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Association of Retinal Nerve Fiber Layer Thinning With Current and Future Cognitive Decline
A Study Using Optical Coherence Tomography

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IMPORTANCE Identifing potential screening tests for future cognitive decline is a priority for developing treatments for and the prevention of dementia.

OBJECTIVE To examine the potential of retinal nerve fiber layer (RNFL) thickness measurement in identifying those at greater risk of cognitive decline in a large community cohort of healthy people.

DESIGN, SETTING, AND PARTICIPANTS UK Biobank is a prospective, multicenter, community-based study of UK residents aged 40 to 69 years at enrollment who underwent baseline retinal optical coherence tomography imaging, a physical examination, and a questionnaire. The pilot study phase was conducted from March 2006 to June 2006, and the main cohort underwent examination for baseline measures from April 2007 to October 2010. Four basic cognitive tests were performed at baseline, which were then repeated in a subset of participants approximately 3 years later. We analyzed eyes with high-quality optical coherence tomography images, excluding those with eye disease or vision loss, a history of ocular or neurological disease, or diabetes. We explored associations between RNFL thickness and cognitive function using multivariable logistic regression modeling to control for demographic as well as physiologic and ocular variation.

MAIN OUTCOMES AND MEASURES Odds ratios (ORs) for cognitive performance in the lowest fifth percentile in at least 2 of 4 cognitive tests at baseline, or worsening results on at least 1 cognitive test at follow-up. These analyses were adjusted for age, sex, race/ethnicity, height, refraction, intraocular pressure, education, and socioeconomic status.

RESULTS A total of 32 038 people were included at baseline testing, for whom the mean age was 56.0 years and of whom 17 172 (53.6%) were women. A thinner RNFL was associated with worse cognitive performance on baseline assessment. A multivariable regression controlling for potential confounders showed that those in the thinnest quintile of RNFL were 11% more likely to fail at least 1 cognitive test (95% CI, 2.0%-2.1%; $P = .01$). Follow-up cognitive tests were performed for 1251 participants (3.9%). Participants with an RNFL thickness in the 2 thinnest quintiles were almost twice as likely to have at least 1 test score be worse at follow-up cognitive testing (quintile 1: OR, 1.92; 95% CI, 1.29-2.85; $P < .001$; quintile 2: OR, 2.08; 95% CI, 1.40-3.08; $P < .001$).

CONCLUSIONS AND RELEVANCE A thinner RNFL is associated with worse cognitive function in individuals without a neurodegenerative disease as well as greater likelihood of future cognitive decline. This preclinical observation has implications for future research, prevention, and treatment of dementia.

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Author Audio Interview

Supplemental content

CME Quiz at jamanetwork.com/learning

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Cognitive decline is part of the spectrum of normal aging and is related to lifestyle.[1,2] Accelerated cognitive decline indicates neurodegenerative pathology, which can be captured preclinically with brain imaging techniques and protein biomarkers.[3,4] Brain imaging evidence for onset of neurodegenerative dementia precedes symptomatic, progressive decline by about 15 years.[5]

Dementia is the neurodegenerative condition that is contributing most substantially to the global disease burden, with an estimated prevalence of 45 956 000 patients worldwide.[1] In high-income North America, dementia is ranked top among other neurological diseases for disability-adjusted life-years.[1,2,6] The prevalence of dementia increases with age, affecting 11%, 32%, and 82% of people older than 65, 75, and 85 years respectively.[6] Some projections suggest that, because of population aging, the prevalence of Alzheimer disease (AD), the most common form of dementia, may triple by 2050.[1,6,7] Globally, an estimated 46 million people are living with dementia, a number that is expected to rise to 131 million by 2050.[1] However, if onset can be delayed by just 1 year, the projected global burden would decrease by 9 million.[8] In summary, the preclinical detection of neurodegeneration will be crucial for secondary prevention trials.[5]

A hindrance to the development of new treatments to prevent dementia is the lack of markers that help predict who will be affected.[3,4] One potential screening test is retinal mophometry. The retina is the only part of the central retinal nervous system that can be directly visualized. Optical coherence tomography (OCT)[9] is a rapid, noninvasive imaging tool that can produce 3-dimensional cross-sectional images of the retina and permits precise and accurate measurement of the thickness of individual retinal components.[10] The retinal nerve fiber layer (RNFL) is the inner most layer of the retina and is comprised of the retinal ganglion cell axons, which link the outer neuroretina to the dorsal lateral geniculate nucleus, where synaptic connections lead to the visual cortex.

