

# Retinal Vessel Caliber and Lifelong Neuropsychological Functioning: Retinal Imaging as an Investigative Tool for Cognitive Epidemiology

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## Abstract

Why do more intelligent people live healthier and longer lives? One possibility is that intelligence tests assess health of the brain, but psychological science has lacked technology to evaluate this hypothesis. Digital retinal imaging, a new, noninvasive method to visualize microcirculation in the eye, may reflect vascular conditions in the brain. We studied the association between retinal vessel caliber and neuropsychological functioning in the representative Dunedin birth cohort. Wider venular caliber was associated with poorer neuropsychological functioning at midlife, independently of potentially confounding factors. This association was not limited to any specific test domain and extended to informants' reports of cohort members' cognitive difficulties in everyday life. Moreover, wider venular caliber was associated with lower childhood IQ tested 25 years earlier. The findings indicate that retinal venular caliber may be an indicator of neuropsychological health years before the onset of dementing diseases and suggest that digital retinal imaging may be a useful investigative tool for psychological science.

## Keywords

cognitive ability, brain, intelligence, cognitive neuroscience, retinal imaging, venular caliber

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Young people with lower intelligence-test scores tend to be in poorer health as adults and to die earlier (Whalley & Deary, 2001). The emerging field of cognitive epidemiology is now focused on uncovering the mechanisms linking early-life intelligence to later illness and early death (Gottfredson & Deary, 2004). The obvious explanations for the intelligence-illness association have not fully explained it; for example, the association is not simply an artifact of low socioeconomic status (SES), and poor health behaviors alone do not account for the link (Gottfredson, 2004; Jokela, Batty, Deary, Gale, & Kivimaki,

2009). One intriguing hypothesis is that intelligence is a marker of system integrity, that is, of a healthy, well-maintained body and brain (Deary, 2010; Deary, Weiss, & Batty, 2010). However, psychological science is limited in the technology available for identifying indicators of

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system integrity. Here, we borrow insights from a surprising quarter (the discipline of ophthalmology) and show that retinal vessel caliber, which provides a window on microcirculation of the brain, may index lifelong neuropsychological health.

The vascular network of the brain contributes to neuropsychological ability by supplying oxygen and nutrients through a dense network of blood vessels (Paulson, 2002). A possible window into the health of the brain's vascular network is provided by the closely related retinal blood vessels of the eye. Retinal and cerebral small vessels share similar embryological origin, as well as structural and physiological features (Patton et al., 2005). Thus, assessing retinal vasculature may provide a useful noninvasive method to visualize the state of the brain's microcirculation *in vivo*, and to investigate the relationship between cerebral vascular state and neuropsychological health.

Advances in fundus photography (photographing the interior surface of the eye) and in retinal image analysis now allow for the accurate quantitative measurement of retinal vessel caliber in large population-based samples (Sun, Wang, Mackey, & Wong, 2009). Of particular interest is the caliber of the arterioles and venules (i.e., the size of the internal space of these vessels). Arterioles are small branches of the arteries. They carry oxygen-rich blood away from the heart to the capillaries, where oxygen and nutrients from the blood diffuse into the surrounding tissue. Arterioles regulate blood flow through changes in caliber (vasodilation and vasoconstriction) and are the primary determinants of blood pressure. Venules, in contrast, carry blood from the capillaries to the veins and back to the heart. Recent studies suggest that individual differences in the caliber of retinal arterioles and in the caliber of retinal venules may represent different vascular pathophysiological processes (Sun et al., 2009). In particular, retinal arteriolar narrowing may be an early sign of hypertensive retinopathy and a prognostic indicator of hypertension (Wong & Mitchell, 2004). In contrast, retinal venular widening is associated with obesity (Wang et al., 2006), inflammatory markers (de Jong et al., 2007), and smoking (Kifley et al., 2007), and predicts the risk of stroke and coronary heart disease (Wong et al., 2001).

