

Supplementary Online Content

Ko F, Muthy ZA, Gallacher J, et al. Association of retinal nerve fiber layer thinning with current and future cognitive decline: a study using optical coherence tomography. *JAMA Neurol*. Published online June 25, 2018. doi:10.1001/jamaneurol.2018.1578

eMethods.

eFigure 1. Inclusion/Exclusion Criteria for Macular RNFL SD-OCT

eFigure 2. Prospective Memory and Retinal Nerve Fiber Layer Thickness at Baseline

eFigure 3. Pairs Matching and Retinal Nerve Fiber Layer Thickness at Baseline

eFigure 4. Numeric and Verbal Reasoning and Retinal Nerve Fiber Layer Thickness at Baseline

eFigure 5. Numeric and Verbal Reasoning and Retinal Nerve Fiber Layer Thickness at Baseline

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

eMethods

Measures and procedure

This study was conducted under generic approval from the NHS National Research Ethics Service (Ref. 11/NW/0382). All participants gave written informed consent. Baseline assessments took place at 22 centres across England, Scotland and Wales between 2006 and 2010. Questionnaires and cognitive assessments were administered in a standardised order via a computerised touchscreen interface, followed by a face-to-face interview with a research nurse to obtain additional data. Assessment took place in a single visit lasting approximately 90 minutes.

Descriptions of Cognitive Testing in UK Biobank

The cognitive tests included in UK Biobank are optimised for use at-scale. The constraints of cognitive testing at-scale include tests being brief, self-explanatory, and automated. At the inception of UKB suitable tests did not exist and were developed specifically for this study.

To maximize comparability with other datasets, for each test a standard and widely used test paradigm was employed as a template. For the tests reported in this study prospective memory is an embedded task and comparable to that used in the CAMCOG interview. Reaction time used a stop-go paradigm. Reasoning included both verbal and numeric items as used in the AH4. The pairs test is a paired associates learning task designed to test episodic memory.

The distributions of test scores are available on the UK Biobank data showcase website <http://biobank.ctsu.ox.ac.uk/crystal/>. As expected, reaction time was log-normally distributed and reasoning score was normally distributed. The pairs test showed a ceiling effect indicating a lack of sensitivity for high performers but good sensitivity for low performers. The distribution of the prospective memory test is relatively uninformative as it has a range of 3! Nevertheless, most individuals achieved the maximum score as might be expected in a non-clinical population.

Reaction time has a monotonic inverse association with age indicating a constant slowing of processing speed with increasing age throughout the age range. Both memory scales also decline monotonically with age. Reasoning is poorer only in older age groups indicating a substantial crystallized intelligence component.

The test requiring further evidence for its validity is the reasoning test, as the test items (not just the paradigm) are critical to the construct being assessed. A recently completed and as yet unpublished study has shown that the reasoning test correlates with Raven's Progressive matrices ($r=0.59$), and with the Cognito Matrix test ($r=0.54$). These correlations are very acceptable for a brief test, particularly as the Ravens and Cognito Matrix tests appear to have a greater fluid:crystallised intelligence ratio.

Reasoning (<http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=20016>).

A task with thirteen logic/reasoning-type questions and a two-minute time limit was labelled as ‘fluid intelligence’ in the UK Biobank protocol but is hereafter referred to as ‘verbal-numerical reasoning’. There were six verbal items. There were seven numerical items, involving sequence recognition and arithmetic. Participants were required to answer all the items within two minutes. All were multiple-choice. An example verbal item is: “Age is to years as height is to?” (answer options were, “Long/Deep/Top/Metres/Tall/Do not know/Prefer not to answer”). An example numerical item is: “150...137...125...114...104... what comes next?” (answer options were, “96/95/94/93/92/Do not know/Prefer not to answer”). The total score out of thirteen was recorded and used for the present study. The Cronbach alpha coefficient for the thirteen items was 0.62. The UK Biobank Field IDs (variable names) used in this test, with each one corresponding to each of the 13 items, were 4935, 4946, 4957, 4968, 4979, 4990, 5001, 5012, 5556, 5699, 5779, 5790, and 5866.