The RNFL is thinner in people with early AD compared with healthy, age-matched controls.[11] Similar findings have been reported in studies of other neurodegenerative conditions that are associated with cognitive decline, such as Parkinson disease[12] and Lewy body dementia.[13] More recently, studies using OCT imaging have shown that the RNFL is thinner in people with early cognitive impairment.[14-16] With 2 exceptions, studies of retinal structure and cognitive function have been small cross-sectional case series and case-control studies. A cross-sectional association between retinal anatomy and cognitive function has been documented in 2 larger community-based studies.[17,18] Only 1 small, prospective study has shown that a mixed cohort of 78 people with normal or mildly impaired cognition who developed future cognitive decline also showed a greater reduction of RNFL thickness as measured by OCT over 25 months.[19] In this context, we examined the association between RNFL thickness and cognitive function (both concurrent and future) in a large community-based cohort of healthy UK Biobank participants to determine the potential role for RNFL measurements as a screening test for preclinical cognitive decline in people without a neurodegenerative disease at baseline.

Key Points

Question Are changes in the retinal nerve fiber layer (RNFL) associated with current or future cognitive function in a large community cohort of healthy participants?

Findings In this community-based cohort study of more than 500 000 UK residents aged 40 to 69 years who received optical coherence tomography measurements of RNFL thickness and cognitive testing, there was a significant association between RNFL thickness and cognitive function at baseline. Furthermore, those with a thinner RNFL were twice as likely to experience cognitive decline over 3 years.

Meaning A thinner RNFL is associated with worse current cognitive function and may have a role in screening those at risk of future cognitive decline.

Methods

UK Biobank is a community-based cohort of 502 656 UK residents aged 40 to 69 years and registered with the UKNHS. Examinations were conducted between April 2007 and October 2010 at 22 study assessment centers (eMethods in the Supplement). The North West Multicenter Research Ethics Committee approved the study in accordance with the principles of the Declaration of Helsinki (reference No. 06/MRE08/65). The overall study protocol (http://www.ukbiobank.ac.uk/resources/) and protocols for individual tests (http://biobank.ctsu.ox.ac.uk/crystal/docs.cgi) are available online. Written consent was obtained via electronic signature pad. Participants answered a wide-ranging touch screen questionnaire that covered demographic, socioeconomic, and lifestyle information; environmental exposures; and personal as well as family medical history. During 2009 to 2010, additional examination components were added, including eye examinations and cognitive function. Visual acuity, autorefraction/keratometry (Tomey RC5000; Erlangen-Tennenlohe), Goldmann-corrected intraocular pressure (IOP), and cornea-corrected IOP (Ocular Response Analyzer; Reichert) were collected from 110 573 consecutive participants during 2009 to 2010, and retinal OCT measurements were undertaken in 67 321 participants (60.9%). Ophthalmic tests were performed at 6 centers and were distributed across the United Kingdom, including Croydon and Hounslow in greater London, Liverpool and Sheffield in northern England, Birmingham in the Midlands, and Swansea in Wales. All baseline examinations for this study were performed during 2009 to 2010, including ophthalmic measurements and basic cognitive function testing. During 2012 to 2013, repeated cognitive testing was performed in a subset of participants.

