< 0.001
Education					< 0.001
No formal education or illiteracy, No. (%)	18 (11.32%)	39 (55.71%) ***	40 (48.19%) ***	119 (88.81%) ***	
Lower education, No. (%)	52 (32.71%)	25 (35.72%)	24 (28.92%)	12 (8.95%)	
Intermediate or high education, No. (%)	89 (55.97%)	6 (8.57%)	19 (22.89%)	3 (2.24%)	
Fasting blood glucose, Mean (SD), mg/dL	101.47 (24.64)	105.22 (37.09)	101.93 (19.27)	102.33 (23.48)	0.790

CD: cognitive dysfunction; SD: standard deviation; IQR: interquartile range; RNFL: retinal rever fiber layer; GC-ILP: ganglion cell layer plus inner plexiform layer.

▯ Chi-square tests were conducted for categorical variables, and Fisher exact tests were conducted when sample was small; ANOVA analyses were conducted for continuous variables, and Kruskal-Wallis rank tests were conducted for high-sensitivity C-reactive protein.

§ The difference between subgroup cognitive impairments and consistently normal cognition group was analyzed by t test or Chi-square test for continuous and categorical variables, respectively. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

	Consistently normal cognition (N = 159)	Progressed to CD (N = 70) §	Reverting or fluctuating CD (N = 83) §	Persistently CD (N = 134) §	P-value ▯
Time up and go test, mean (SD), m/s	9.31 (2.34)	10.59 (2.67) **	10.80 (3.99) **	10.60 (2.46) ***	< 0.001
Grip strength, mean (SD), kg	26.90 (7.50)	19.87 (6.16) ***	21.25 (7.39) ***	17.33 (5.54) ***	< 0.001
Triglyceride, mean (SD), mmol /L	1.32 (0.80)	1.38 (0.67)	1.50 (1.20)	1.48 (1.10)	0.408
High-density lipoprotein, mean (SD), mmol /L	1.64 (0.34)	1.69 (0.34)	1.67 (0.37)	1.73 (0.39) *	0.244
Low density lipoprotein, mean (SD), mmol /L	3.10 (0.67)	3.09 (0.70)	3.17 (0.79)	3.28 (0.83) *	0.167
Serum creatinine, mean (SD), μmol/L	78.75 (17.54)	68.24 (18.44) ***	70.11 (17.35) ***	65.16 (14.86) ***	< 0.001
High-sensitivity C-reactive protein, median (IQR), mg/L	1.40 (0.90, 2.80)	1.60 (1.00, 3.17)	1.60 (0.80, 4.30)	1.40 (0.70, 3.10)	0.489
The 15-item Geriatric Depression Scale, mean (SD)	2.17 (1.77)	3.09 (2.59) *	2.29 (2.30)	2.66 (2.14) *	0.017
Revised Hasegama's dementia scale, mean (SD)	28.03 (2.92)	17.91 (2.73) ***	24.46 (4.04) ***	15.39 (3.44) ***	< 0.001
Major cardiovascular disease, No. (%)	16 (10.06%)	6 (8.57%)	10 (12.05%)	19 (14.18%)	0.596
Hypertension, No. (%)	75 (47.17%)	40 (57.14%)	50 (60.244)	84 (62.69%) **	0.044
Diabetes mellitus, No. (%)	18 (13.32%)	8 (11.43%)	7 (8.43%)	16 (11.94%)	0.871

CD: cognitive dysfunction; SD: standard deviation; IQR: interquartile range; RNFL: retinal rever fiber layer; GC-ILP: ganglion cell layer plus inner plexiform layer.

▯ Chi-square tests were conducted for categorical variables, and Fisher exact tests were conducted when sample was small; ANOVA analyses were conducted for continuous variables, and Kruskal-Wallis rank tests were conducted for high-sensitivity C-reactive protein.

