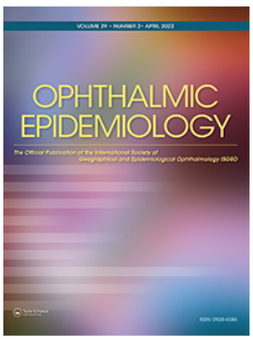

Ophthalmic Epidemiology

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/iope20

Optic Nerve Parameters and Cognitive Function in the Northern Finland Birth Cohort Eye Study

Joel Pitkänen, Juha Veijola, Jennifer Barnett, Johanna Liinamaa & Ville Saarela

To cite this article: Joel Pitkänen, Juha Veijola, Jennifer Barnett, Johanna Liinamaa & Ville Saarela (2022) Optic Nerve Parameters and Cognitive Function in the Northern Finland Birth Cohort Eye Study, Ophthalmic Epidemiology, 29:2, 189-197, DOI: 10.1080/09286586.2021.1910317

To link to this article: https://doi.org/10.1080/09286586.2021.1910317

OPHTHALMIC EPIDEMIOLOGY
2022, VOL. 29, NO. 2, 189–197
https://doi.org/10.1080/09286586.2021.1910317

Taylor & Francis
Taylor & Francis Group

ARTICLE

Optic Nerve Parameters and Cognitive Function in the Northern Finland Birth Cohort Eye Study

Joel Pitkänen [a], Juha Veijola [b], Jennifer Barnett [c], Johanna Liinamaa [a], and Ville Saarela [a]

[a]Department of Ophthalmology, PEDEGO Research Unit and Medical Research Center, University of Oulu and Oulu University Hospital, Oulu, Finland; [b]Department of Psychiatry, Research Unit of Clinical Neuroscience and Medical Research Center, University of Oulu and Oulu University Hospital, Finland; [c]Department of Psychiatry, University of Cambridge, Cambridge Cognition Ltd, Cambridge, UK

ABSTRACT

Purpose: The optic nerve head (ONH) is a part of the brain that can be easily studied through the transparent medium of the eye. We explored the relationship between the properties of the optic nerve head, the retinal nerve fiber layer (RNFL) and cognitive function.

Methods: Participants of the Northern Finland Birth Cohort (NFBC) 1966 underwent an ophthalmic and cognitive assessment after randomization at age 46. The ophthalmological parameters obtained were the disc area and the neuroretinal rim volume of the ONH and the average RNFL thickness. The surrogates used for cognitive function were the paired associates learning test (PAL), level of education, grade point average (GPA) and Humphrey 24–2 perimetric test time (HFA). We did exploratory research between the ophthalmological parameters and the surrogates for cognition and the correlations between the surrogates for cognition.

Results: We found that a larger disc area was associated with a higher level of education, faster accomplishment of the HFA (R = −0.065) but a lower GPA (R = −0.084). An increase in neuroretinal rim volume was associated with fewer errors in the PAL test (R = −0.056), higher level of education, higher GPA (R = 0.072) and faster accomplishment of the HFA (R = −0.047). A thicker RNFL was associated with faster accomplishment of the HFA (R = −0.047).

Conclusion: We were able to find statistically significant associations between the parameters of the optic nerve head, the RNFL and cognition in the NFBC Eye study. However, the correlations were negligible at best and of limited predictive value.

ARTICLE HISTORY
Received 5 December 2020
Revised 14 March 2021
Accepted 25 March 2021

KEYWORDS
Optic nerve head; cognition; retinal nerve fiber layer; imaging; cohort study

Introduction

Cognition refers to the ability to process external or internal stimuli, to establish the relevant from the irrelevant from these stimuli and to generate appropriate responses as well as aspects of storing of the processed information.[1] The process takes place in the central nervous system (CNS).[1] The optic nerve and the forebrain both develop from the same embryonic origin and retinal neurons share anatomical, molecular and pathological similarities with neurons of the cerebrum.[2,3] The optic nerve head (ONH) is the only part of the CNS that can be studied directly as it can be viewed through the transparent medium of the eye. The retinal nerve fibre layer (RNFL) represents the unfolding of the fibres of the optic nerve.[4] Thus, it can be theorized that by examining the properties or pathological changes occurring in the optic nerve, it may be possible to reveal certain attributes or pathological findings of the brain.

Many of the published studies evaluating ocular findings in neurodegenerative diseases or cognitive decline have reported conflicting results. In fact, most of the studies have focussed on elderly populations.[2,5] Some studies have concentrated on the correlation between cognition and properties of the optic nerve or the RNFL: In their unselected study population aged 46 to 67 years, Jonas et al. reported that the size of the optic nerve head was associated with the level of education and the perimetric test time.[6] Another study postulated that the thickness of the RNFL correlated with better scores in cognitive function tests in their cohort population aged 40 to 79 years.[7]

Less is known about whether there is a correlation between cognitive function and the optic nerve or the RNFL parameters before neurodegeneration has taken place or the optic nerve has been affected by pathological changes. There are several different tests used to measure cognitive capabilities but little research has been done on the correlation between the tests themselves.