The OCT protocol is described in greater detail by Ko et al[20] and Patel et al[21] and is compliant with the APOSTEL guidelines.[22] In brief, high-resolution spectral-domain OCT imaging of undilated eyes was performed in a dark, enclosed room using the Topcon 3D OCT 1000 Mk2 (Topcon Inc), on the same day as other physical measurements. We excluded OCT scans of poor quality according to the OSCAR-IB criteria.[23] In addition to the comorbidities listed as exclusion criteria by the

Table 1. Baseline Characteristics (2009-2010) of All Participants Recruited With Baseline Optical Coherence Tomography (OCT) Results, Those Included in This Study, and Those With Follow-up Assessment (2012-2013)

Characteristic	% (95% CI)		
	Excluded Participants Who Received OCT (N = 35238)	Participants With OCT Results Included in This Study (N = 32 038)	Participants With Follow-up During 2012-2013 (N = 1251)
Age, mean (95% CI), y	57.3 (57.2 to 57.3)	56.0 (55.9 to 56.1)	58.1 (57.7 to 58.5)
Female sex, No. (%) [95% CI]	19460 (54.4) [54.8 to 54.0]	17163 (53.6) [53.0 to 54.1]	639 (51.1) [53.9 to 48.3]
Race/ethnicity, No. (%) [95% CI]			
White	30970 (90.6) [90.4 to 90.8]	29576 (92.7) [92.4 to 92.9]	1232 (98.6) [97.8 to 99.2]
Chinese	192 (4.6) [4.1 to 5.2]	117 (0.4) [0.3 to 0.4]	2 (0.2) [0.0 to 0.6]
Asian/Indian	1462 (3.3) [3.1 to 3.4]	716 (2.2) [2.1 to 2.4]	2 (0.2) [0.0 to 0.6]
Black	1323 (3.2) [3.1 to 3.3]	836 (2.6) [2.4 to 2.8]	3 (0.2) [0.1 to 0.7]
Mixed/Other	972 (2.5) [2.3 to 2.6]	673 (2.1) [2 to 2.3]	10 (0.8) [0.4 to 1.5]
Townsend deprivation index, mean (95% CI)	−1.01 (−1.03 to −0.99)	−1.18 (−1.21 to −1.14)	−2.49 (−2.63 to −2.36)
Education, No. (%) [95% CI]			
College degree	11718 (35.7) [35.3 to 36.0]	11956 (37.6) [37.1 to 38.1]	596 (47.7) [45.0 to 50.5]
Prof qual or A-level	8030 (23.4) [23.1 to 23.7]	7505 (23.6) [23.1 to 24.1]	290 (23.2) [21.0 to 25.6]
GCSE or O-level	7102 (21.1) [20.8 to 21.4]	6891 (21.7) [21.2 to 22.1]	253 (20.3) [18.1 to 22.6]
CSE	1851 (5.6) [5.4 to 5.8]	1857 (5.8) [5.6 to 6.1]	39 (3.1) [2.3 to 4.2]
Lower than CSE	5894 (14.3) [14.0 to 14.6]	3599 (11.3) [11 to 11.7]	71 (5.7) [4.5 to 7.1]
Laterality = right eye	NA	49.6 (49.1 to 50.2)	49.2 (46.4 to 51.9)
Visual acuity, mean (95% CI), logMAR	0.02 (0.02 to 0.03)[a]	−0.04 (−0.04 to −0.04)	−0.05 (−0.06 to −0.04)
Intraocular pressure, mean (95% CI), mm Hg	15.8 (15.8 to 15.8)[a]	15.0 (15.0 to 15.1)	15.2 (15.0 to 15.4)
Refraction, mean (95% CI), D	−0.37 (−0.39 to −0.35)[a]	−0.07 (−0.1 to −0.05)	−0.1 (−0.21 to 0.02)
Height, mean (95% CI), cm	168.7 (168.6 to 168.8)	169.3 (169.2 to 169.4)	170 (169.5 to 170.5)
Men	175.8 (175.7 to 175.9)	176.4 (176.3 to 176.5)	176.7 (176.2 to 177.2)
Women	162.7 (162.6 to 162.8)	163.2 (163.1 to 163.3)	163.5 (163.1 to 164)
Smoker, No.			
No	90.3 (90.1 to 90.5)	90.6 (90.3 to 90.9)	94.6 (93.2 to 95.8)
Occasional	2.9 (2.7 to 3.0)	3.0 (2.8 to 3.2)	1.6 (1.0 to 2.5)
Yes	6.8 (6.6 to 7.0)	6.4 (6.1 to 6.6)	3.8 (2.8 to 5.0)

Abbreviations: A-Level, general certificate of education advanced level (typically taken at age 18 years); CSE, certificate of secondary education (a less demanding exam usually taken at age 16 years); GCSE, general certificate of secondary education (formerly O-Level; typically taken at age 16 years); NA, not applicable; O-Level, general certificate of education ordinary level (typically taken at age 16 years); OCT, optical coherence tomography; Prof qual, professional or vocational qualification (including higher national diploma).