§ The difference between subgroup cognitive impairments and consistently normal cognition group was analyzed by t test or Chi-square test for continuous and categorical variables, respectively. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

	Consistently normal cognition (N = 159)	Progressed to CD (N = 70) §	Reverting or fluctuating CD (N = 83) §	Persistently CD (N = 134) §	P-value ▯
mRNFL thickness, mean (SD), μm	26.93 (3.75)	27.43 (3.55)	26.84 (4.23)	26.13 (4.53)	0.144
GC-IPL thickness, mean (SD), μm	74.40 (7.74)	73.87 (9.25)	73.48 (9.19)	71.78 (8.89) **	0.071

CD: cognitive dysfunction; SD: standard deviation; IQR: interquartile range; RNFL: retinal rever fiber layer; GC-ILP: ganglion cell layer plus inner plexiform layer.

▯ Chi-square tests were conducted for categorical variables, and Fisher exact tests were conducted when sample was small; ANOVA analyses were conducted for continuous variables, and Kruskal-Wallis rank tests were conducted for high-sensitivity C-reactive protein.

§ The difference between subgroup cognitive impairments and consistently normal cognition group was analyzed by t test or Chi-square test for continuous and categorical variables, respectively. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

The association of retinal thickness with cognitive subgroups in primary analyses

Table 2 showed the association of retinal thickness with prevalence of different CD. Thinner GC-IPL was associated with persistent CD (odds ratio [OR] per 1-μm decrease: 1.04, 95% confidence interval [CI]: 1.01–1.07, p = 0.015; OR per standard deviation [SD] decrease: 1.37, 95%CI: 1.08–1.77, p = 0.012) in unadjusted models, with consistently normal cognition group as reference. Similarly, thinner GC-IPL was still strongly associated with persistent CD (OR per 1-μm decrease: 1.09, 95% CI: 1.02–1.18, p = 0.012; OR per SD decrease: 1.78, 95%CI: 1.04–3.19, p = 0.041) after adjusting for demographic, physiologic and clinical confounder factors. However, compared with consistently normal cognition group, per 1-μm or SD decrease of GC-IPL and mRNFL was not associated with prevalence of reverting or fluctuating CD, or Progressed to CD in unadjusted and adjusted groups with p-value greater than 0.05.

Table 2
Cognitive dysfunction subgroups with consistently normal cognition group in all participants

	Model 1		Model 2		Model 3		Model 4	
	OR (95%CI)	P-value	OR (95%CI)	P-value	OR (95%CI)	P-value	OR (95%CI)	P-value
GC-IPL thickness								
Persistently CD								
Per 1-μm decrease	1.04 (1.01, 1.07)	0.015	1.07 (1.01, 1.13)	0.019	1.07 (1.01, 1.13)	0.029	1.09 (1.02, 1.18)	0.012
Per SD decrease	1.37 (1.08, 1.77)	0.012	1.63 (1.04, 2.61)	0.036	1.58 (0.99, 5.94)	0.060	1.78 (1.04, 3.19)	0.041
Reverting or fluctuating CD								
Per 1-μm decrease	0.99 (0.95, 1.03)	0.511	0.97 (0.92, 1.03)	0.335	1.00 (0.94, 1.06)	0.938	1.01 (0.94, 1.07)	0.836
Per SD decrease	1.16 (0.81, 1.64)	0.416	1.28 (0.81, 2.00)	0.267	1.20 (0.71, 2.02)	0.498	1.04 (0.59, 1.80)	0.892
Progressed to CD								
Per 1-μm decrease	0.99 (0.96, 1.03)	0.653	0.99 (0.94, 1.03)	0.586	0.99 (0.95, 1.04)	0.771	1.00 (0.95, 1.05)	0.991
Per SD decrease	1.09 (0.82, 1.44)	0.536	1.11 (0.78, 1.60)	0.571	1.08 (0.73, 1.60)	0.712	0.98 (0.62, 1.51)	0.919

CD: Cognitive decline; SD: standard deviation; mRNFL: macular retinal rever fiber layer; GC-ILP: ganglion cell layer plus inner plexiform layer.

Model 1: unadjusted.

Model 2: adjusted for age, body mass index, sex, smoking, alcohol accumulation, married status, and education.

Model 3 adjusted for model 2 + serum fasting glucose, triglyceride, high-density lipoprotein, low density lipoprotein, creatinine and Hs-CRP.

Model 4 adjusted for model 3 + CVD, hypertension, diabetes mellitus, mobility, grip strength and depressive status.