Additional studies have shown associations specifically between retinal venular widening and brain-related vascular events such as stroke, cerebral infarction, and cerebral hypoxia (de Jong et al., 2008; Doubal, Hokke, & Wardlaw, 2009; Ikram, de Jong, Bos, et al., 2006; Ikram, De Jong, Van Dijk, et al., 2006; Wong, Kamineni, et al., 2006). These associations support the hypothesis that retinal venular caliber is connected to cerebrovascular function. Several studies have also linked retinal vascular abnormalities, including venular widening, with neuropsychological dysfunction, and particularly impaired

memory or dementia. However, most of these studies have examined the elderly or midlife adults with diabetes (reviewed in Ding et al., 2008). Neuropsychological impairment related to advanced age and diabetes may have different underlying mechanisms than neuropsychological dysfunction in the general population. Moreover, whether or not retinal vessel caliber is associated with neuropsychological status in younger people, prior to declines seen in late life, remains to be addressed.

The purpose of this study was to examine the association between retinal vessel caliber and neuropsychological functioning in a representative birth cohort. First, we tested our central hypothesis that retinal vessel caliber (arteriolar and venular caliber) is associated with concurrent neuropsychological functioning in adulthood (age 38 years). On the basis of the prior studies already cited, we expected the association with neuropsychological test scores to be stronger for venular caliber than for arteriolar caliber. An important step in cognitive epidemiology is to make sure that the correlates of neuropsychological functioning are untangled from other influences on such functioning (Lubinski, 2009). Thus, we tested whether poor health, lifestyle factors, or environmental factors could explain the association between retinal vessel caliber and neuropsychological functioning, as all of these factors have been found to predict both retinal vessel caliber and neuropsychological test scores (Hubbard et al., 1999; Klein, Klein, Knudtson, Wong, & Tsai, 2006; Nguyen et al., 2008; Plassman, Williams, Burke, Holsinger, & Benjamin, 2010; Wong, Islam, et al., 2006).

Second, we tested whether retinal vessel caliber was associated with specific or generalized neuropsychological impairment. Studies linking retinal vessel caliber to neuropsychological performance have assessed a narrow set of neuropsychological domains, which raises questions about the breadth of the intellectual deficits (Ding et al., 2008). Specific impairment might indicate a link with brain pathology (e.g., stroke), whereas generalized impairment would be more consistent with a link with the theoretical concept of brain-body system integrity. Third, we tested whether retinal vessel caliber was associated with third parties' reports of cognitive problems, to determine if retinal signs translate into functional problems in daily living. Fourth, we tested the hypothesis that the association between retinal vessel caliber and neuropsychological functioning begins early in life by examining whether retinal vessel caliber was associated with childhood IQ tested more than 25 years earlier.

## Method

### Participants

Participants were members of the Dunedin Multidisciplinary Health and Development Study, a longitudinal

investigation of health and behavior in a complete birth cohort. Study members ( $N = 1,037$ ; 91% of eligible births; 52% male, 48% female) were all individuals born between April 1972 and March 1973 in Dunedin, New Zealand, who were eligible for the longitudinal study on the basis of residence in the Otago province at age 3 and who participated in the first follow-up assessment at age 3. The cohort represents the full range of SES in the general population of New Zealand's South Island and is primarily White. Assessments were carried out at birth and at ages 3, 5, 7, 9, 11, 13, 15, 18, 21, 26, 32, and, most recently, 38 years, when 95% of the 1,007 living study members underwent assessment (2010–2012). At each assessment wave, each study member was brought to the Dunedin Multidisciplinary Health and Development Research Unit for a full day of interviews and examinations. The protocol for the present study was approved by the institutional ethical review boards of the participating universities. Study members gave informed consent before participating.

### ***Neuropsychological functioning***

Intelligence tests were administered in childhood at ages 7, 9, 11, and 13 years (scores were averaged over ages 7 to 13 years) and again in adulthood at age 38 years. We report results from the Wechsler Intelligence Scale for Children-Revised (Wechsler, 1974) and the Wechsler Adult Intelligence Scale—Fourth Edition (Wechsler, 2008). These tests comprise a series of subtests that yield indices standardized to population norms ( $M = 100$ ,  $SD = 15$ ). At age 38, additional neuropsychological tests were administered: the Trail Making Test (War Department, Adjutant General's Office, 1944); the Mental Control and Verbal Paired Associates tests (total and delayed recall) from the Wechsler Memory Scale (Wechsler, 1997); the Rey Auditory Verbal Learning test (total and delayed recall; Lezak, 2004); the grooved-pegboard, one-legged balance, and grip-strength tests of motor function; and three tasks from the Cambridge Neuropsychological Test Automated Battery (CANTAB; Cambridge Cognition, 2013; Sahakian & Owen, 1992). (See Table S1 in the Supplemental Material available online for further details on these tests.) Tests were administered in the morning in counterbalanced order.

