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Joel Pitkänen

MORPHOLOGY OF THE OPTIC NERVE HEAD AND THE RETINAL NERVE FIBER LAYER AND FACTORS AFFECTING THEM IN THE NORTHERN FINLAND BIRTH COHORT EYE STUDY

UNIVERSITY OF OULU GRADUATE SCHOOL;
UNIVERSITY OF OULU,
FACULTY OF MEDICINE;
OULU UNIVERSITY HOSPITAL

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Academic dissertation to be presented with the assent of the Doctoral Programme Committee of Health and Biosciences of the University of Oulu for public defence in Auditorium A101 (Aapistie 7 A), on 10 November 2023, at 12 noon

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Abstract

The optic nerve head (ONH) is the intraocular part of the optic nerve, while the retinal nerve fiber layer (RNFL) is the expansion of the optic nerve fibers at the fundus of the eye. The evaluation of these structures is essential in diagnosing various ophthalmological diseases. However, the variance in their appearance is broad, which can make it difficult to distinguish a healthy structure from a pathological one.

The aim of this dissertation is to explore factors that may affect the morphology of the ONH and the RNFL in the Northern Finland Birth Cohort (NFBC): perinatal factors, physiological and anatomical factors, and cognition.

We used the data from the long-term NFBC and more recent NFBC Eye Study for the analyses. The Heidelberg Retina Tomograph (HRT) 3 was used to measure ONH morphology, and optical coherence tomography (OCT) was employed to measure the average peripapillary RNFL thickness. We used paired associates learning (PAL) test, grade point average (GPA), level of education, and standard automated perimetry (SAP) as surrogates for cognition. For perinatal factors, we explored the data for maternal illness, medication, smoking, physiological and newborn measurements. In addition, anatomical measurements of the body, eye, and blood pressure were performed for subjects aged 45–49 years.

Neuroretinal rim volume was correlated with faster SAP performance, fewer errors in the PAL test, and a higher GPA. A thicker RNFL was correlated with faster performance in the SAP. Maternal chronic pulmonary disease and highest systolic blood pressure (SBP), weeks of gestation, and birth length all affected ONH morphology. Notably, the disc area substantially affected the other parameters of ONH morphology and the RNFL. The effects of other ocular, anatomical, and physiological factors were weak.

Although we found many statistically significant correlations, most were of limited predictive value. The optic nerve head seems to be well protected during pregnancy. Greater RNFL thickness, disc area, or rim volume might enable better performance in cognitive testing. The physiological and anatomical factors studied here can largely be ignored in clinical work but may be used in computer-based diagnostics where more minor effects can be considered.

Keywords: anatomy, birth length, birthweight, cognition, gestational age, morphology, optic nerve head, physiology, population study, retinal nerve fiber layer

Pitkänen, Joel, Näköhermonpään ja verkkokalvon hermosäiekerroksen morfologia ja niihin vaikuttavat tekijät Pohjois-Suomen syntymäkohortissa.
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Tiivistelmä

Näköhermon nysty eli papilla on näköhermon silmänsisäinen osa ja verkkokalvon hermosäiekerros koostuu näköhermon silmänpohjaan levittäytyneistä säikeistä. Molempien rakenteiden tutkiminen on olennainen osa silmäsairauksien tutkimista. Terveen papillan ja hermosäiekerroksen erottaminen vaurioituneesta voi olla kuitenkin hankalaa niiden vaihtelevan ulkonäön vuoksi.

Väitöskirjassani kartoitan tekijöitä, jotka vaikuttavat papillan ja hermosäiekerroksen rakenteeseen Pohjois-Suomen syntymäkohortissa. Tutkittavia tekijöitä ovat raskauden ajan ja vastasyntyneen mittaukset, fysiologiset ja anatomiset tekijät, sekä kognitio.

Aineistona käytän Pohjois-Suomen syntymäkohortista kerättyä materiaalia. Näköhermonpään rakenne mitattiin HRT 3:lla ja hermosäiekerroksen paksuus valokerroskuvauksella. Älykkyyttä kuvaavat tekijät ovat lyhytaikaista muistia testaava älykkyystesti, lukuaineiden keskiarvo, koulutusaste ja standardoitu näkökenttätutkimus. Raskauden ajan tekijöitä ovat äidin sairaudet, lääkitys, tupakointi ja fysiologiset mittaukset. Lisäksi kehon ja silmän anatomiset mittaukset, sekä verenpaine kartoitettiin 45–49-vuotiaana.