	Model 1		Model 2		Model 3		Model 4	
mRNFL thickness								
Persistently CD								
Per 1-μm decrease	1.05 (0.99, 1.11)	0.100	1.03 (0.93, 1.13)	0.566	1.03 (0.93, 1.13)	0.587	1.07 (0.95, 1.22)	0.298
Per SD decrease	1.28 (1.02, 1.62)	0.033	1.16 (0.80, 1.70)	0.441	1.14 (0.78, 1.70)	0.501	1.36 (0.85, 2.30)	0.218
Reverting or fluctuating CD								
Per 1-μm decrease	1.00 (0.91, 1.09)	0.955	0.98 (0.87, 1.09)	0.671	1.03 (0.91, 1.16)	0.602	1.02 (0.89, 1.16)	0.767
Per SD decrease	1.09 (0.78, 1.56)	0.608	1.13 (0.74, 1.74)	0.583	0.92 (0.58, 1.48)	0.718	0.93 (0.56, 1.59)	0.784
Progressed to CD								
Per 1-μm decrease	1.04 (0.96, 1.12)	0.348	1.06 (0.96, 1.17)	0.269	1.06 (0.96, 1.18)	0.263	1.03 (0.91, 1.17)	0.599
Per SD decrease	0.94 (0.69, 1.27)	0.671	0.87 (0.58, 1.29)	0.484	0.84 (0.55, 1.29)	0.421	0.94 (0.57, 0.78)	0.805
CD: Cognitive decline; SD: standard deviation; mRNFL: macular retinal rever fiber layer; GC-ILP: ganglion cell layer plus inner plexiform layer.								
Model 1: unadjusted.								
Model 2: adjusted for age, body mass index, sex, smoking, alcohol accumulation, married status, and education.								
Model 3 adjusted for model 2 + serum fasting glucose, triglyceride, high-density lipoprotein, low density lipoprotein, creatinine and Hs-CRP.								
Model 4 adjusted for model 3 + CVD, hypertension, diabetes mellitus, mobility, grip strength and depressive status.								

The association of retinal thickness with cognitive subgroups in sensitive analyses

In order to validate our results, we conducted sensitive analyses in older adults without major CVD and/or diabetes. Table 3 showed the association of retinal thickness with prevalence of different CD. Thinner GC-IPL was associated with persistent CD (OR per 1-μm decrease: 1.05, 95%CI: 1.01–1.08, p = 0.005; OR per SD decrease: 1.41, 95%CI: 1.08–1.87, p = 0.012) in unadjusted models, with consistently normal cognition group as reference. Similarly, thinner GC-IPL was still strongly associated with persistent CD (OR per 1-μm decrease: 1.11, 95% CI: 1.03–1.21, p = 0.011; OR per SD decrease: 1.98, 95%CI: 1.08–3.87, p = 0.033) after adjusting for demographic, physiologic and clinical confounder factors. However, compared with consistently normal cognition group, per 1-μm or SD decrease of GC-IPL and mRNFL was not associated with prevalence of reverting or fluctuating CD or Progressed to CD in unadjusted and adjusted models (p > 0.05).

Table 3
Cognitive Subgroups with Cognitively Normal Group in participants without CVD and/or diabetes

	Model 1		Model 2		Model 3		Model 4	
	OR (95%CI)	P-value	OR (95%CI)	P-value	OR (95%CI)	P-value	OR (95%CI)	P-value
GC-IPL thickness								
Persistently CD								
Per 1-um decrease	1.05 (1.01, 1.08)	0.005	1.07 (1.01, 1.14)	0.036	1.07 (1.00, 1.14)	0.046	1.11 (1.03, 1.21)	0.011
Per SD decrease	1.41 (1.08, 1.87)	0.012	1.52 (0.94, 2.51)	0.095	1.52 (0.91, 2.62)	0.117	1.98 (1.08, 3.87)	0.033
Reverting or fluctuating CD								
Per 1-um decrease	0.98 (0.94, 1.02)	0.330	0.99 (0.95, 1.03)	0.687	1.00 (0.96, 1.05)	0.903	1.01 (0.96, 1.06)	0.805
Per SD decrease	1.12 (0.82, 1.51)	0.472	1.03 (0.72, 1.46)	0.859	0.97 (0.66, 1.41)	0.894	0.98 (0.63, 1.46)	0.893
Progressed to CD								
Per 1-um decrease	0.98 (0.93, 1.04)	0.678	0.98 (0.93, 1.03)	0.516	0.98 (0.93, 1.03)	0.377	0.99 (0.95, 1.02)	0.432
Per SD decrease	1.13 (0.83, 1.53)	0.403	1.17 (0.80, 1.73)	0.423	1.14 (0.75, 1.74)	0.543	1.08 (0.67, 1.72)	0.774