The properties of the optic nerve can be assessed by measuring the size of the optic disc, the volume of the neuroretinal rim and the thickness of the RNFL. The size of the optic disc is an anatomical measurement of the

CONTACT Joel Pitkänen joel.pitkanen@student.oulu.fi Department of Ophthalmology, 90029 Oulu University Hospital, Finland.

optic nerve whereas the neuroretinal rim constitutes the functioning part of the second cranial nerve. The neuroretinal rim is formed by the RNFL which accumulates at the edge of the ONH to continue forward via the optic nerve. The purpose of this study is to explore possible associations between cognitive function and the neural parameters of the eye in an unselected middle-aged birth cohort.

Materials and methods

The Northern Finland Birth Cohort 1966 eye study

The Northern Finland Birth Cohort 1966 (NFBC) consists of subjects born in the two most northern provinces of Finland in the year 1966. It is an unselected and geographically defined population of Caucasian ancestry. Data on the cohort has been prospectively collected throughout the years.[8] The original NFBC study population consisted of 12058 subjects. In 2012, when the cohort was 46 years old, the 10300 subjects living in Finland were sent a questionnaire and an invitation to an extensive clinical examination of overall health. The NFBC eye study is a randomized prospective cohort study investigating the ocular health of the NFBC. Half of the cohort (n = 5155) was randomized to the eye screening group. Randomization was based on gender, postcode and birth month. Randomization was performed using Resampling Stats Software (Resampling Stats Inc., Arlington, Virginia, USA).[9] Altogether, 3070 randomized subjects took part in the eye examination protocol. The study was conducted following the principles of the Declaration of Helsinki and was approved by the Ethical Committee of Northern Ostrobothnia Hospital District.

Ophthalmological assessments

The eye examination protocol has been published previously in detail.[9] There was a particular interest in the evaluation of glaucomatous damage. Therefore, the protocol included an assessment of the ONH and RNFL. The ONH parameters evaluated in this analysis include the disc area and the rim volume. The parameters were obtained using the Heidelberg Retinal Tomograph (HRT3, Heidelberg Engineering, Heidelberg, Germany; software version 3.1.2a, Heyex 1.6.2.0).

Spectral domain optical coherence tomography (OCT) (Cirrus HD-OCT 4000, software version 6.0.0, Carl Zeiss Meditec) was used to evaluate the RNFL. The device measures the optical interference between a signal from the retina and a reference signal and produces a cross-section image of the retina. The overall average of RNFL thickness was chosen for the analyses in this study.

Assessment of cognitive function

Cognition refers to a range of mental processes relating to acquisition, storage, manipulation and retrieval of information. We applied several surrogates for cognitive function: paired associates learning test (PAL), the level of education, the grade point average (GPA) in the 8th grade and the time it took the participant to complete a standardized automated perimetry test (Humphrey field analyzer, HFA).

The PAL test has been shown to predict conversion from mild cognitive decline to dementia and predict a cognitive decline.[10,11] It assesses episodic memory and new learning. The test comprises colored boxes shown on a touch screen. One or more of the boxes reveal a pattern after which the pattern(s) are displayed one by one and the participant must choose the box that originally revealed that pattern. The test involves eight stages with increasing difficulties. The total numbers of errors made, adjusted for the number of stages completed, was the parameter used in the study.

The HFA 24–2 is a standardized automated perimetry test of the central 24 degrees visual field.[12] The SITA Standard algorithm of Humphrey field analyzer II–i (HFA) (Humphrey Instruments, San Leandro, California) was used. The task is a relatively simple one and involves visual perception and the psychomotor speed of simple cognitive processing. In subjects with normal visual fields, the faster the subject reacts to the isopter, the more quickly the test is completed. The HFA test time has previously been used as a surrogate for cognition.[6]

The present level of education of the study subjects was acquired from the questionnaire. It was divided into four categories: no vocational education, vocational course or vocational education, post-secondary education or degree from university of applied sciences, master's degree from a university.

The GPA of the theoretical school subjects in the 8th grade of comprehensive school was obtained from a questionnaire which had been sent to the participants when they were 14 years of age as a part of an earlier data collection. In the Finnish comprehensive school system, the grading scale is between four and ten, with four being the lowest and 10 the highest grade.

Statistical analysis

Statistical analysis was performed using IBM SPSS Software version 25. Left eye of each participant was

chosen for the analysis. Pearson's correlation coefficient was used to study the correlation between the parameters of the optic disc, the average thickness of the RNFL and the GPA. The assumptions for Pearson's correlation coefficient were confirmed by graphical analysis. Spearman's correlation coefficient was calculated to examine the correlation between the ONH parameters, the average RNFL thickness, the total errors in the PAL test and the duration of the HFA. Spearman's correlation coefficient was also used to evaluate the correlation between the GPA, the total errors and the duration of the HFA. Spearman's correlation coefficient was used instead of Pearson's correlation coefficient because of the outliers in the data and the deviation from the normal distribution of the total errors in the PAL and the duration of the HFA.