Informants' reports of study members' neuropsychological functioning were obtained at age 38 years. Study members nominated people "who knew them well." Each informant was mailed a questionnaire and asked to complete a checklist that included seven items asking whether the study member had experienced problems with attention and memory over the past year. Specifically, the informant indicated whether the study member "is easily distracted, gets sidetracked easily"; "can't concentrate,

mind wanders"; "tunes out instead of focusing"; "has difficulty organizing tasks that have many steps"; "has problems with memory"; "misplaces wallet, keys, eyeglasses, paperwork"; and "forgets to do errands, return calls, pay bills" ( $\alpha = .875$ ). These reports of cognitive problems were significantly correlated with study members' IQ scores ( $r = -.22$ ,  $p < .001$ ).

### ***Additional variables***

Physical examinations were conducted at age 38, and study members provided blood samples (always between 4:15 p.m. and 4:45 p.m.). The following variables were assessed:

- *High-sensitivity C-reactive protein* (hsCRP) was measured on a Hitachi 917 analyzer (Roche Diagnostics, Mannheim, Germany) using a particle-enhanced immunoturbidimetric assay. The Center for Disease Control and Prevention and the American Heart Association's definition of high cardiovascular risk (hsCRP  $> 3$  mg/L) was adopted to identify study members who were at risk (Ridker, Wilson, & Grundy, 2004). According to this criterion, 20.4% of the cohort members were identified as having high hsCRP levels.
- The American Diabetes Association's cutoff points were used to identify study members who were *prediabetic* (glycated hemoglobin = 5.7–6.4%) or *diabetic* (glycated hemoglobin  $\geq 6.5\%$ ; Seino et al., 2010). According to these criteria, 18.2% of the study members were prediabetic or diabetic.
- *High blood pressure* was assessed according to standard protocols (Perloff et al., 1993) using a Hawksley random-zero sphygmomanometer (Hawksley & Sons Ltd., Lancing, United Kingdom) with a constant deflation valve. According to a definition of high blood pressure as systolic blood pressure greater than 140 mm Hg or diastolic blood pressure greater than 90 mm Hg (Chobanian et al., 2003), 12.5% of the study members had high blood pressure.
- Height was measured to the nearest millimeter using a portable Harpenden Stadiometer (Holtain, Crymych, United Kingdom). Weight was recorded to the nearest 0.1 kg using a Tanita calibrated scale (Tanita, Tokyo, Japan). Body mass index (BMI) was computed as follows: weight (kg)/height<sup>2</sup> (m<sup>2</sup>). According to a definition of *obesity* as a BMI of 30 or more (National Institutes of Health, 1998), 23.7% of the cohort members were obese.
- Study members were asked about their *smoking* status; 22.6% were smokers.

Study members' occupations were coded according to a 6-point scale for contemporary occupations (1 = unskilled laborer, 6 = professional) based on the education and income associated with these occupations in the New Zealand census. The SES of homemakers and study members who were not working was estimated from their education. *Low adult SES* was defined as 1 or 2 on the SES scale, and 30.2% of the study members were identified as having low adult SES.

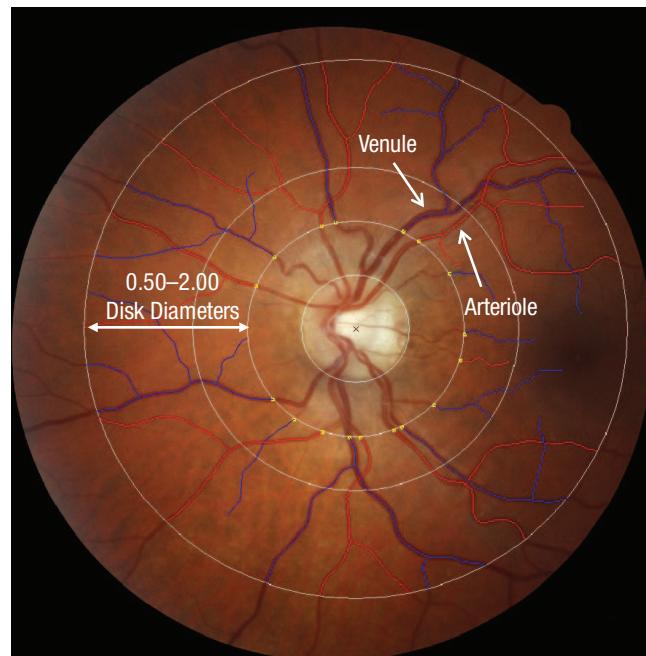
### **Assessment of retinal vessel caliber**