CD: Cognitive decline; SD: standard deviation; mRNFL: macular retinal rever fiber layer; GC-ILP: ganglion cell layer plus inner plexiform layer.

Model 1: unadjusted.

Model 2: adjusted for age, body mass index, sex, smoking, alcohol accumulation, married status, and education.

Model 3 adjusted for model 2 + serum fasting glucose, triglyceride, high-density lipoprotein, low density lipoprotein, creatinine and Hs-CRP.

Model 4 adjusted for model 3 + CVD, hypertension, diabetes mellitus, mobility, grip strength and depressive status.

	Model 1		Model 2		Model 3		Model 4	
mRNFL thickness								
Persistently CD								
Per 1-um decrease	1.05 (0.99, 1.12)	0.134	1.03 (0.93, 1.14)	0.550	1.05 (0.94, 1.18)	0.391	1.11 (0.97, 1.31)	0.161
Per SD decrease	0.79 (0.61, 1.02)	0.071	0.86 (0.57, 1.29)	0.461	0.81 (0.51, 1.27)	0.359	0.63 (0.33, 1.10)	0.129
Reverting or fluctuating CD								
Per 1-um decrease	0.98 (0.91, 1.07)	0.691	0.98 (0.89, 1.07)	0.636	1.00 (0.90, 1.11)	0.974	0.99 (0.88, 1.11)	0.846
Per SD decrease	1.16 (0.85, 1.61)	0.352	1.14 (0.80, 1.66)	0.470	1.03 (0.69, 1.55)	0.883	1.12 (0.70, 1.81)	0.642
Progressed to CD								
Per 1-um decrease	1.04 (0.95, 1.13)	0.424	1.07 (0.95, 1.19)	0.259	0.07 (0.95, 1.20)	0.256	1.04 (0.91, 1.19)	0.548
Per SD decrease	0.94 (0.66, 1.32)	0.704	0.84 (0.53, 1.31)	0.443	0.80 (0.50, 1.30)	0.376	0.89 (0.51, 1.55)	0.674
CD: Cognitive decline; SD: standard deviation; mRNFL: macular retinal rever fiber layer; GC-ILP: ganglion cell layer plus inner plexiform layer.								
Model 1: unadjusted.								
Model 2: adjusted for age, body mass index, sex, smoking, alcohol accumulation, married status, and education.								
Model 3 adjusted for model 2 + serum fasting glucose, triglyceride, high-density lipoprotein, low density lipoprotein, creatinine and Hs-CRP.								
Model 4 adjusted for model 3 + CVD, hypertension, diabetes mellitus, mobility, grip strength and depressive status.								

Discussion

To our knowledge, it is still lacking evidences to validate the association of retinal thickness with CD using repeated assessments in older adults. This is the first study, involving 3 times repeated

assessments of cognitive function among 5-years follow-up, to investigate the association. In this community-based study, we found that thinner GC-IPL was associated higher risk of persistent CD but not progressed to CD, or reverting or fluctuating CD, independent of demographic, physiologic and clinical confounder factors, with consistently normal cognition groups as reference. In contrast, no significant association of mRNFL with any CD subgroup was found.

The association of GC-IPL with cognitive function was widely studied. Our study illustrated significant association of GC-IPL with persistent CD. Similarly, previous studies found that patients with AD and MCI had thinner GC-IPL than controls [7, 11, 29]. Thinner GC-IPL was also associated with lower brain white matter microstructure integrity and grey matter volume [30, 31]. Additionally, animal models also suggested the close association of GC-IPL with cognitive function. GC-IPL is composed of retinal ganglion cells (RGCs), while amyloid-β deposits in the RGCs layer may cause neurodegeneration in the retina of a transgenic mouse model of AD [32]. More importantly, previous animal study illustrated that dendritic changes in RGCs preceded cell loss in a mouse model of AD [33]. Therefore, the GC-IPL may be a useful biomarker for the diagnosis of CD.