Papillan hermoreunuksen suurempi tilavuus korreloi nopeamman näkökenttätutkimuksen, älykkyystestissä vähempien virheiden ja korkeamman lukuaineiden keskiarvon kanssa. Äidin krooninen keuhkosairaus, korkein mitattu systolinen verenpaine, raskausviikot ja tutkittavan syntymäpituus vaikuttivat tilastollisesti merkittävästi papillan morfologiaan. Papillan pinta-ala vaikutti merkittävästi muihin papillan rakenteisiin, sekä hermosäiekerroksen paksuuteen. Muiden silmän ja anatomisten rakenteiden, sekä fysiologisten tekijöiden vaikutus oli vähäinen.

Vaikka tutkimuksessa löytyi useita tilastollisesti merkittäviä korrelaatioita tutkittujen tekijöiden välillä, niin suurimman osan ennustearvo oli vähäinen. Voidaankin todeta, että näköhermonpää vaikuttaa olevan hyvin suojattu tutkituilta tekijöiltä raskauden aikana. Älykkyystesteissä suoriutumisen ja papillan mittausten väliset tilastollisesti merkittävätkin yhteydet olivat heikkoja. Tutkitut fysiologiset ja anatomiset tekijät voidaan jättää huomiotta kliinisessä työssä, mutta tietokonepohjaisissa diagnostisissa ohjelmistoissa pienemmätkin vaikuttimet voi olla perusteltua ottaa huomioon.

Asiasanat: anatomia, fysiologia, hermosäiekerros, kognitio, papilla, raskausviikko, syntymäpaino, syntymäpituus, väestötutkimus

To my family

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I want to thank the members of my follow-up group, Joonas Kauppila, MD, professor, Fredrik Yannopoulos, MD, PhD and Henri Sova, MD, PhD for giving up their time to this project and for our easygoing meetings. I wish to express my gratitude to the official reviewers of this thesis, doctor Juha Hagman and docent Joni Turunen for their valuable comments and constructive criticism that helped me to improve the quality of the thesis.

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15.8.2023 Joel Pitkänen

Abbreviations

3MSE	Modified Mini-Mental State Examination
ADAGES	African descent and glaucoma evaluation study
AFEDS	African American Eye Disease Study
AD	african descent
ANOVA	analysis of variance
AOD	anterior chamber angle opening distance
BMI	body mass index
CANTAB	Cambridge Neuropsychological Test Automated Battery
CDR	cup-to-disc ratio
CERAD	Consortium to Establish a Registry for Alzheimer's Disease
CNS	central nervous system
D	diopter
DBP	diastolic blood pressure
E3	European Eye Epidemiology Consortium
ED	european descent
EPIC	European Prospective Investigation for Cancer
ERF	Erasmus Rucphen Family
GDxVCC	scanning laser polarimetry with the variable corneal compensator
GPA	gradepoint average
HFA	Humphrey field analyzer
HRT	Heidelberg Retinal Tomograph
IOP	intraocular pressure
IQ	intelligence quotient
LIFE	Leipzig Research Centre for Civilization Diseases
MCI	mild cognitive impairment
MMSE	mini mental state examination
NFBC	Northern Finland Birth Cohort
OCT	optical coherence tomograph
OECD	Organisation for Economic Co-operation and Development
ONH	optic nerve head
PAL	paired associates learning
PCA	primary component analysis
RNFL	retinal nerve fiber layer
SAP	standard automatic perimetry
SBP	systolic blood pressure

SITA	Swedish Interactive threshold algorithms
S-F	structure-function
WAIS	Wechsler Adult Intelligence Scale
WISC-R	Wechsler Intelligence Scale for Children-Revised

List of the original publications

This thesis is based on the following publications, which are referred throughout the text by their Roman numerals:

I Pitkänen, J., Veijola, J., Barnett, J., Liinamaa, J., & Saarela, V. (2022). Optic Nerve Parameters and Cognitive Function in the Northern Finland Birth Cohort Eye Study. *Ophthalmic Epidemiology, 29(2)*, 189–197. https://doi.org/10.1080/09286586.2021.1910317.