Digital fundus photographs were taken at the Dunedin Research Unit after 5 min of dark adaptation. The same camera (Canon NMR-45 with a 20D single-lens reflex backing; Canon, Tokyo, Japan) was used for all photographs, to avoid artifactual variation from different cameras. Both the left and the right eyes were photographed, and we report analyses of the average for the two eyes. Retinal photographs were graded at the Singapore Eye Research Institute, National University of Singapore, using semiautomated computer software, Singapore I Vessel Assessment (SIVA) Version 3.0. Trained graders, blind to participants' characteristics, used the SIVA program to measure the retinal vessel diameters according to a standardized protocol with high intergrader reliability (Cheung et al., 2011). Diameter (or caliber) denotes the size of the lumen, which is the internal space of the vessel. Measurements were made for arterioles and venules where they passed through a region located 0.50 to 2.00 disk diameters from the optic disk margin (Cheung et al., 2011; see Fig. 1). Vessel calibers were based on the six largest arterioles and venules passing through this region and were summarized as central retinal artery equivalent (CRAE) and central retinal vein equivalent (CRVE) using the revised Knudtson-Parr-Hubbard formula (Cheung et al., 2010; Knudtson et al., 2003).

Of 938 study members with retinal images, only 7 could not be graded because their images were either too dark or not centered on the optic disk. An additional 9 study members were excluded from analyses because of pregnancy. This left 922 study members with retinal vessel data. Arteriolar and venular calibers were normally distributed within our population-representative cohort. The mean arteriolar caliber among the 922 study members was 137.33 measuring units ( $SD = 10.86$ , median = 137.30, range = 105.66–179.47), and the mean venular caliber was 196.20 measuring units ( $SD = 14.83$ , median = 195.51, range = 141.07–245.68).

### **Statistical analysis**

Linear regression was used to test the hypotheses that retinal vessel caliber was related to (a) neuropsychological test performance at 38 years of age (beginning with

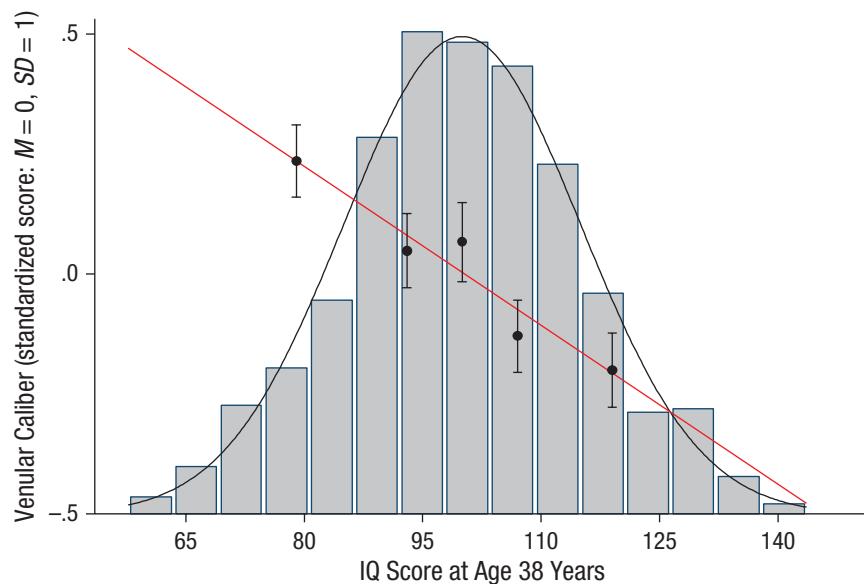


**Fig. 1.** Illustration of the assessment of retinal vessel caliber. Measurements were made for the six largest arterioles (red) and six largest venules (blue) passing through the region 0.50 to 2.00 disk diameters from the optic disk margin.