[a] For those excluded, the random selection of right/left eyes was not performed; thus, for the "all participants recruited" category, visual acuity, intraocular pressure, and refraction were calculated for right eyes only.

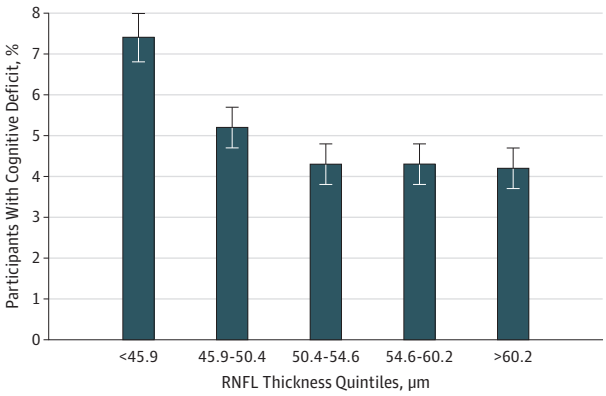
OSCAR-IB criteria, we also excluded patients with a visual acuity that was less than 6 of 7.5, an IOP that was 22 mm Hg or higher or 5 mm Hg or lower, self-reported ocular disorders (eg, recent eye surgery, corneal graft, ocular injury, glaucoma, macular degeneration), self-reported diabetes, or self-reported neurodegenerative disease. Finally, if both eyes of 1 participant were eligible for inclusion in this analysis, 1 eye was chosen at random. We used Stata/SE, version 13.1 (StataCorp) for the analysis. The selection of participants is described in eFigure 1 in the Supplement.

Basic cognitive function was tested using touch screens at UK Biobank Assessment Centre, with baseline assessment conducted during 2009 to 2010 and a repeated assessment (including cognitive function) during 2012 to 2013. These tests included prospective memory, pairs matching, numeric and verbal reasoning, and reaction time. Numeric and verbal reasoning tested the capacity to solve logic problems and reasoning capacity independent of acquired knowledge. Test failure at baseline was defined as an incorrect answer on the first attempt of prospective memory, or doing worse than 95% of participants in pairs matching (>2 incorrect matches), numeric and verbal reasoning tests (score, <3), or reaction time (>770 milliseconds). The repeated assessment of cognitive function was performed during 2012 to 2013. A participant's performance was considered worse on follow-up testing if the number of attempts increased on the prospective memory test, the number of incorrect matches increased on pairs matching, there was a decrease in the numeric and verbal reasoning test scores, or a reaction time slowed by at least 100 milliseconds.

Statistical Analysis

Stata/SE, version 13.1 (StataCorp) was used for the analysis, including the svy suite of commands extension package. Linear regression analyses were first used to test associations between the RNFL and cognitive function, both at baseline (number of tests failed) and on follow-up testing (number of tests with a worse result at follow-up). A logistic regression was then used to determine odds ratios for cognitive deficits and

Figure 1. Proportion of UK Biobank Participants Exhibiting a Cognitive Deficit at Baseline Testing



The cross-sectional data showing the proportion (with 95% CIs) of 32 038 UK Biobank participants with a cognitive deficit (a failing score on 2 or more of 4 tests), according to quintile of retinal nerve fiber layer (RNFL) thickness measured in the outer nasal retinal subfield by optical coherence tomography.