Reaction time (<http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=20023>)

Participants completed a timed test of symbol matching, similar to the common card game ‘Snap’ conceptually similar to some ‘Go/No-Go’ reaction time (RT) tasks. Two cards with simple symbols (e.g. a square or equals sign), were presented to participants on a computer screen. Participants were instructed to push an adjacent button box as quickly as possible, using their dominant hand, if the two cards had identical symbols. After completing four practice trials, participants completed eight experimental trials, of which four included identical pairs; these four required a button to be pressed. Each participant’s RT score was calculated as the mean time (in ms) to push the button for the four trials in which the stimuli were identical. The score on this task was the mean response time in milliseconds across trials which contained matching pairs.

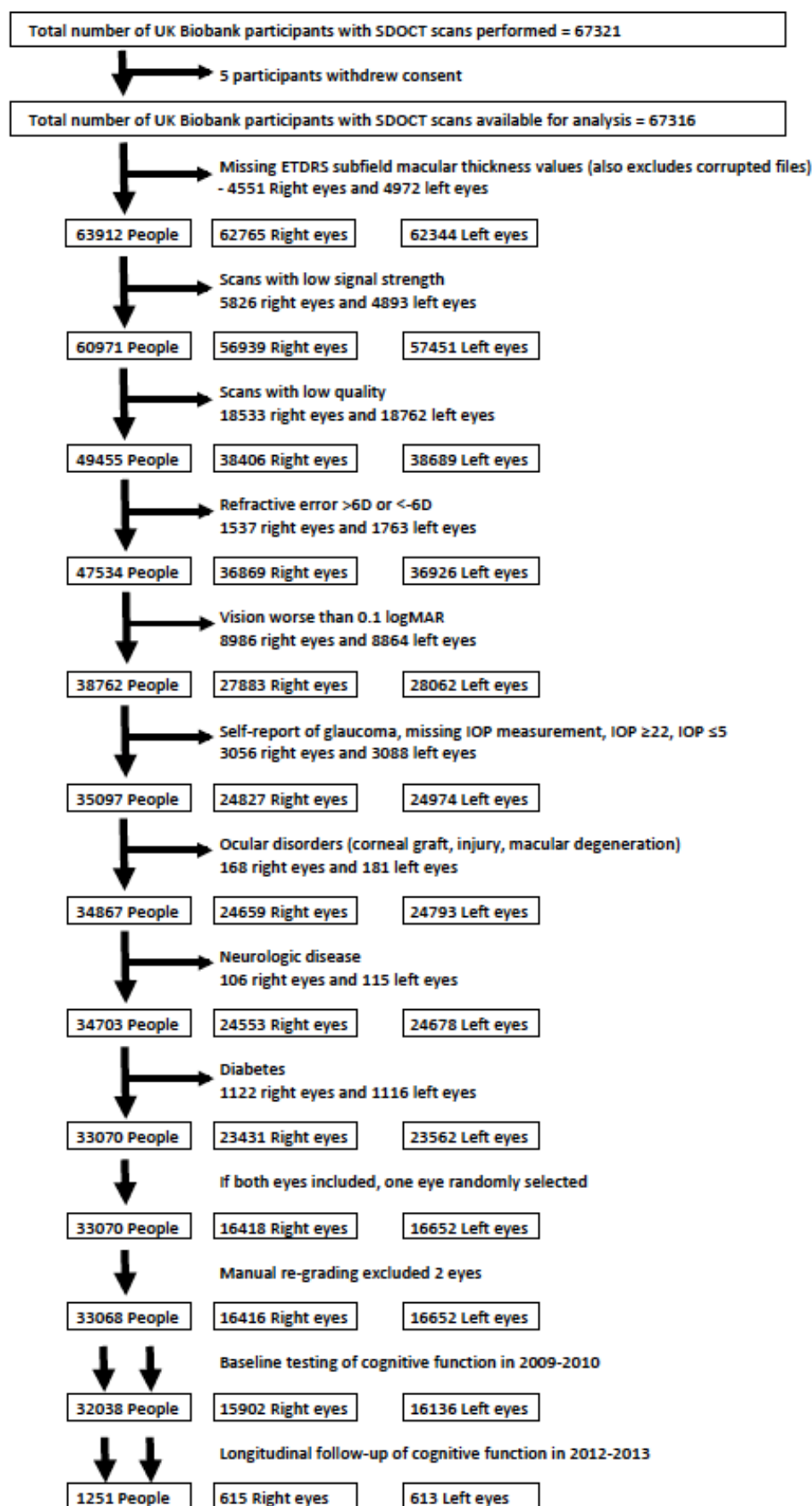
Visual memory (<http://biobank.ctsu.ox.ac.uk/crystal/label.cgi?id=100030>),