Analysis of variance (ANOVA) was used to study the correlation between the ONH parameters, the average RNFL thickness and the level of education. ANOVA was also conducted to investigate the relationship between the total errors, the GPA and the duration of Humphrey visual field test with the level of education. Unpaired t-test was used to determine the difference between genders when comparing the ONH parameters, the average thickness of RNFL, the total errors in the PAL test, the GPA and the duration of HFA. The difference between the level of education between genders was tested using the Chi-Square test of independence.

Results

The number of study subjects in this study was 3068. Level of education was acquired from 2585 and PAL test was performed by 2484 participants. The best result was 0 and the worst was 116 errors and the mean number of errors was 13. HFA test was performed by 3041 participants and the test time varied from 3 minute 40 seconds to 13 minutes 34 seconds, the mean being 4 minutes 45 seconds. The GPA was available from 2670 participants. The lowest GPA was 5.0 and the highest 9.9, the mean being 7.7. The ONH disc area and rim volume were measured from 2970 study subjects. The disc area varied from 0.74 mm2 to 4.35 mm2, the mean being 2.19 mm2. The rim volume varied from 0.01 mm^3 to 1.96 mm^3, the mean being 0.47 mm^3. The average RNFL thickness was measured from 2960 study subjects and it varied from 20.0 μm to 141 μm, the mean being 90.4 μm (Table 1).

Table 1. Study variables.

	N	Minimum	Maximum	Mean	Std. Deviation
Participants	3068				
Level of education	2585	1	4		
Total errors in PAL test	2484	0	116	12.88	11.593
Disc area [mm2]	2970	0.74	4.35	2.19	0.47
Rim volume [mm^3]	2970	0.01	1.96	0.47	0.17
Average RNFL thickness	2960	20.00	141.00	90.42	9.45
HFA test time [mm:ss]	3041	0:03:40	0:13:34	0:04:45	0:00:39
School grade point average	2670	5.0	9.9	7.74	0.96

Level of education: 1, no vocational education; 2, vocational courses or vocational education; 3, post-secondary education or degree from University of Applied Sciences; 4, master's degree; PAL, paired associates learning test; RNFL, retinal nerve fiber layer; HFA, Humphrey field analyzer.

The optic disc parameters and cognitive function parameters

Although the correlations between the participants' disc area and the level of education, the GPA and the duration of the HFA were found to be statistically significant, the actual correlation coefficients were low. No statistical significance was found between the disc area and the total errors in the PAL test. The statistically significant correlations were found to be negative meaning that the larger the disc area, the faster the HFA was completed and the lower was the GPA. (Figure 1, Table 2)

A statistically significant correlation was found between the volume of the neuroretinal rim, the total errors in the PAL test, the level of education and the duration of the HFA. The correlation coefficients were low and negative indicating that the larger the rim volume, the faster the HFA was completed and the fewer errors were made in the PAL test. A statistically significant positive correlation was found between the volume of the neuroretinal rim and the GPA indicating that the GPA was higher when the neuroretinal rim volume was larger.(Figure 1, Table 2).

The same analyses were conducted for men and women separately. In women, the rim volume and in men, the disc area displayed a significant correlation with the duration of the HFA. The correlations were negative and stronger than when tested in the entire study population. The women's rim volume had a significant correlation with the level of education. The disc areas in both genders and the rim volume in men had a significant correlation with the GPA. The remaining optic disc parameters did not exhibit any significant correlations with the surrogates for cognition when tested separately between genders (Table 2).

The average RNFL thickness and the cognitive function parameters

The average RNFL thickness displayed a statistically significant correlation with the duration of the HFA. This was also found in men, but not in women when tested

