Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods. Assessment of covariates and statistical analysis

Covariates

Blood pressure was measured twice at the right brachial artery with a random-zero sphygmomanometer, and the average was used for the analysis. Body mass index was computed as weight (kg) divided by height squared (m^2). Fasting serum total and high-density lipoprotein cholesterol concentrations (mmol/L) were determined by an automated enzymatic procedure. Diabetes mellitus was considered present if fasting serum glucose level was equal to or greater than 7.0 mmol/L, or when anti-diabetic medication use was reported. Information on smoking (non-, former or current), education (low, intermediate, or high) and blood pressure-lowering medication use was obtained during the home interview by a questionnaire.

Statistical analysis

We first categorized the RNFL by taking the median. Subsequently, given an overall cumulative incidence of 3% of dementia in our sample and an α of 5%, we calculated a sample size of n=2533 in order to achieve a power of 80% and to detect a hazard ratio of 1.90 (i.e. ratio of the hazard rates of the quantiles for RNFL). In view of this calculation our current sample size (n=3289 and n=2998) is sufficient to examine this association.

We used analysis of covariance, adjusted for age and sex, to assess differences in baseline characteristics between individuals included and excluded from the analysis.

As two different OCT devices were used during the course of the study, we standardized measurements of the retinal layer thickness for each device separately by calculating z-scores. Statistical procedures for combining data have been discussed in literature, and pooling raw data from samples have been suggested when the samples are similar.[1,2]

Percentage of missing values for all variables was less than 2%, and were imputed using fivefold multiple imputation based on determinant, outcome and included covariates. Covariates in the imputed dataset had a similar distribution compared to covariates in the non-imputed dataset. All continuous variables were normally distributed. We imputed the

covariates, because without imputation, the statistical software performs analysis on complete cases without any missing. Consequently, this lowers the number of dementia cases from 86 to 80. Although missing data is a limitation of the study, in order to make optimal use of our incident cases, we imputed any missing covariate data.

In cross-sectional analysis, we assessed the association of retinal layer thicknesses with prevalent dementia using logistic regression. Using analysis of covariance, adjusted for age, sex, subcohort, and education, we assessed mean differences in retinal layer thickness between individuals with and without dementia. In a subsample where both left and right eyes were scanned, we assessed differences in retinal layer thickness between eyes using a paired t-test. In longitudinal analysis, we excluded individuals with prevalent dementia at baseline (at time of OCT scanning), and assessed the association of retinal layer thicknesses with the risk of developing dementia and AD using Cox proportional-hazards regression. We adjusted the cross-sectional and longitudinal analyses for the same set of covariates i.e. covariates that are generally considered to be important confounders for dementia. In Model 1, we adjusted for age, sex, subcohort, and education. In Model 2, we additionally adjusted for systolic blood pressure, diastolic blood pressure, use of blood pressure-lowering medication, body mass index, total cholesterol, high-density lipoprotein cholesterol, diabetes mellitus, and smoking. The proportionality assumption in the Cox regression models was tested by plotting the Schoenfeld residuals against follow-up time, which showed no deviation from a horizontal line i.e. the proportionality assumption was satisfied.[3] We also studied the association of retinal layer thickness with dementia and AD by making quartiles of the retinal layers taking the highest quartile as reference. We determined Pearson correlation coefficients between the retinal layers, and investigated the association of retinal layers with prevalent and incident dementia by adjusting the retinal layers for each other. Also, we investigated the longitudinal associations by primarily using measurements from the left eyes.