In our study, there was no significant association of mRNFL thickness with any CD groups after adjusted for potential confounder factors. The results were consistent with a recent study conducted in biomarker-confirmed preclinical AD population, in which no difference were found in macular or peripapillary RNFL between amyloid positive (Aβ+) and negative (Aβ-) individuals [34]. Similar results were also observed in the Rotterdam Study [13]. In that study, Mutlu et.al illustrated that thinner peripapillary RNFL was not associated with prevalent dementia in the Rotterdam Study. While Ko et.al found that thinner mRNFL was associated with worse cognitive function as well as future cognitive decline in UK biobank [14]. The heterogeneity of included population may be the reason of the inconsistency. The age of subjects in the Rotterdam Study (mean age: approximately 68.9 years) and RuAS (mean age: approximately 80.0 years) were much older than that in UK biobank (mean age: approximately 56.0 years). Due to the retinal thickness was thinner with increased age [35]; the real and accurate association of RNFL with cognitive function might be concealed by aging process of retina. Interestingly, a recent study with wide adult age range (mean age: 54.3 years; age range: 30–94 years) found no significant association of peripapillary RNFL with performance in any cognitive domain in the Rhineland Study [36], which proved our results in some degree.

As we all known, the RNFL is composed of RGCs axons, while GC-IPL is composed of RGCs bodies and dendrites [37, 38]. The damage of optic nerve may gradually swell from bodies and dendrites to axons [39, 40]. RNFL thickness may decrease gradually over very long time. The similar condition was also observed in the Rotterdam study that thinner GC-IPL but not RNFL thickness was associated with prevalent dementia [13]. Due to the cross-sectional setting of community-based cohort and the older age in analyses, it was limited to explore reasons of different effects of GC-IPL and mRNFL on cognitive function. Despite this, our study was first to explore the association of retinal thickness with cognitive function using repeated measurements and found exciting results. In the future, larger prospective and

community-based cohort study with wider age range and repeated measurements would be conducted to validate our results.

There were several limitations in our study. Firstly, a cross-sectional study was conducted to evaluate the association of retinal thickness with CD. Our findings only illustrated a correlative rather than causative relationship. Hence, longitudinal studies should be conducted to validate our findings in the future. Secondly, the sample in our study was relative small, which limited the statistic power in some degree. Despite this, we found robust and independent association of GC-IPL with persistent CD. More subjects would be recruited to validate the results in further studies. Lastly, we just measured the right eye using SD-OCT in our study, which may partly affect the measurement of retinal thickness. However, previous study did not find significant difference in retinal layer thicknesses between left and right eye in the Rotterdam Study [13]. Moreover, the thinning of retina was generalized in older adults and it should not be limited to one eye. Therefore, the signal-eyes measurements did not influence our findings.

Strengths were also included in our study. Firstly, we assessed the cognitive function for three times in each subjects among 5-years follow-up. Previous studies concentrated on the relationship between retinal thickness and cognitive function assessed by single one-point and found close relationship between them [7, 41–43]. However, not all individuals with CD progressed to dementia or consistently stabilized CD, while 18%-24% of mild cognitive impairments individuals reverted to normal cognition [26, 44–46], which potentially leading to partial association of neurodegeneration with retinal thickness. Using repeated assessments would increase the consistency and accuracy of assessing cognitive function. Therefore, we could accurately explore the relationship between retinal thickness and cognitive function. Secondly, only one experienced physician (Dr. Shen) using the same machine performed the SD-OCT, which will significantly reduce the measurement errors. Finally yet importantly, structural retinal changes are not unique to preclinical or clinical AD. Similar changes may occur in other disease, such as hydroxychloroquine retinal toxicity [47] and glaucoma [48]. Exactly, we conducted the study according to rigorously exclusion criteria, which excluded individuals with retina-related disease, such as glaucoma, age-related macular degeneration, diabetic retinopathy and pathological myopia.