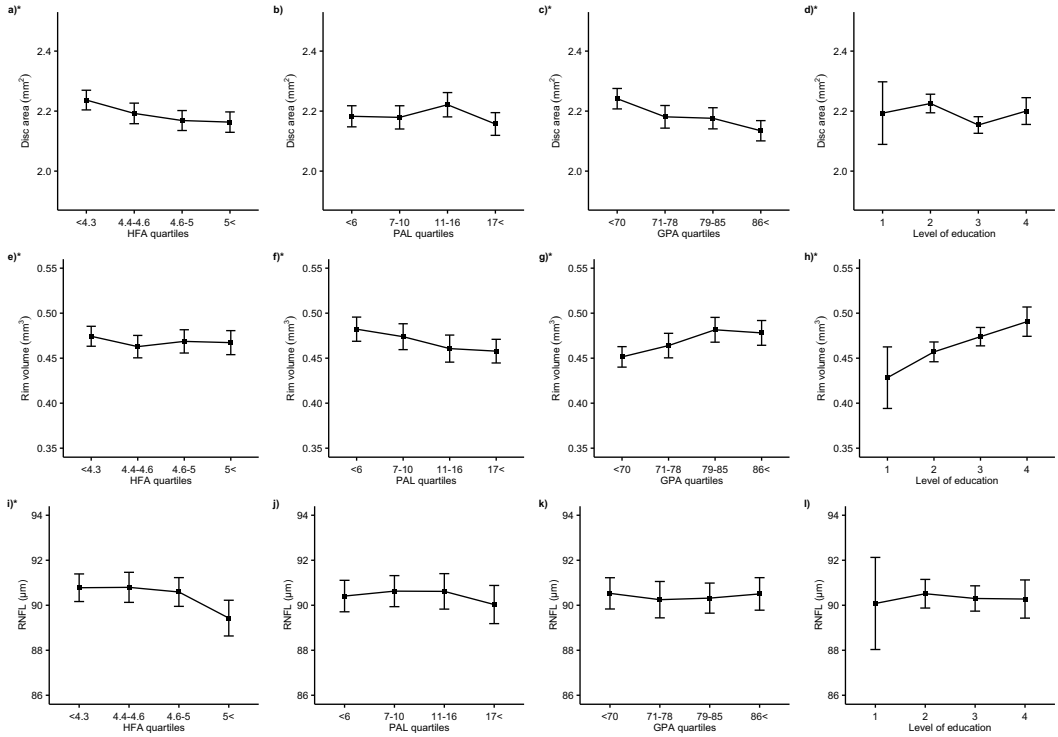

Figure 1. The means and 95% confidence intervals of the optic nerve head parameters and retinal nerve fiber layer in correlation to the level of education and the quartiles of surrogates for cognition. Statistically significant correlations are indicated by asterisk (*).HFA, Humphrey field analyzer; PAL, paired associates learning test; Level of education: 1, no vocational education; 2, vocational course or vocational education; 3, post-secondary education or degree from university of applied sciences; 4, master's degree.

Table 2. Correlation between properties of ONH and surrogates for cognition.

	HFA test time	Total errors in PAL test	Gradepoint average
Disc area [mm2]			
All subjects (N = 2970)	p < .001, R = −0.065	p = .932, R = −0.002	p < .001, R = −0.084
Men (N = 1334)	p = .001, R = −0.093	p = .298, R = −0.033	p = .012, R = −0.073
Women (N = 1636)	p = .181, R = −0.033	p = .673, R = 0.011	p = .001, R = −0.085
Rim volume [mm^3]			
All subjects (N = 2970)	p = .011, R = −0.047	p = .006, R = −0.056	p < .001, R = 0.072
Men (N = 1334)	p = .283, R = −0.030	p = .303, R = −0.032	p = .004, R = 0.082
Women (N = 1636)	p = .001, R = −0.085	p = .074, R = −0.048	p = .331, R = 0.025
Avg. thickness of the RNFL [µm]			
All subjects (N = 2943)	p = .012, R = −0.047	p = .845, R = −0.004	p = .936, R = 0.002
Men (N = 1330)	p = .015, R = −0.067	p = .613, R = 0.016	p = .351, R = −0.027
Women (N = 1613)	p = .153, R = −0.036	p = .688, R = −0.011	p = .624, R = 0.013

ONH, optic nerve head; HFA, Humphrey field analyzer; PAL, paired associates learning test.

separately for genders. The correlations were found to be negative, meaning that the thicker the RNFL, the more quickly the HFA was accomplished. No statistically significant correlation was found between the average RNFL thickness and the total errors in the PAL test, the level of education or the GPA and the same results applied when tested separately for men and women. (Figure 1, Table 2)

Correlation between the cognitive function parameters

The correlation between the total errors in the PAL test and the level of education was statistically significant (N = 2324, $p < .001$) as was the correlation between the total errors in the PAL test and the duration of the HFA (N = 2465 $p < .001$, R = 0.080). There was a statistically significant correlation between the duration of the HFA and the level of education (N = 2566, $p < .001$). The correlation coefficients indicated that the longer it took for the participant to complete the HFA, the more total errors in the PAL test were produced. Faster completion of the HFA correlated to higher education level not including people with no vocational education. It was also found that those study subjects with a master's degree made fewer errors in the PAL test than their counterparts with lower levels of education. There was a statistically significant negative correlation between

the GPA and the total errors in the PAL test (N = 4478, $p < .001$) meaning that the study participants' who had a higher GPA made fewer errors in the PAL test. A statistically significant positive correlation was found between the GPA and the level of education. This implies that participants with a higher GPA had a higher level of education, except in the comparison of the participants with no vocational education to participants with vocational courses or vocational education. (Figure 2)

Difference between genders

A statistically significant difference was found between men and women with respect to the rim volume, the average RNFL thickness, the total errors in the PAL test, the GPA, the duration of the HFA and the distribution in the level of education. Men had larger disc areas, but the difference was not statistically significant. Men had less rim volume and their average RNFL thickness was thinner. Men had a lower GPA. Men completed the HFA faster but made more errors in the PAL test and had a lower level of education than women (Figure 3, Table 3).