Next, retinal layer thicknesses were combined to assess their combined effect. Finally, we investigated the association of RNFL and GC-IPL with incident dementia after censoring for

stroke. All analyses were performed at the significance level of 0.05 (two-tailed) using SPSS 21.0 (IBM Corporation, Armonk, NY) for Windows.

eReferences

1. Whitlock MC. Combining probability from independent tests: the weighted Z-method is superior to Fisher's approach. *J Evol Biol.* 2005;18(5):1368-1373.
2. Zaykin DV. Optimally weighted Z-test is a powerful method for combining probabilities in meta-analysis. *J Evol Biol.* 2011;24(8):1836-1841.
3. Hess KR. Graphical methods for assessing violations of the proportional hazards assumption in Cox regression. *Stat Med.* 1995;14(15):1707-1723.

eTable 1. Number of individuals classified according to the Clinical Dementia Rating Scale, and number of dementia subtypes.				
	Sample I – peripapillary RNFL		Sample II – perimacular GC-IPL	
	Prevalent dementia	Incident dementia	Prevalent dementia	Incident dementia
Overall dementia	41	86	34	63
CDR				
0.5	1 (2%)	2 (2%)	1 (3%)	2 (3%)
1.0	5 (12%)	40 (47%)	6 (18%)	31 (49%)
2.0	25 (61%)	29 (34%)	19 (56%)	19 (30%)
3.0	0 (0%)	6 (7%)	0 (0%)	4 (6%)
Missing	10 (24%)	9 (10%)	8 (24%)	7 (11%)
Dementia subtypes				
Alzheimer's disease	34 (83%)	63 (73%)	28 (82%)	47 (75%)
Vascular dementia	1 (2%)	3 (3%)	1 (3%)	3 (5%)
Mixed Alzheimer's disease and vascular dementia	1 (2%)	5 (6%)	1 (3%)	5 (8%)
Another type of dementia	2 (5%)	7 (8%)	2 (6%)	5 (8%)
Undetermined	3 (7%)	8 (9%)	2 (6%)	3 (5%)
Person-time				
Total person-years (*)	-	14674 (94.9)	-	13493 (94.8)
Mean person-years	-	4.5	-	4.6
Abbreviations: CDR, Clinical Dementia Rating Scale; RNFL, retinal nerve fiber layer; GC-IPL, ganglion cell-inner plexiform layer. *Percentage of potential person-years if there was no loss to follow-up.				

eTable 2. Association of retinal layer thickness in quartiles with risk of dementia and Alzheimer's disease.

	All dementia			
	Hazard ratio (95% CI)			
Quartiles	n/N	Retinal nerve fiber layer	n/N	Ganglion cell – inner plexiform layer
4th quartile	14/812	1.00 (reference)	9/741	1.00 (reference)
3rd quartile	16/812	1.11 (0.54-2.28)	8/741	0.74 (0.29-1.92)
2nd quartile	13/812	1.09 (0.51-2.33)	20/741	1.39 (0.63-3.09)
1st quartile	43/812	2.58 (1.38-4.83)	26/741	1.48 (0.68-3.21)
P-value for trend		0.001		0.130
	Alzheimer's disease			
	Hazard ratio (95% CI)			
Quartiles	n/N	Retinal nerve fiber layer	n/N	Ganglion cell – inner plexiform layer
4th quartile	11/812	1.00 (reference)	7/741	1.00 (reference)
3rd quartile	12/812	1.02 (0.45-2.32)	7/741	0.83 (0.29-2.37)
2nd quartile	11/812	1.13 (0.49-2.64)	17/741	1.44 (0.59-3.50)
1st quartile	34/812	2.44 (1.20-4.95)	21/741	1.41 (0.59-3.37)
P-value for trend		0.001		0.256

Abbreviations: CI, confidence interval; n/N, number of individuals with dementia/total number of individuals.
Values are adjusted for age, sex, subcohort, and education.
Minimum to maximum (mean) retinal nerve fiber layer thickness for each quartile was: 32.87-86.63 (75.32) µm for the first quartile, 86.63-96.27 (91.58) µm for the second quartile, 96.27-105.40 (100.88) µm for the third quartile, and 105.41-210.10 (113.69) µm for the fourth quartile. Minimum to maximum (mean) ganglion cell layer-inner plexiform layer thickness for each quartile was: 27.73-66.63 (61.19) µm for the first quartile, 66.64-70.84 (68.76) µm for the second quartile, 70.84-75.04 (72.73) µm for the third quartile, and 75.04-119.40 (79.16) µm for the fourth quartile.