II Pitkänen, J., Leiviskä, I., Liinamaa, J., & Saarela, V. (2022). Antenatal and neonatal factors and morphology of the optic nerve head in the Northern Finland birth cohort. *Acta Ophthalmologica, 100(8),* e1657–e1664. https://doi.org/10.1111/aos.15164.

III Pitkänen, J., Liinamaa, J., Leiviskä, I., & Saarela, V. (2023). Morphology of the optic nerve head and factors affecting it in the Northern Finland birth cohort. *Acta Ophthalmologica, 101(5),* 575–581. https://doi.org/10.1111/aos.15642.

Contents

1 Introduction

The optic nerve connects the eye to the brain. The optic nerve head (ONH) is the part that we, as ophthalmologists, can see at the fundus of the eye. The expansion of the optic nerve fibers also forms the retinal nerve fiber layer (RNFL). The ONH is easily studied and imaged through the transparent medium of the eye using several different techniques. Often, just by looking at it, the ophthalmologist can diagnose certain diseases. Although we have been able to examine the fundus since 1851, when the first ophthalmoscope was invented, variations in the appearance of a healthy optic nerve head still makes distinguishing a normal ONH from a pathological one difficult (Levy, 1951). If we can identify developmental, anatomical, or physiological factors that affect the appearance of the ONH, it would make differential diagnosis easier.

Started in 2013, the Northern Finland Birth Cohort (NFBC) Eye Study explores the prevalence and efficiency of screening for glaucoma in a middle-aged population from northern Finland (Saarela et al., 2013). The appearance, imaging, and measuring of the ONH and retinal nerve fiber layer are integral parts of glaucoma diagnosis. Furthermore, diagnosing and monitoring glaucoma has become more objective, and computer-based analyses are available to help with the diagnosis. Thus, vast amounts of high-quality data were gathered during the study. In addition, the NFBC is a prospective cohort, and extensive information on other aspects of life, health, and disease have been acquired since it was initiated in 1966. This provides us with a unique opportunity to explore factors that may affect ONH and RNFL morphologies.

The NFBC was set up to study risk factors for preterm birth, perinatal morbidity, and mortality. We were therefore able to find detailed, prospectively gathered information from the prenatal and perinatal periods of the study participants. As there is limited knowledge of the perinatal factors that may affect the morphology of the ONH, these data provides an opportunity for the most extensive exploration of this subject in a randomized adult study population thus far.

The human species exhibits a broad spectrum of anatomical and physiological variance in all parts of the body and its functions. Many of these features are associated with each other. During the NFBC Eye Study, the cohort members also participated in extensive health examinations, and we combined these data for the present dissertation. At best, this could provide us with tools to make the diagnosis and monitoring of glaucoma more accurate. Not only could computer-based analyses include multiple reference population databases, but they can consider smaller individual associations than an ophthalmologist is able to.

Many of our cognitive capabilities rely heavily on visual input (Arsiwala et al., 2022; Kaido et al., 2020). The optic nerve has many features in common with the central nervous system, and information is processed in the retina before it reaches the cortex of our brain (London et al., 2013; Vlasiuk & Asari, 2021). Are there aspects of the ocular structures that reflect cognitive capabilities? Or, vice versa, do certain properties of the ONH support better performance in cognitive testing? The NFBC gives us an opportunity to explore these questions in a population not yet affected by neurodegeneration, using several surrogates for cognition.

The NFBC Eye Study combined with the data from the NFBC gives us vast research opportunities. For the present dissertation, we have chosen three subjects that may interest the reader. We also aim to escape the pitfalls of exploring an almost limitless resource, i.e., data mining, by critically analyzing the results of our research.