Discussion

Cognition is a complex and multifactorial entity that refers to mental processes relating to the acquisition, storage, manipulation and retrieval of information. In the present study, the subjects were tested for psychomotor speed (HFA), short-term memory (PAL), long-term memory, linguistic and mathematical cognitive function (GPA and level of education). The biological theory for the correlation between cognition and ocular findings is based on the embryological, anatomical and immunological similarities between the optic nerve and the brain.[2] The retina is not a simple receiver of information; it also processes and packages information before it is transmitted to the brain via the optic nerve. It has been shown that children born with early acquired brain lesions of septo-optic dysplasia have a reduced size of an optic disc area.[13] In our study, the subjects were of working age, hence our study differs from many previous investigations which have focused on searching for ocular findings that might correlate with or even predict neurodegeneration.[14,15]

In the present study, all cognitive function parameters were statistically significantly correlated. It has been previously reported that the level of education is associated with a shorter duration to complete the perimetric test.[6] The clinical examination of the present study did not include verbal testing, but linguistic cognitive function may be reflected in the educational parameters. There is extensive variation in testing for cognitive function even in different studies regarding the correlation to ophthalmological neuro-anatomy.[6,7,14,16,17]

By exploring the data of the NFBC Eye Study we were able to find statistically significant correlations between the ONH parameters and surrogates for cognition: A higher education level and a faster HFA were associated with larger disc areas. These same correlations have been reported in the Beijing Eye Study.[6] Contrary to these results a larger disc area correlated to a lower GPA in the present study. This would suggest that disc area does not show consistent correlation to cognitive function parameters. Larger neuroretinal rim volume was correlated to higher GPA, faster HFA completion and fewer errors in the PAL test. However, the correlation coefficients were very low. The average thickness of the RNFL correlated negatively with the duration of the HFA test meaning that participants with thicker retinal nerve fiber layers completed the HFA test faster. No statistically significant correlation was found with the other surrogates for cognition. A population-based study found that HRT-derived RNFL measures correlated with poor performance in cognitive tests.[7] It has been reported that there is a strong correlation between RNFL thickness measured with scanning laser polarimetry and cognitive function in younger age groups, but the correlation diminishes after 40 years of age.[16] An increased RNFL thickness was related to decreased cognitive function in a birth cohort examined at the age of 72.[14] A study of twins between 18 and 89 years of age concluded that the correlation between RNFL thickness and cognition was largely explained by genetic factors.[17]

Although statistically significant results were found the actual correlation coefficients were negligible at best. An ophthalmological parameter (ONH size) explained only up to 0.9% (R^2) of the variability in a cognitive test (HFA duration). The lack of correlation may be due to to the multifactorial nature of both ophthalmological neuroanatomy and cognitive development.

We investigated differences between genders and found that men had larger ONH, but smaller rim volumes and thinner average RNFL thicknesses. Women completed the HFA slower but made fewer errors in the PAL test. The women also had a higher school GPA and a higher education level. These results are somewhat contrary to the Beijing Eye Study where women were reported to have lower educational levels and larger optic disc areas.[6]

Finland is a country with a fairly low hierarchy and a high level of social mobility. The subjects of the 1966 birth cohort have received their education in the Finnish comprehensive school system which