IQ and then progressing to other neuropsychological scores), (b) informants' ratings of cognitive impairment at age 38 years, and (c) IQ performance in childhood (averaged across ages 7, 9, 11, and 13 years). Individuals with wider arterioles tended to have wider venules ( $r = .67$ ,  $p < .001$ ); following recommended procedures, we included both arteriolar and venular caliber in all analyses to control for the confounding effects of the fellow vessel (Liew et al., 2007; Sun et al., 2009). To rule out the possibility that the observed association between retinal vessel caliber and IQ was a spurious artifact of current poor health, lifestyle factors, or socio-environmental factors, we reanalyzed the association between retinal vessel caliber and IQ controlling for these potential confounds. High levels of hsCRP, diabetes, high blood pressure, obesity, cigarette smoking, and low adult SES were significantly correlated with retinal vessel caliber—a finding replicating previous medical and epidemiological studies—as well as with IQ (with the exception of high blood pressure; see Table S2 in the Supplemental Material). Gender was included as a covariate in all analyses. We present results both with and without adjustment for the covariance between arteriolar and venular retinal caliber.

### **Results**

Wider venular caliber was associated with lower IQ scores at age 38 years,  $\beta = -0.155$ , 95% confidence interval



**Fig. 2.** The association between retinal venular caliber and IQ. The histogram depicts the distribution of study members' IQ scores at age 38 years. The scatter plot and regression line show the association between venular caliber and IQ score; mean venular caliber is plotted as a function of mean IQ for each of the quintiles of the IQ distribution (scores of 79.7, 92.7, 100.7, 107.7, and 119.6, respectively). Error bars represent standard errors.

(CI) = [−0.220, −0.091],  $p < .001$ , even after adjusting for arteriolar caliber,  $\beta = -0.194$ , 95% CI = [−0.282, −0.108],  $p < .001$  (Fig. 2; Table 1). Similar adjusted associations between wider venular caliber and lower IQ scores were observed among both males,  $\beta = -0.212$ , 95% CI = [−0.350, −0.092],  $p = .001$ , and females,  $\beta = -0.177$ , 95% CI = [−0.288, −0.054],  $p = .004$ .

Retinal arteriolar caliber was significantly associated with IQ scores,  $\beta = -0.071$ , 95% CI = [−0.137, −0.006],  $p = .032$ , but not after adjusting for venular caliber,  $\beta =$

0.060, 95% CI = [−0.027, 0.148],  $p = .178$ . Moreover, after adjustment for venular caliber, retinal arteriolar caliber was not significantly associated with IQ scores among either males,  $\beta = 0.074$ , 95% CI = [−0.053, 0.208],  $p = .245$ , or females,  $\beta = 0.046$ , 95% CI = [−0.073, 0.162],  $p = .455$ . Given the null association with arteriolar caliber, all further analyses were performed on venular caliber only.

We ruled out several explanations for the observed association between wider venular caliber and lower adult IQ, namely, that this association could be an artifact

**Table 1.** Results of Regression Models Using Venular Caliber to Predict IQ at Age 38 Years

Sample <sup>a</sup>	Model 1			Model 2		
	$\beta$	95% CI	$p$	$\beta$	95% CI	$p$
Total cohort ( $n = 916$ )	−0.155	−0.219, −0.091	< .001	−0.194	−0.282, −0.108	< .001
Samples with exclusions						
No high hsCRP ( $n = 708$ )	−0.161	−0.234, −0.088	< .001	−0.233	−0.334, −0.131	< .001
No prediabetes or diabetes ( $n = 718$ )	−0.174	−0.238, −0.099	< .001	−0.221	−0.309, −0.118	< .001
No high blood pressure ( $n = 800$ )	−0.155	−0.222, −0.086	< .001	−0.178	−0.272, −0.083	< .001
No obesity ( $n = 699$ )	−0.186	−0.267, −0.117	< .001	−0.204	−0.313, −0.107	< .001
No smokers ( $n = 709$ )	−0.124	−0.198, −0.051	.001	−0.192	−0.292, −0.094	< .001
No low adult SES ( $n = 638$ )	−0.175	−0.249, −0.097	< .001	−0.210	−0.309, −0.107	< .001

Note: The regression coefficients in this table reflect the change in test performance associated with an increase of 1 SD unit in retinal venular caliber. Model 1 controlled for gender; Model 2 added a control for arteriolar caliber. CI = confidence interval; hsCRP = high-sensitivity C-reactive protein; SES = socioeconomic status.