Table 2. Multivariable Logistic Regression Modeling of the Association Between Retinal Nerve Fiber Layer (RNFL) Thickness and Risk of Failing 1 or More Tests (Compared With 0 Tests) at Baseline[a]

RNFL, µm	Odds Ratio (95% CI)	*P* Value
≤45.9	1.11 (1.02-1.21)	.01
45.9-50.4	0.99 (0.90-1.07)	.74
50.4-54.6	1.00 (0.92-1.09)	.96
54.6-60.2	1.02 (0.94-1.11)	.67
≥60.2	1 [Reference]	NA

Abbreviations: NA. not applicable; RNFL, retinal nerve fiber layer.

[a] Controlled for age, sex, height, race/ethnicity, intraocular pressure, socioeconomic deprivation, and education.

the decline for each quintile of RNFL thickness. We further tested to determine whether effects were additive (ie, doing poorly on 0/1/2/3/4 tests at baseline). Multivariable regression modeling was performed to adjust for potential confounders. When appropriate, 2-sided hypothesis testing was performed. The null hypothesis was rejected if $P < .05$ (also an indicator of statistical significance).

Results

Between September 2009 and June 2010, 67 321 people underwent OCT imaging. Of these, 32 038 people (47.6%) had high-quality OCT imaging results, scores for all cognitive tests, reported no neurological or ocular disease, and did not have diabetes (eFigure 1 in the Supplement). Of these, 1251 people (3.9%) with high-quality OCT scans and full additional data at baseline completed follow-up cognitive testing during 2012 to 13. **Table 1** summarizes demographic, morphometric, and ophthalmic variables at baseline (2009-2010) for all participants with an OCT measure, the 32 038 included in this study, and the subset of those who also underwent follow-up assessment during 2012 to 2013. Compared with all participants who were recruited with an OCT measure available, participants in this study were less economically deprived, more highly educated, had a lower refractive error, and were less racially/ethnically diverse. The subset of participants with follow-up data were slightly older, more often white, had higher educational attainment, and included more nonsmokers when compared with the 32 038 who were included at baseline.

The mean (SD) age of the participants included in this study was 56.0 (8.21) years (95% CI 55.9-56.1), with a higher percentage of women (17 172 [53.6%]; 95% CI, 52.0-54.1) than men. The mean (SD) age at the second visit was 58.1 (7.1) years (95% CI, 57.7-58.5), with approximately equal numbers of women (637 [51.1%]) and men (609 [48.9%]). There was a predominance of white participants at both baseline and follow-up (29 576 [92.7%]; 95% CI, 92.4-92.9; and 1232 [98.6%]; 95% CI, 97.8-99.2, respectively). The mean (SD) Townsend deprivation index was −1.18 (2.91) at baseline (95% CI, −1.21 to −1.14; interquartile range, 4.23; more positive scores indicate greater deprivation; UK average, 0). Those included at follow-up were less disadvantaged than the UK average and less so than those at baseline (mean Townsend deprivation index, −2.49; 95% CI, −2.63 to −2.36; interquartile range, 2.62). More than one-third of participants at baseline had a degree and another quarter had a professional qualification or A-levels. Of participants who were undergoing follow-up cognitive testing, almost half (596 [47.7%]; 95% CI, 45.0-50.5) reported having a degree, less than one-quarter had a professional qualification or A-levels (290 [23.2%]; 95% CI, 21.0-25.6) and the remainder had a General Certificate of Secondary Education or lower.

A thinner baseline RNFL measurement was associated with worse performance on baseline cognitive tests (eFigures 2-5 in the Supplement; **Figure 1**). For each cognitive test (prospective memory, pairs matching, numeric and verbal reasoning, and reaction time) there was worse performance for each quintile of people with a thinner RNFL (eFigures 2-5 in the Supplement). Of those in the thinnest RNFL quantile, 475 people (7.4%) (95% CI, 6.8-8.1%) failed at least 2 of 4 cognitive tests (Figure 1) as compared with 267 (4.2%) (95% CI, 3.7%-4.7%) of those in the thickest RNFL quintile ($P < .001$). To quantify the association and account for other potential confounding, a multivariable logistic regression was used to adjust for the associations of age, sex, race/ethnicity, Townsend deprivation index, educational attainment, refractive error, and IOP, and to calculate the odds ratio of a cognitive deficit (**Table 2**). Those in the thinnest RNFL quintile were 11% (95% CI, 2%-21%; $P = .01$) more likely to fail 1 or more cognitive tests (as defined in the Methods previously), compared with those in the thickest quintile (Table 2).