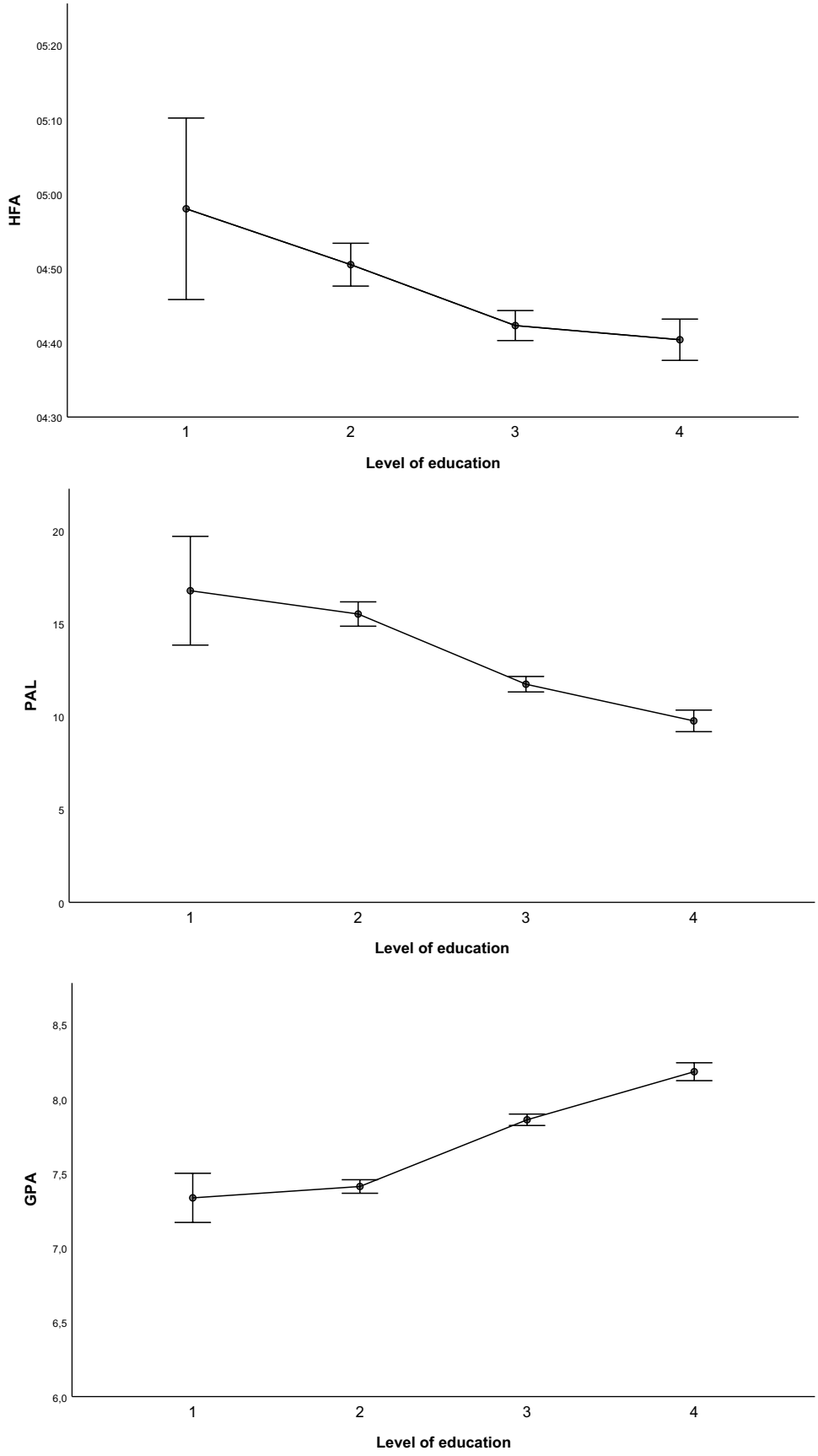

Figure 2. Boxplots of the different surrogates of cognition (number of errors in the PAL test, HFA duration and school grade point average) and the level of education; HFA, Humphrey field analyzer; PAL, paired associates learning test; Level of education: 1, no vocational education; 2, vocational course or vocational education; 3, post-secondary education or degree from university of applied sciences; 4, master's degree.