Memory was measured using a computerised ‘pairs matching’ game. There were three pairs of cards with matching simple symbols, arranged randomly in a grid, were presented to participants on a computer screen for three seconds. The cards were then ‘turned’ face down. The participants were instructed to select, from recall and in the fewest number of attempts, the pairs of cards that had matching symbols. Pairs were identified by the participant’s touching identical cards on the screen consecutively. There was no time limit and the participants could make as many attempts as they needed to find all the pairs. Higher scores reflect poorer cognitive function.

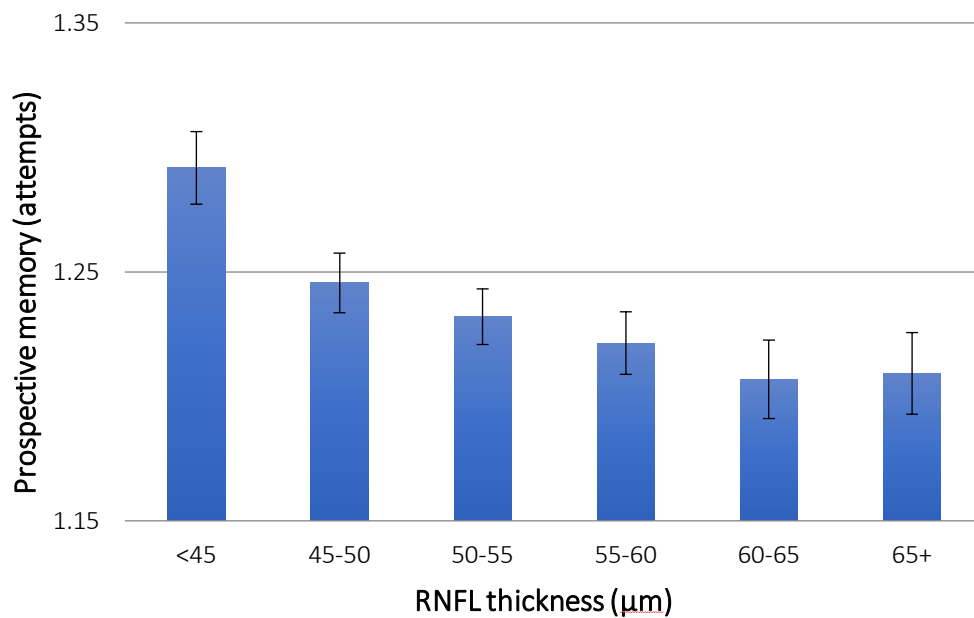
Prospective Memory (<http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=20018>).

For the Prospective Memory (PM) test, participants were asked to engage in a specific behaviour later in the assessment: ‘At the end of the games we will show you four colored symbols and ask you to touch the blue square. However, to test your memory, we want you to actually touch the Orange Circle instead’. We scored participants as zero or one, depending on whether they completed the task on first attempt or not.