Multivariable regression modeling of association between RNFL thickness and future worsening on 1 or more follow-up cognitive tests was performed, controlling for age, sex, height, race/ethnicity, refraction, IOP, Townsend deprivation index, and education (**Table 3**). Compared with those in the thickest RNFL quintile, those in the 2 thinnest quintiles were almost twice as likely (odds ratio, 1.92; 95% CI, 1.29-2.85; $P < .001$) to score worse on at least 1 cognitive test at follow-up (Table 3). Per quintile of RNFL thinning, there was an 18% increased risk of cognitive decline at

Table 3. Multivariable Logistic Regression Modeling of the Association Between Retinal Nerve Fiber Layer (RNFL) Thickness and Risk of Worsening on 1 or More Follow-up Cognitive Function Tests (Compared With 0 Tests)[a]

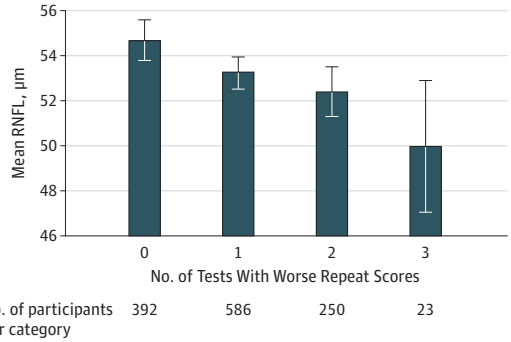
Characteristic	Odds Ratio (95% CI)	*P* Value
RNFL quintile, μm		
≤45.9	1.92 (1.29-2.85)	<.001
45.9-50.4	2.08 (1.40-3.08)	<.001
50.4-54.6	1.48 (1.01-2.18)	.05
54.6-60.2	1.51 (1.05-2.19)	.03
≥60.2	1 [Reference]	NA
RNFL, μm		
Per quintile	1.18 (1.08-1.29)	.001

Abbreviations: NA, not applicable; RNFL, retinal nerve fiber layer.

[a] Controlled for age, sex, height, race/ethnicity, refraction, intraocular pressure, socioeconomic deprivation, and education.

3-year follow-up (95% CI, 8%-29%; $P < .001$; Table 3). Baseline RNFL thickness was compared with the total number of cognitive tests with worse scores on follow-up testing (ie, whether a participant did worse on 0, 1, 2, 3, or 4 tests) (**Figure 2**). A thinner baseline RNFL was significantly associated with a future decline in a greater number of cognitive tests (linear regression, $P < .001$), even after controlling for potential confounders (Figure 2).

Figure 2. Proportion of UK Biobank Participants Exhibiting a Decline in Cognitive Function on Repeat Assessment



The number of cognitive tests with worse scores on follow-up testing was significantly associated with baseline retional nerve fiber layer (RNFL) thickness. The regression coefficient was 1.2 μm per test failed ($P < .001$). After controlling for potential confounders, including age, sex, race/ethnicity, Townsend deprivation index, height, refraction, and intraocular pressure, the regression coefficient was 1.1 μm per test failed ($P < .001$).

Discussion

To our knowledge, this is the largest study of its kind and the first to identify that future decline in cognitive function is associated with a thinner RNFL in a large, healthy community-based cohort. Those in the lowest 2 quintiles of baseline RNFL distribution had twice the likelihood of a developing a decline in cognitive function over a 3-year follow-up interval compared with those in the top RNFL quintile (Table 3). As we expected, we observed a strong, consistent association between a thinner RNFL and poorer cognition in cross-sectional data. Furthermore, there was an incremental relationship between a thinner RNFL and poorer cognition in the longitudinal data (Figure 2). Our findings show that a thinner RNFL is a potential indicator for current impaired cognition and may have a potential role in screening for those at an increased risk of a future decline in cognitive function. These cognitive deficits and declines spanned a range of functional domains.