Conclusion

In this community-based cohort, we found thinner GC-IPL was associated with persistent CD rather than progressed to CD, or reverting or fluctuating CD, independent of demographic, physiologic and clinical confounder factors. Thinner GC-IPL thickness may be a promising biomarker for persistent CD.

Abbreviations

CD: cognitive decline; GC-IPL: ganglion cell-inner plexiform layer; SD-OCT: spectral-domain optical coherence tomography, MCI: cognitive impairment, AD: Alzheimer’s disease, RuLAS: Rugao Longevity and Ageing Study, HDS-R: Hasegawa’s dementia scale, ETDRS: Early Treatment Diabetic Retinopathy Study, mRNFL: Macular retinal nerve fiber layer, BMI: body mass index, HDL: high-density lipoprotein , LDL: low-

density lipoprotein, FBG: fasting blood glucose, Hs-CRP: high-sensitivity C-reactive protein , CVD: cardiovascular disease, SD: standard deviation

Declarations

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Author Contributions

Zhang H, Shen H, Xu X, Luo D and Wang X: study design, interpretation of results, preparation and editing manuscript. Zhang H: data analysis. Wang J, Jiang X: study design. Zhang H, Shen H, Zhang N, Yao S, Sun X, Xu X, Luo D, Wei G and Wang X: data collection. All authors were involved in preparation of the manuscript and final approval of the submitted and published versions.

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Data Accessibility Statement

All data generated or analyzed during this study are included in this published article.

Conflict of interest Statement

The authors report no conflicts of interest in this work.

Ethics approval and consent to participate

We state that subjects have given their written informed consent and this study was approved by the Human Ethics Committee of the School of Life Sciences, Fudan University.