2 Review of the literature

2.1 Method of the literature review

We conducted a literature review in September and October 2022. The aim was to find relevant literature concerning associations between ONH and RNLF morphologies, and perinatal, physiological, anatomical and cognitive factors. We used the following search terms: “optic nerve head development”, “optic nerve head development fetal”, “optic nerve head cognition”, “retinal nerve fiber layer cognition”, “tajimi eye study”, “tanjong pagar eye study”, “african descent glaucoma evaluation study”, “tandan eye study”, “beijing eye study”, “norfolk eye study”, “kumejima eye study”, “blue mountains eye study optic nerve head”, “blue mountains eye study retinal nerve fiber layer”, “bridlington eye assessment”, “rotterdam eye study optic nerve head”, “rotterdam eye study retinal nerve fiber layer”, “reykjavik eye study”, “optic nerve head racial differences”, and “retinal nerve fiber layer racial differences”.

The searches yielded thousands of publications that we skimmed through: If the heading seemed relevant, we explored the abstract and the article. With this method, we found 108 publications that we included in the literature review. The rest of the publications we found from the references within those articles already chosen. We checked if the articles were published in journals included in the JUFO classification. If not, we checked that the publication was not published in a so-called predatory journal, listed on Beall’s list of potential predatory journals, and assessed ourselves whether the research met the standards required for this dissertation.

2.2 Optic nerve head (ONH) and retinal nerve fiber layer (RNFL)

2.2.1 Structure and function

The ONH is the intraocular part of the optic nerve. It consists of an optic disc, a neuroretinal rim, and an optic cup (Samarawickrama et al., 2012). The neuroretinal rim is formed on the edge of the optic disc, where the axons of retinal ganglion cells exit the retina and form the optic nerve, traversing toward the central nervous system (CNS). The optic cup is the depression in the middle of the neuroretinal rim. The RNFL is a layer of the retina formed by the same axons of the retinal ganglion cells that form the neuroretinal rim (Bowling, 2016; Moore et al., 2014). The function of the optic nerve is to transfer visual information from the retina to the visual center of the brain (Purves et al., 2005; Smith & Czyz, 2022).

Although the optic nerve is considered the second of 12 paired cranial nerves, in terms of function it may be regarded as a part of the CNS. During gestation, the optic nerve, the ONH, and the retina develop from the diencephalon (Ono et al., 1997; Smith & Czyz, 2022). The eye resembles the CNS in that the blood-retinal barrier surrounds and protects it (the blood-brain barrier protects the CNS), while the aqueous humor of the anterior chamber is similar to cerebrospinal fluid (Cunha-Vaz et al., 2011; Daneman & Prat, 2015; Martinelli et al., 2022; Steuer et al., 2005; Toda et al., 2011). In addition, both are particularly immune privileged (Forrester, 2009; Louveau et al., 2015). The retinal ganglion cells also have similarities with CNS neurons comprising a cell body, dendrites, and an axon (Kim et al., 2021). Like other fiber tracts in the CNS, the optic nerve is covered with myelin, and its sheath consists of all three meningeal layers: the pia mater, the arachnoid, and the dura mater (Smith & Czyz, 2022). The optic nerve axons react to an injury in the same way as other CNS axons (Benowitz & Yin, 2008).

Evaluating the appearance of the ONH and the RNFL is an integral part of an ophthalmologist's work. Diseases such as glaucoma, neurodegenerative diseases of the CNS, and inflammatory and ischemic pathologies of the optic nerve can affect the appearance of the ONH and the RNFL (Bambo et al., 2015; Chrysou et al., 2019; Costello et al., 2006; Hayreh & Jonas, 2001; Pilat et al., 2016; Rebolleda et al., 2009; Tsai et al., 1991; Tuulonen & Airaksinen, 1991). Thus, discerning a normal ONH or RNFL from a pathological one is paramount. In addition, the morphology of both structures vary substantially between different populations, different individuals, and even between the right and left eye of the same person (Chi et al., 1989; Knight et al., 2012; Mansour, 1991; Nousome et al., 2021; Townsend & Comer, 1987; Varma et al., 1994). Therefore, identifying the factors that may affect the development, appearance, and degeneration of the ONH and the RNFL can help differentiate a healthy ONH or RNFL from pathological examples. (Figure 1)