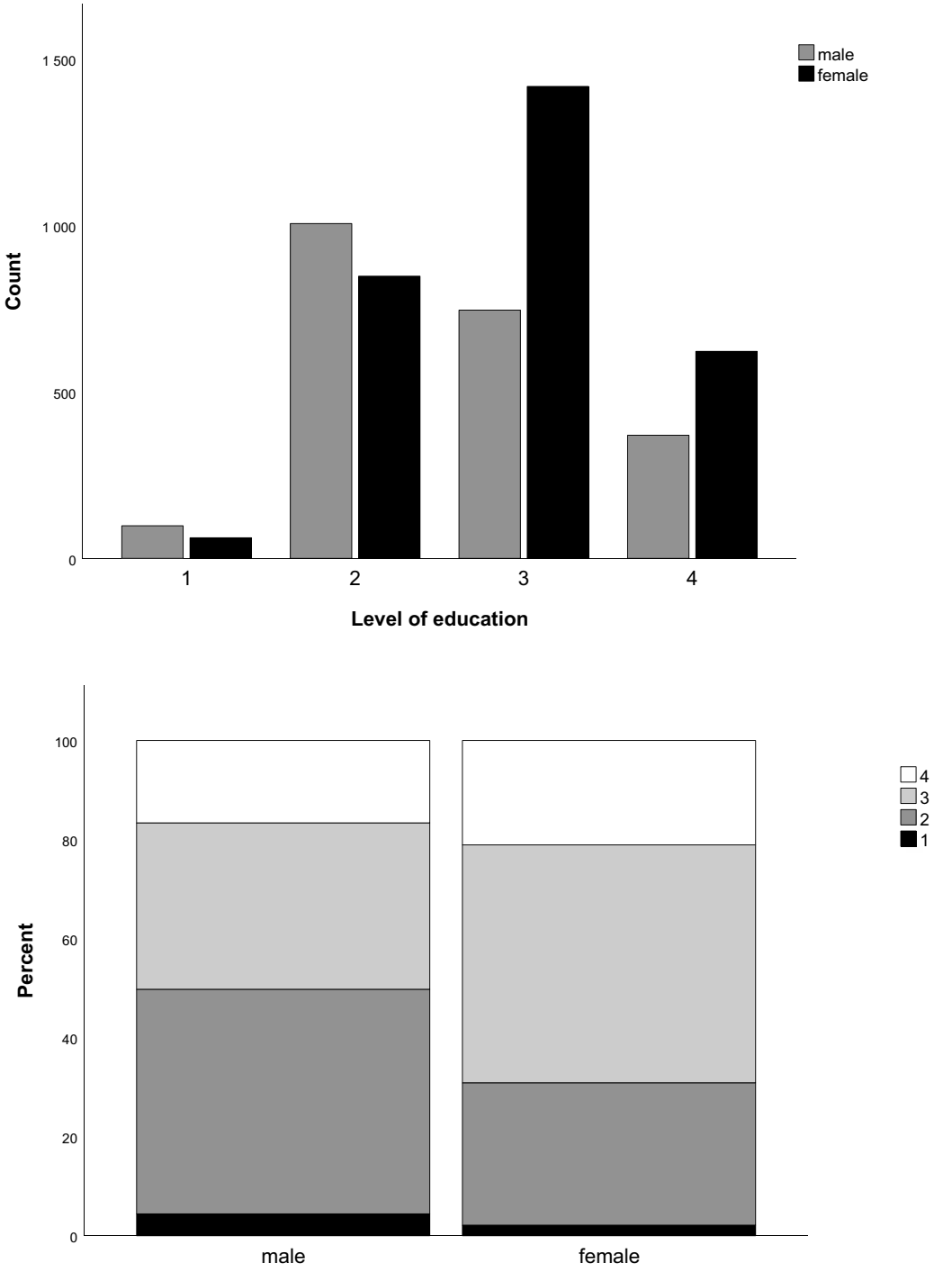

Figure 3. The proportional and absolute distribution in the level of education. 1, no vocational education; 2, vocational course or vocational education; 3, post-secondary education or degree from university of applied sciences; 4, master's degree.

guarantees equal primary education for nine years; this schooling system was adopted in the early 1970s starting from Northern Finland. Comprehensive schooling has further increased the equalization of opportunities and improved social mobility.[18] The achievements of Finnish comprehensive school have been reflected in the results of the Program of International Student Assessment (PISA).[19]

The strength of our study is the birth cohort i.e. because the participants had the same year and area of birth, the subjects have had relatively similar educational opportunities.[18,19] For this reason, the level of education in our study may be considered as a fairly accurate surrogate for long-term cognitive function. The longitudinal prospective birth cohort data allow the use of school GPA data to be

Table 3. Comparison of disc parameters, RNFL and surrogates for cognition between genders.

	Male		Female		Significance
	Mean	N	Mean	N	
Duration of the HFA [mm: ss]	04:44	1367	04:53	1674	<0.001
Total errors in the PAL test	14.31	1049	11.83	1435	<0.001
Grade point average	7.55	2470	7.9	3050	<0.001
Disc area [mm2]	2.21	1334	2.17	1640	0.100
Rim volume [mm^3]	0.44	1334	0.49	1640	<0.001
Average thickness of the RNFL	90.43	1346	91.10	1628	0.042

RNFL, retinal nerve fiber layer; HFA, Humphrey field analyzer; PAL, paired associates learning test

combined with other surrogates that measure different aspects of cognition. The subjects were in their late 40s at the time of the eye examinations. The age may be considered optimal in the light of the study parameters. The majority of the cohort had completed their education but were examined before the onset of the common age-related neurodegenerative and ophthalmological disorders. A recent report found no statistically significant association between cognitive function and age-related macular degeneration, open-angle glaucoma, diabetic retinopathy or cataract.[20] However, these conditions may confound the correlation between ophthalmological and cognitive parameters particularly in an elderly population.

The response rate to the clinical examination and the questionnaire may be considered as a limitation of the study. However, a response rate of 60%, as obtained in the present study, is considered relatively high in a population-based cohort, especially as the same subjects have been examined repeatedly over decades.

In summary, in this relatively large population-based study in an unselected middle-aged population, there was merely negligible correlation at best between ONH and RNFL parameters and cognitive function. An ophthalmological parameter explained only up to 0.9% of the variability in a cognitive test.

Financial support

This study was supported by the Silmäsäätiö Foundation under Grant 20160006; the Suomen Silmälääkäriyhdistys; the Glaukooma Tukisäätiö Lux Foundation.

Conflict of interest: None of the following authors have any proprietary interests or conflicts of interest related to this submission.

Funding

This work was supported by the Suomen silmälääkäriyhdistys; Glaukoomatukisäätiö Lux; Silmäsäätiö [20160006].