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Figures

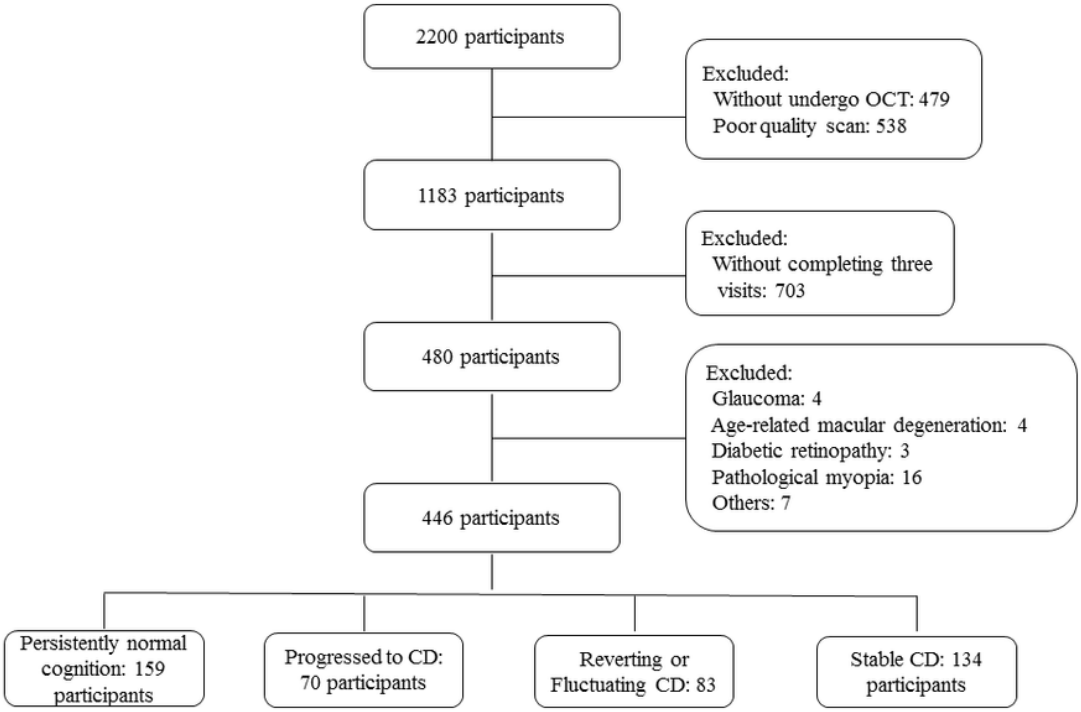

Figure 1

Flow diagram of study population

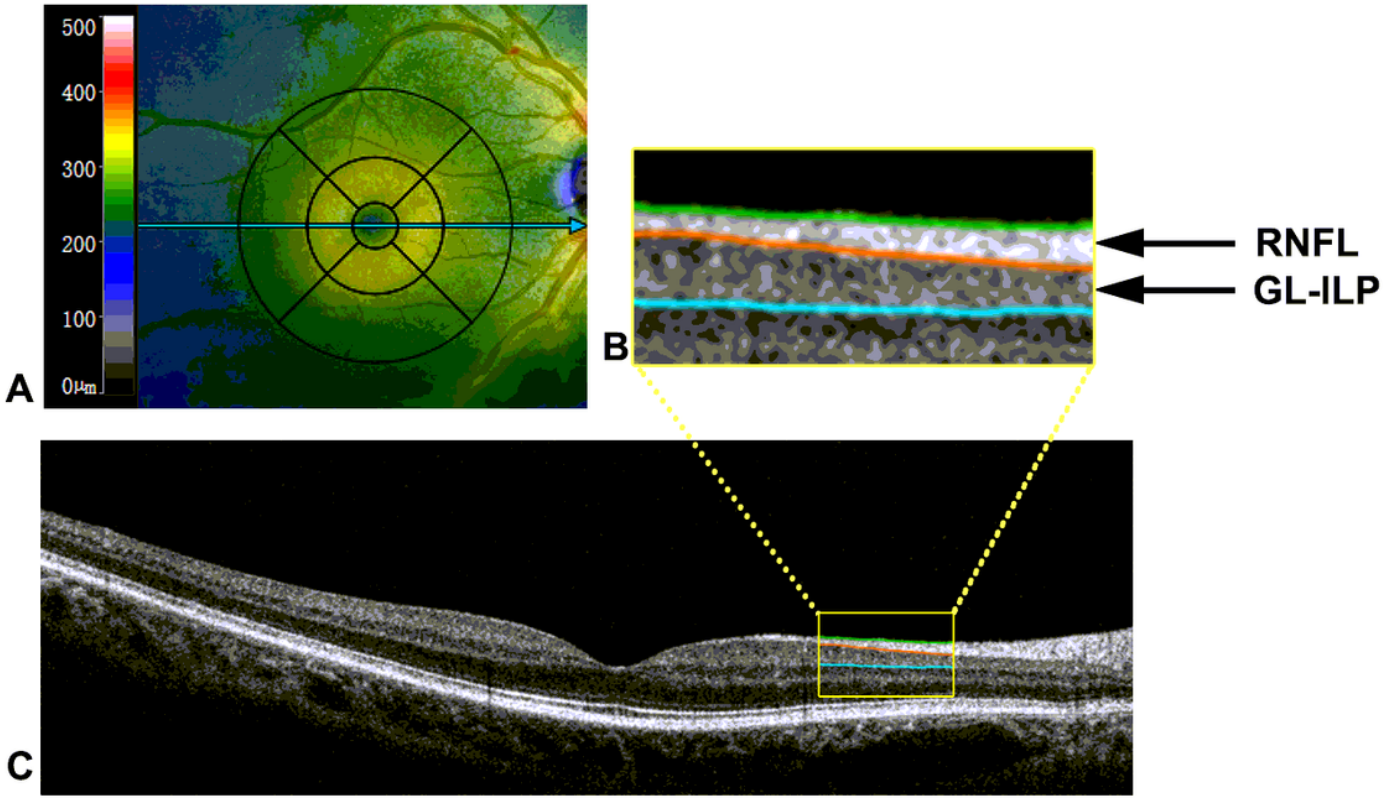

Figure 2

Output of spectral-domain optical coherence tomography retinal measurements. A. Macular thickness map with the Early Treatment Diabetic Retinopathy Study grid sectors. B and C. Corresponding cross-sectional imaging of macular and segmentation of intraretinal layers. RNFL, retinal nerve fiber layer; GC-IPL, ganglion cell layer-inner plexiform layer.