Strengths and Limitations

An important limitation of this study is that although UK Biobank participants were enrolled from a sampling frame that represented a cross-section of the UK population, the response rate was low. Consequently, the representativeness of the study is limited, as participants were more often white, middle class, and educated. This means that the rates of cognitive impairment identified here will not necessarily be the same as those in the UK population, or of another Western European or North American population. However, we believe that the associations that we have identified are unlikely to be the result of an intrinsic bias in the data, and therefore we feel the overall conclusions are valid for populations of Western European descent.

The number of participants enrolled in UK Biobank required that a balance be struck between detailed, in-depth full clinical testing and the need to complete a cognitive assessment efficiently on hundreds of thousands of participants. Whether the resultant large cognitive data set is strengthened or weakened by this approach is unclear. By using tests that were sensitive to the population range of performance, declines across the population can be detected. This increases the sensitivity of the study to detect changes and its relevance to population-based early disease stage screening. From an etiologic perspective, this study does not attempt to identify specific cognitive domains linked with RNFL thickness. The range of tests available to test the hypothesis include basic mechanisms, such as processing speed (reaction time), and high level functions, such as intelligence (reasoning). As such, they are suitable for investigating an overall association of cognition with the eye. Further work would be required to identify the underlying mechanisms linking RNFL thickness with specific cognitive domains.

Our findings are consistent with those from several previous studies of people with an established disease. Hinton et al[24] described an association between dementia and thinner RNFL. Others have made similar observations in mild, moderate, and severe cognitive impairment in cases series.[13,15,19,25-27] A thinner RNFL has been recorded in Parkinson disease[28] and Lewy body dementia.[13]

Although most of the previous data suggesting an association between RNFL thickness and cognition come from case series, 2 studies have identified a cross-sectional association between thinner RNFL and poorer cognitive function in community-based cohorts—one in a geographically and genetically isolated population in the Netherlands,[17] and the other in the European Prospective Investigation of Cancer (EPIC) Norfolk cohort in the United Kingdom. In the EPIC cohort of 8623 people, a thinner RNFL was associated with poorer scores from cognitive tests that assessed global function, recognition, learning, episodic memory, and premorbid intelligence. While EPIC Norfolk described a similar association as this study, the cross-sectional

associations were of small effect size, with RNFL thickness appearing to be ineffective as a potential screening test for cognitive function.[18] In contrast, the association between baseline RNFL and future cognitive decline in this study is stronger. A possible explanation for this is that the RNFL measurements in EPIC were generated using scanning laser ophthalmoscopy, which is a less precise measure than OCT. Another recent community-based study that assessed a cohort of Chinese people linked poorer cognitive function to thinner subfoveal choroidal thickness.[29] We were not able to assess this parameter in our study because of differences in scanning technology, but it adds weight to the concept that ophthalmic imaging can detect features that are associated with poorer cognitive function.

Of particular interest and relevance are results from a small, prospective study that examined the longitudinal trends in RNFL thickness in a mixed group of 78 people with normal or mildly impaired cognition over a 2-year period in Shanghai, Peoples' Republic of China.[19] Sixty (77%) retained stable cognitive function, while 18 (23%) developed a cognitive decline and then received a diagnosis of mild cognitive impairment (8 [10%]) or AD (10 [13%]). Using retinal OCT to measure RNFL (as we did), they observed a greater reduction of RNFL thickness among those who showed a cognitive decline than the stable participants (mean [SD] reduction, −11.0 [12.8] μm vs −0.4 [15.7] μm; $P = .01$).

In our study, we specifically excluded participants who reported neurological, diabetic, and ocular diseases and included only people with good visual acuity because of the well-recognized association these conditions have with RNFL measurements. Consequently, our results are more representative of a premorbid population, further strengthening the principle of an association between a thin RNFL and cognitive decline. Others have reported that markers of ill health, particularly cardiovascular, are risk factors for future cognitive decline; such risk factors include atrial fibrillation, diabetes, heart failure, intermittent claudication, previous stroke, and frailty markers, such as poor exercise tolerance.[30-32] We chose not to exclude people with these risk factors.