<sup>a</sup>Retinal imaging information was available for 922 study members, 6 of whom did not have IQ scores. Thus, the effective group size for the total cohort was 916. For the subsamples, the  $n$ s are the sample sizes after the indicated exclusions.

of current poor health (high hsCRP, diabetes, high blood pressure), lifestyle (smoking, obesity), or socio-environmental risk factors (low adult SES). Table 1 shows that in linear regression analyses excluding study members with each of these conditions, the initial finding was not altered. Further, a multivariate regression analysis, controlling for all of these confounding factors and arteriolar caliber simultaneously, showed that wider venular caliber remained significantly associated with lower IQ scores,  $\beta = -0.107$ , 95% CI = [-0.195, -0.022],  $p = .014$ .

Table 2 shows that wider venular caliber was associated with lower scores on tests of verbal comprehension, perceptual reasoning, working memory, processing speed, executive function, memory, and motor functions. Thus, general rather than specific neuropsychological deficits appear to be associated with wider venular caliber. Moreover, informants reported observing more cognitive problems among cohort members with wider

venular caliber,  $\beta = 0.133$ , 95% CI = [0.067, 0.194],  $p < .001$ , even after controlling for arteriolar caliber,  $\beta = 0.130$ , 95% CI = [0.042, 0.213],  $p = .004$ .

Finally, we tested the hypothesis that the association between retinal venular caliber and IQ begins early in life by examining participants' childhood IQ scores. Wider venular caliber at age 38 was associated with lower childhood IQ,  $\beta = -0.117$ , 95% CI = [-0.171, -0.049],  $p < .001$ , even after controlling for arteriolar caliber,  $\beta = -0.152$ , 95% CI = [-0.226, -0.061],  $p = .001$ .

## Discussion

Wider venular caliber was associated with worse neuropsychological functioning in a population-based cohort of adults as they approached midlife. This study extends current knowledge in several ways. First, wider venular caliber (but not arteriolar caliber) assessed at age 38

**Table 2.** Results of Regression Models Using Venular Caliber to Predict Performance on Specific Neuropsychological Tests at Age 38 Years

Neuropsychological test	Model 1			Model 2		
	$\beta$	95% CI	$p$	$\beta$	95% CI	$p$
WAIS-IV						
Verbal Comprehension	-0.141	-0.207, -0.078	<b>&lt; .001</b>	-0.181	-0.269, -0.095	<b>&lt; .001</b>
Perceptual Reasoning	-0.103	-0.168, -0.039	<b>.002</b>	-0.124	-0.211, -0.037	<b>.005</b>
Working Memory	-0.096	-0.161, -0.032	<b>.003</b>	-0.147	-0.234, -0.061	<b>.001</b>
Processing Speed	-0.124	-0.186, -0.061	<b>&lt; .001</b>	-0.141	-0.224, -0.055	<b>.001</b>
Executive function						
Trail Making Test B (War Department, Adjutant General's Office, 1944) <sup>a</sup>	0.098	0.034, 0.163	<b>.003</b>	0.114	0.027, 0.201	<b>.010</b>
WMS-III Mental Control	-0.123	-0.186, -0.060	<b>&lt; .001</b>	-0.096	-0.180, -0.010	<b>.028</b>
CANTAB Rapid Visual Information Processing: A Prime	-0.075	-0.141, -0.010	<b>.023</b>	-0.126	-0.215, -0.039	<b>.005</b>
Memory						
Rey Auditory Verbal Learning: total recall (Lezak, 2004)	-0.086	-0.150, -0.025	<b>.006</b>	-0.113	-0.198, -0.029	<b>.008</b>
Rey Auditory Verbal Learning: delayed recall (Lezak, 2004)	-0.060	-0.122, 0.002	.060	-0.087	-0.171, -0.003	<b>.043</b>
WMS-III Paired Associates: total recall	-0.048	-0.113, 0.017	.145	-0.068	-0.155, 0.019	.126
WMS-III Paired Associates: delayed recall	0.008	-0.057, 0.073	.801	0.040	-0.048, 0.128	.372
CANTAB Visual Paired Associates Learning: total errors <sup>a</sup>	0.083	0.018, 0.144	<b>.012</b>	0.080	-0.007, 0.164	.072
Motor function						
Grooved pegboard <sup>a</sup>	0.103	0.040, 0.166	<b>.001</b>	0.113	0.028, 0.198	<b>.009</b>
One-legged balance	-0.061	-0.126, 0.004	.067	-0.152	-0.240, -0.065	<b>.001</b>
Grip strength	0.011	-0.033, 0.054	.629	0.025	-0.034, 0.083	.408
CANTAB Reaction Time: 5-choice reaction time <sup>a</sup>	0.011	-0.053, 0.075	.739	0.007	-0.079, 0.094	.872