eTable 3. Association of retinal layer thickness with prevalent and incident dementia adjusting the retinal layers for each other.				
	All dementia			
	Odds ratio (95% CI)		Hazard ratio (95% CI)	
	n/N: 34/3026		n/N: 62/2964	
Per SD decrease in	Model 1	Model 2	Model 1	Model 2
Retinal nerve fiber layer	1.17 (0.82-1.67)	1.32 (0.93-1.88)	1.53 (1.21-1.95)	1.52 (1.18-1.95)
Ganglion cell – inner plexiform layer	1.38 (0.97-1.97)	1.53 (1.04-2.24)	1.21 (0.92-1.58)	1.08 (0.83-1.40)
Abbreviations: CI, confidence interval; SD, standard deviation; n/N, number of individuals with dementia/total number of individuals. Model 1: adjusted for age, sex, subcohort, and education. Model 2: as in model 1 and additionally adjusting the retinal layers for each other.				

eTable 4. Cross-sectional and longitudinal associations of retinal layer thickness with cognition.

	Cross-sectional		Longitudinal	
Cognitive domain	**Retinal nerve fiber layer**	**Ganglion cell-Inner plexiform layer**	**Retinal nerve fiber layer**	**Ganglion cell-Inner plexiform layer**
N	**3243**	**2959**	**2456**	**2276**
Mini mental state examination	**-0.056 (-0.090; -0.022)**	**-0.063 (-0.099; -0.028)**	-0.004 (-0.040; 0.032)	-0.027 (-0.065; 0.011)
Global cognition	**-0.044 (-0.074; -0.013)**	**-0.043 (-0.075; -0.012)**	-0.007 (-0.030; 0.017)	-0.015 (-0.040; 0.009)
Executive function				
Letter-digit substitution test	**-0.049 (-0.079; -0.019)**	**-0.067 (-0.098; -0.035)**	-0.011 (-0.036; 0.014)	-0.015 (-0.041; 0.011)
Stroop 1	**0.047 (0.013; 0.081)**	**0.044 (0.009; 0.080)**	0.007 (-0.024; 0.038)	0.030 (-0.002; 0.061)
Stroop 2	0.033 (-0.001; 0.068)	**0.052 (0.016; 0.088)**	0.011 (-0.019; 0.040)	0.020 (-0.009; 0.050)
Stroop 3	**0.056 (0.023; 0.089)**	**0.038 (0.003; 0.072)**	**0.052 (0.021; 0.083)**	0.005 (-0.028; 0.038)
Word fluency test	-0.027 (-0.061; 0.006)	-0.021 (-0.056; 0.015)	-0.004 (-0.036; 0.028)	-0.026 (-0.059; 0.008)
Memory				
Word learning test immediate	-0.007 (-0.041; 0.027)	**-0.042 (-0.078; -0.006)**	-0.015 (-0.049; 0.018)	**-0.036 (-0.071; -0.001)**
Word learning test delayed	0.006 (-0.028; 0.041)	-0.028 (-0.064; 0.009)	0.001 (-0.032; 0.034)	-0.029 (-0.062; 0.005)
Word learning test recognition	0.016 (-0.019; 0.052)	-0.008 (-0.046; 0.029)	-0.021 (-0.058; 0.017)	**-0.050 (-0.088; -0.012)**
Fine motor speed				
Purdue pegboard test	-0.013 (-0.043; 0.018)	-0.029 (-0.061; 0.003)	-0.008 (-0.037; 0.021)	-0.013 (-0.044; 0.017)

Values are z-scores per SD decrease in retinal layer thickness (95% confidence interval) adjusted for age, sex, subcohort, education, systolic blood pressure, diastolic blood pressure, blood pressure lowering medication, total cholesterol, high density lipoprotein cholesterol, diabetes mellitus, body mass index, and smoking.
Bolded values are p-value < 0.05.

eFigure. Scatterplots of RNFL (upper) and GC-IPL (lower) thickness between left and right eyes.