We identified an incremental association between a progressively thinner baseline RNFL and a future decline that spanned different cognitive domains. Gao et al[27] sought to but did not find such a correlation between retinal features and severity of cognitive impairment. One possible explanation is that they used the Mini-Mental State Examination as the index of cognitive impairment; the Mini-Mental State Examination has a strong ceiling effect and is likely to be insensitive to early changes at the upper end of the distribution.[24] The association between baseline RNFL and baseline cognitive scores appears to be curvilinear, showing a threshold effect with a greater deficit shown in RNFL quintiles 1 and 2 (Figure 1). The evidence for a curvilinear association between baseline RNFL and future cognitive decline was less convincing, although the number of observations was smaller by a factor of 30.

Some have argued against a retinal involvement in generalized neurodegenerative disease.[33-37] Van Koolwijk et al[17] proposed that while there may be an association between RNFL thickness and cognitive function, it is not sufficient to explain the variance in cognitive test scores and is not a useful predictor of cognitive ability. The UK Biobank cohort benefits from having numerous participants and consequently has greater statistical power. We recognize that statistical significance is not equivalent to clinical relevance; however, while most previous research has focused on later-stage cognitive impairment and on older participants, our findings suggest the potential of RNFL thickness measurement as a screening test for relatively younger and healthier people. Furthermore, the preponderance of white people of relative socioeconomic prosperity (as demonstrated by the favorable mean Townsend deprivation index [Tables 1 and 3]) suggests that our results are even more applicable to a low-risk group and provide a conservative estimate of the association. More recently, preclinical and translational data revealed that in at least one of the neurodegenerative dementias—frontotemporal dementia caused by progranulin haploinsufficiency—retinal layer changes are associated with a demonstrable pathological substrate.[38] Nevertheless, in response to Van Koolwijk et al,[17] it would be unlikely for any screening test to be used in isolation. Our study strengthens the argument of an association between neurodegenerative processes that affect the brain and the eye and indicates that OCT measurement of the RNFL is a potential noninvasive, relatively low-cost and time-efficient screening test for early cognitive changes.

There is strong evidence that a thinner RNFL is associated with adverse cognitive function. Our data also suggest that RNFL thinning precedes cognitive decline in many people and predicts cognitive deterioration. The wide availability of OCT technology in ophthalmic and optometric practices may accelerate the general uptake of this potential screening test. However, one must be careful in its interpretation so as to avoid an unnecessary psychological burden for people who may not ultimately experience cognitive decline. Further, attempting to risk-stratify people would be most appropriate if there is a viable treatment or preventative measure available. Additional research is required to define a possible role for these observations in health policies and to determine the relevance at an individual level. It is unclear whether RNFL thinning continues as cognitive decline occurs or whether it is a precursor to cognitive deterioration. While UK Biobank did perform follow-up OCT testing, later retinal measures were not available for analysis. Future research may focus on the association between longitudinal RNFL changes and cognitive function. It may be that RNFL imaging is more useful for certain demographic, racial/ethnic, or medical subgroups. We believe that it is plausible that a thinner RNFL is a marker of a currently ill-defined clinical syndrome, which includes cognitive decline.

Conclusions

The finding that a thinner RNFL is associated with significant future cognitive decline in a large cohort of people aged 40 to 69 years, drawn from communities around the United Kingdom, consolidates the case for regarding retinal anatomical measures as a useful potential screening test for identifying those at risk of future cognitive loss. However, macular retinal measures are now being promoted as a tool for diagnosis and monitoring glaucoma, with measurements focused on the

ganglion cell complex (ganglion cell complex = RNFL + the ganglion cell layer and inner plexiform layer).[39] The parallels between glaucoma and cognitive decline therefore suggest that the ganglion cell layer and the inner plexiform layer would be useful targets for a similar analysis. The potential for OCT measurement of retinal layers as a predictor of cognitive decline is particularly attractive because it is rapid, noninvasive, and widely available, with high potential for uptake.

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