Note: The regression coefficients in this table reflect the change in test performance associated with an increase of 1 SD unit in retinal venular caliber. Model 1 controlled for gender; Model 2 added a control for arteriolar caliber. Significant  $p$  values are highlighted in boldface. CI = confidence interval; WAIS-IV = Wechsler Adult Intelligence Scale—Fourth Edition (Wechsler, 2008); WMS-III = Wechsler Memory Scale—Third Edition (Wechsler, 1997); CANTAB = Cambridge Neuropsychological Test Automated Battery (Cambridge Cognition, 2013; Sahakian & Owen, 1992).

<sup>a</sup>On these tests, higher scores indicate slower performance or more errors, and thus worse functioning.

years was correlated with poorer neuropsychological functioning, years before onset and diagnosis of age-related diseases. Second, the association between wider venular caliber and poorer neuropsychological performance was not limited to any specific neuropsychological domain, and could not be explained by poor health, lifestyle factors, or environmental factors that might affect both the condition of the retinal vessel and neuropsychological performance. Third, third-party reports of cognitive problems were associated with wider venular caliber, a result suggesting that retinal venular caliber also can predict cognitive problems in everyday life among relatively young adults. Finally, poorer neuropsychological functioning in childhood antedated wider venular caliber in adulthood.

Previous studies have documented an association between wider retinal venules and dementia (Ikram, Ong, Cheung, & Wong, 2013; Sun et al., 2009). However, to date, it has not been clear whether retinal venular caliber is related to neuropsychological status prior to declines seen later in life or specifically to those declines associated with illness and disease. To us, it seems unremarkable that venular caliber in the eye is abnormal in elderly individuals who have documented vascular disease, yet rather more remarkable that venular caliber in the eye is related, however modestly, to mental test scores of individuals in their 30s, and even to IQ scores in childhood. Taken together, these findings suggest that the developmental processes linking retinal vessel abnormalities to neuropsychological functioning begin at much younger ages than previously assumed in studies of retinal vasculature and memory loss in the elderly. It appears that digital retinal imaging may serve as a tool for testing the theory that general intelligence represents brain-body system integrity across the life course.

The pathophysiological mechanism that links wider venular caliber with poorer neuropsychological functioning is not well understood. It is possible that low oxygen perfusion in the brain results in damaged cerebral (and retinal vessel) microvasculature, which in turn has a negative impact on cognitive functioning (Qaum et al., 2001). This is consistent with studies showing that venular caliber indicators are associated with low cerebral oxygen supply, progression of cerebral small vessel disease, and stroke, chronic ischemia and cerebral atrophy (de Jong et al., 2008; Doubal et al., 2009; Ikram, de Jong, Bos, et al., 2006; Ikram, De Jong, Van Dijk, et al., 2006; Wong, Kamineni, et al., 2006). As arterioles are the main source for supplying the tissue with oxygen and nutrients, it may seem surprising that only venular caliber was linked to IQ. Previous studies have emphasized the specific link between venules and neuropsychological functioning. In contrast, the lack of association between arterioles and neuropsychological functioning is not entirely understood. One potential explanation for this discrepancy

may lie with the underlying structural differences between arterioles and venules. Arterioles have higher relative proportions of connective tissue and smooth muscle compared with venules; thus, arterioles are less elastic and may not be as good an indicator of brain health as venules. Whatever the process, our finding that IQ was lower during childhood among individuals with wider retinal venular caliber as adults suggests that it is under way as early as childhood.