ORCID

Joel Pitkänen http://orcid.org/0000-0003-1182-7954
Juha Veijola http://orcid.org/0000-0002-4139-9981
Jennifer Barnett http://orcid.org/0000-0002-4851-5949
Johanna Liinamaa http://orcid.org/0000-0003-3424-7207
Ville Saarela http://orcid.org/0000-0003-3189-7626

References

1. Kandel ER, Schwartz JH, Jessel TM, Siegelbaum SA, Hudspeth AJ. *Principles of Neural Science*. 5th. New York: McGraw-Hill; 2013.
2. London A, Benhar I, Schwartz M. The retina as a window to the brain - From eye research to CNS disorders. *Nat Rev Neurol*. 2013;9(1):44–53. doi:10.1038/nrneurol.2012.227.
3. Bowling B. *Kanski's Clinical Ophthalmology*. 8th ed. Amsterdam: Elsevier Inc.; 2016.
4. Rakic P, Riley KP. Overproduction and elimination of retinal axons in the fetal rhesus monkey. *Science*. 1983;219(4591):1441–1444. doi:10.1126/science.6828871.
5. Lee MJ, Abraham AG, Swenor BK, Sharrett AR, Ramulu PY. Application of optical coherence tomography in the detection and classification of cognitive decline. *J Curr Glaucoma Pract*. 2018;12(1):10–18. doi:10.5005/jp-journals-10028-1238.
6. Jonas JB, Wang YX, Li JJ, Xu L. Optic nerve head size and cognitive function. *Acta Ophthalmol*. 2013;91(1):83–84. doi:10.1111/j.1755-3768.2012.02417.x.
7. Khawaja AP, Chan MPY, Yip JLY, et al. Retinal nerve fiber layer measures and cognitive function in the EPIC-Norfolk cohort study. *Investig Ophthalmol Vis Sci*. 2016;57(4):1921–1926. doi:10.1167/iovs.16-19067.
8. Rantakallio P. The longitudinal study of the northern Finland birth cohort of 1966. *Paediatr Perinat Epidemiol*. 1988;2(1):59–88. doi:10.1111/j.1365-3016.1988.tb00180.x.
9. Saarela V, Karvonen E, Stoor K. et al. The Northern Finland Birth Cohort eye study: design and baseline characteristics. *BMC Ophthalmol*. 2013;13:1. doi:10.1186/1471-2415-13-51.
10. Fowler KS, Saling MM, Conway EL, Semple JM, Louis WJ. Computerized neuropsychological tests in the early detection of dementia: prospective findings. *J Int Neuropsychol Soc*. 1997;3(2):139–146. http://www.ncbi.nlm.nih.gov/pubmed/9126855 Accessed September 14, 2019
11. De Jager C, Blackwell AD, Budge MM, Sahakian BJ. Predicting cognitive decline in healthy older adults. *Am J Geriatr Psychiatry*. 2005;13(8):735–740. doi:10.1097/00019442-200508000-00014.
12. Bengtsson B, Olsson J, Heijl A, Rootzén H. A new generation of algorithms for computerized threshold perimetry, SITA. *Acta Ophthalmol Scand*. 1997;75(4):368–375. doi:10.1111/j.1600-0420.1997.tb00392.x.
13. Hellström A. Optic nerve morphology may reveal adverse events during prenatal and perinatal life-digital image analysis. *Surv Ophthalmol*.

1999;44((2 SUPPL):1. doi:10.1016/S0039-6257(99)00067-3.
14. Laude A, Lascaratos G, Henderson RD, Starr JM, Deary IJ, Dhillon B. Retinal nerve fiber layer thickness and cognitive ability in older people: the Lothian Birth Cohort 1936 study. *BMC Ophthalmol*. 2013;13(1):1. doi:10.1186/1471-2415-13-28.
15. Knoll B, Simonett J, Volpe NJ, et al. Retinal nerve fiber layer thickness in amnestic mild cognitive impairment: case-control study and meta-analysis. *Alzheimer's Dement Diagnosis, Assess Dis Monit* 2016;4:85–93. DOI:10.1016/j.dadm.2016.07.004
16. Lme VK, Despriet DDG, Van Duijn CM, et al. Association of cognitive functioning with retinal nerve fiber layer thickness. *Invest Ophthalmol Vis Sci*. 2009;50(10):4576–4580.doi:10.1167/iovs.08-3181.
17. Jones-Odeh E, Yonova-Doing E, Bloch E, Williams KM, Steves CJ, Hammond CJ. The correlation between cognitive performance and retinal nerve fibre layer thickness is largely explained by genetic factors. *Sci Rep*. 2016;6:(September):1–8. doi:10.1038/srep34116
18. Pekkarinen T, Uusitalo R, Kerr S. School tracking and intergenerational income mobility: evidence from the Finnish comprehensive school reform. *J Public Econ*. 2009;93(7–8):965–973. doi:10.1016/j.jpubeco.2009.04.006.
19. OECD. Programme for International Student Assessment. Reading, mathematical and scientific literacy 2015. Result in focus. 2015:2–5. https://www.oecd.org/pisa/pisa-2015-results-in-focus.pdf
20. Jonas JB, Wei W Bin, Zhu LP, Xu L, Wang YX. Cognitive Function and Ophthalmological Diseases: The Beijing Eye Study. *Sci Rep*. 2018;8(1):1–11. doi:10.1038/s41598-017-17765-5.