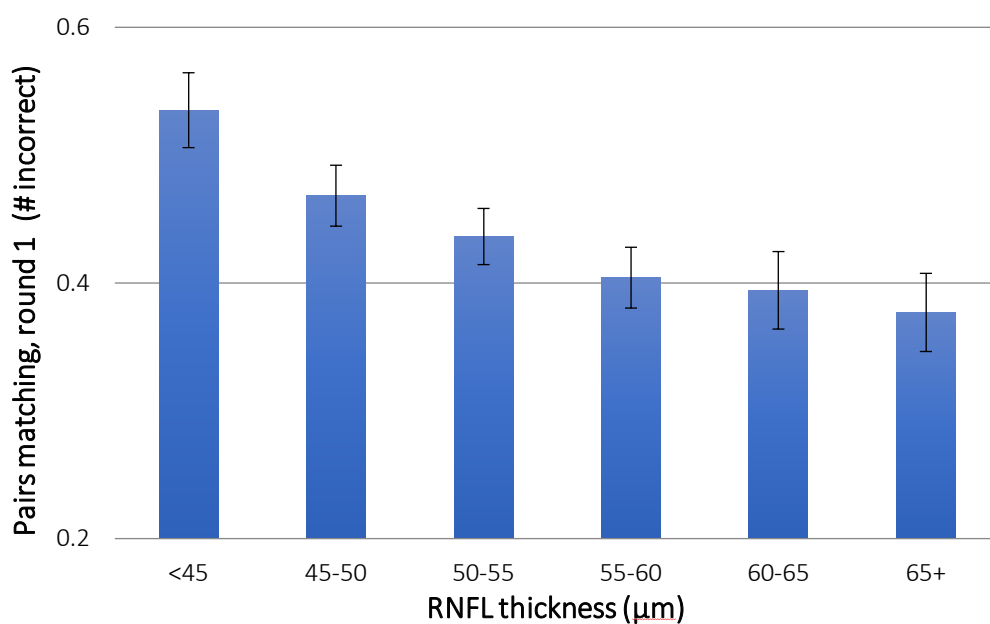
eFigure 1. Inclusion/exclusion criteria for macular RNFL SD-OCT.



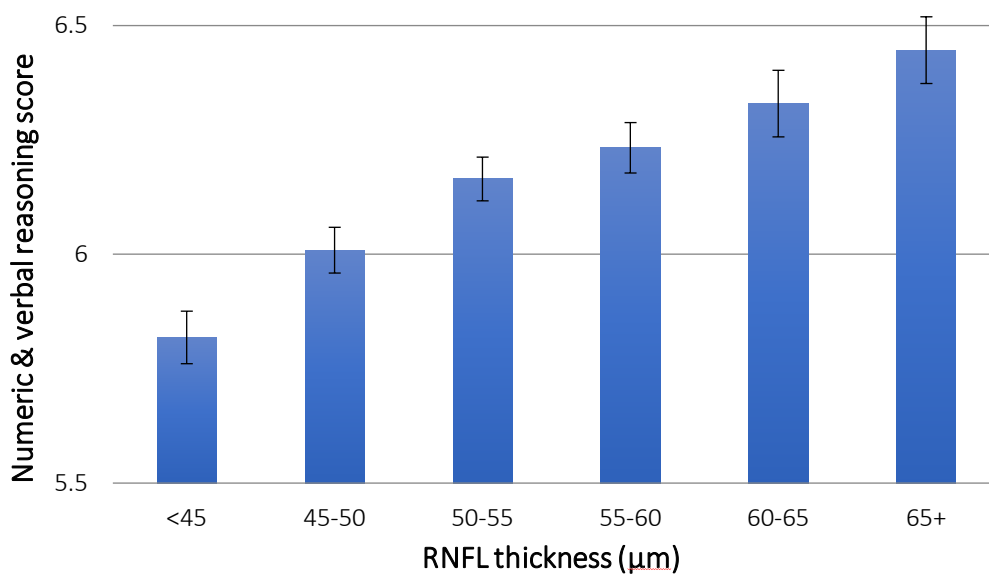
eFigure 2. Prospective memory and retinal nerve fibre layer thickness at baseline. (A greater number of attempts indicate worse performance.) Regression coefficient -0.02 (95% CI -0.02 – -0.01, $p < 0.001$).



eFigure 3. Pairs matching and retinal nerve fibre layer thickness at baseline. (A greater number of incorrect matches indicates worse performance.) Regression coefficient -0.03 (95% CI -0.04 – -0.02, $p < 0.001$).



eFigure 4. Numeric & verbal reasoning and retinal nerve fibre layer thickness at baseline. (Lower score indicates worse performance.) Regression coefficient 0.12 (95% CI 0.11 – 0.14, $p < 0.001$).



eFigure 5. Numeric & verbal reasoning and retinal nerve fibre layer thickness at baseline. (Longer reaction time indicates worse performance.) Regression coefficient -4.47 (95% CI -5.29 – -3.64, $p < 0.001$).