Our findings must be interpreted in the context of several limitations. First, as digital retinal imaging is a relatively new technology, we assessed retinal vessel caliber at one time point only: when study members were 38 years old. Thus, we could not estimate change in retinal vessel caliber from childhood to adulthood, or rule out whether factors associated with low childhood IQ caused change in retinal vessel caliber. However, we ruled out key mechanisms by which low premorbid IQ might affect retinal vasculature (high levels of hsCRP, diabetes, high blood pressure, obesity, cigarette smoking, and low adult SES; Table 1). Second, although we ruled out these numerous possible explanations of the association between retinal venular caliber and neuropsychological impairment, it is possible that other unmeasured factors may explain the results.

Third, we noticed that venular caliber was unrelated to another measure that has been proposed to index brain-body integrity, choice reaction time (Deary & Der, 2005; see Table 2). In our cohort, choice reaction time was correlated with IQ ( $r = -.21$ , controlling for gender); thus, perhaps both reaction time and venular caliber can help to account for the IQ-health connection, albeit via complementary mechanisms. Fourth, the association between neuropsychological health and retinal venular caliber had a small effect size in the population as a whole ( $r \approx .2$ ). However, at the extremes, the effects were more marked: Study members in the highest and lowest quintiles of IQ differed in their venular caliber by 0.5 SD units (Fig. 2). Effect sizes for new research findings should be evaluated against other, well-established findings. The effect sizes we observed for the association between IQ and venular caliber can be evaluated against correlations between IQ and factors such as occupational status ( $r \approx .4$ ) and income ( $r \approx .2$ ; Deary, 2012), birth weight ( $r \approx .2$ ; Shenkin et al., 2001), and reaction time ( $r \approx .3$ ; Deary, 2012). The modest effect size we observed means that researchers should be cautious about using retinal vessel caliber as a surrogate marker for general IQ, but digital retinal imaging may prove to be a useful tool as an indicator of brain-body system health. Finally, the present findings need to be confirmed in independent samples.

Retinal imaging may prove to be a valuable new tool for psychological science in studying development, aging, and health. It is noninvasive, can be administered to children and adults, allows for repeated measurements, and

allows comparisons across different populations. Several new research directions suggest themselves. Developmental research is needed to establish when in the life course associations between retinal vessel caliber and neuropsychological functioning begin to emerge. Neuroscience research is needed to combine retinal and neuroimaging tools to test associations between retinal caliber and brain structure (e.g., gray matter volume) and function (e.g., changes in blood flow). Longitudinal research is needed to test if changes in retinal vasculature track with changes in neuropsychological functioning over time. Epidemiological research is needed to test whether retinal caliber may, in part, explain the associations between IQ and morbidity and mortality, and whether these associations are specific to illnesses and causes of death involving vascular pathology in the brain, a topic we hope to pursue as the Dunedin cohort ages. More knowledge about retinal vessels could inform prevention and intervention strategies aimed at increasing oxygenation of the brain and preventing age-related worsening of neuropsychological problems (de Jong et al., 2008).

Our initial findings support the hypothesis that retinal venular caliber may be an indicator of neuropsychological health throughout the life course and that its application need not be limited to the study of age-related diseases such as dementia. We think these findings open the door for digital retinal imaging to be used as an investigative tool for psychological science.

### Author Contributions

I. Shalev, T. E. Moffitt, A. Caspi, and R. Poulton developed the study concept. I. Shalev, T. E. Moffitt, A. Caspi, and R. Poulton contributed to the study design. T. E. Moffitt, A. Caspi, and R. Poulton collected the data. T. Y. Wong, J. Ding, C. Y. Cheung, and M. K. Ikram performed the retinal imaging assessments. I. Shalev, M. H. Meier, and R. M. Houts performed the data analysis. I. Shalev, T. E. Moffitt, and A. Caspi drafted the manuscript. All authors provided critical revisions and approved the final version of the manuscript for submission.

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### Declaration of Conflicting Interests

The authors declared that they had no conflicts of interest with respect to their authorship or the publication of this article.

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### Supplemental Material

Additional supporting information may be found at <http://pss.sagepub.com/content/by-supplemental-data>

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