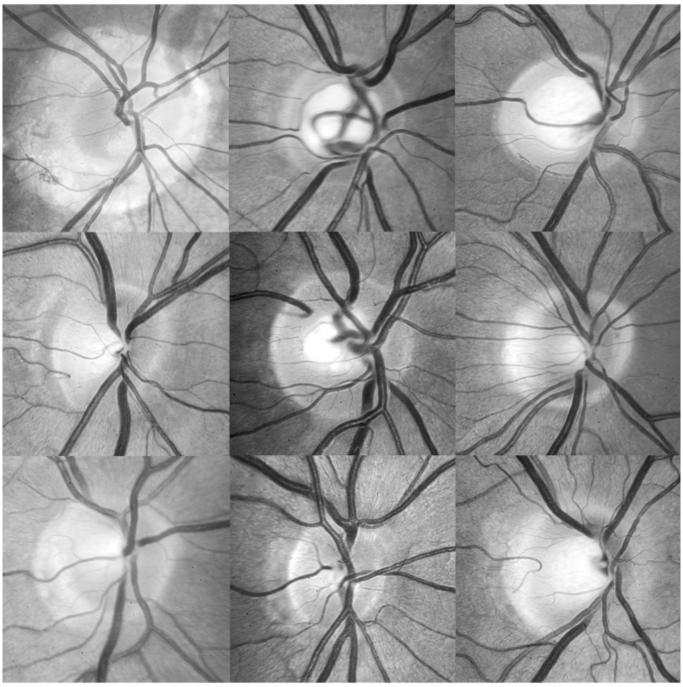

Fig. 1. Nine optic nerve head images from the study population demonstrating the variance of normal optic nerve head appearance.

2.2.2 Heidelberg Retina Tomograph

The Heidelberg Retina Tomograph (HRT) uses a confocal scanning laser imaging device to measure the topography of the ONH and the peripapillary RNFL. A 670 nm diode laser scans the retinal surface at a 15 degree angle in vertical and horizontal directions in multiple planes equally distanced from each other (Zinser et al., 1990). Between 16 and 64 planes are scanned, depending on the depth of the optic cup and the height of the neuroretinal rim. These planes form a three-dimensional image. This scanning process is performed three times, and the mean of the three results is presented as the final image (Rohrschneider et al., 1994; Weinreb et al., 1993). For the NFBC Eye Study, the HRT 3 was used. A contour line was drawn manually on the edge of the ONH. The HRT 3 uses the plane 50 μm posterior to the temporal disc margin as a reference plane to calculate the morphology of the ONH. The disc area is calculated from the area within a contour line. The cup volume is calculated from the space below the reference plane, and the cup area is calculated at the level of the reference plane. The rim volume is calculated from the topographical data above the reference plane and within the contour line. The rim area is the area of the rim at the level of the reference plane (Burk et al., 1990). HRT was developed to precisely measure the morphology of the ONH and its changes in order to diagnose and monitor glaucoma (Strouthidis & Garway-Heath, 2008). (Figure 2)

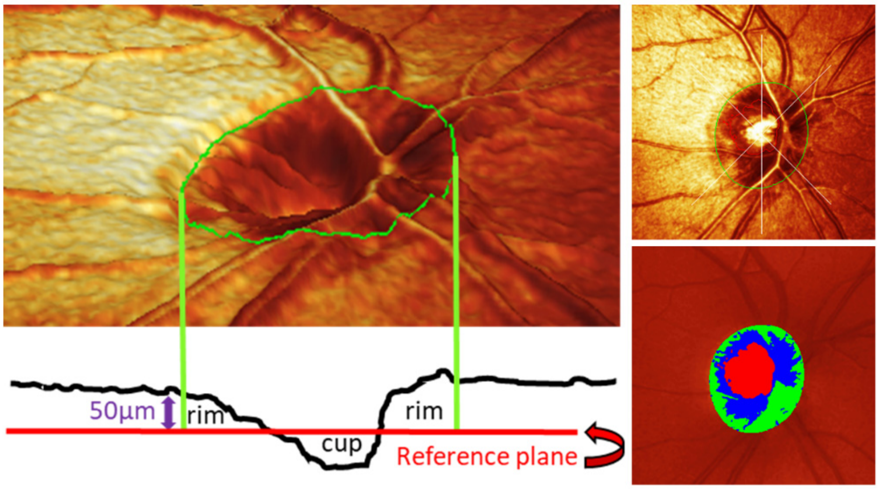

Fig. 2. Optic nerve head topography measured with the HRT. On the upper left and right: HRT images of the ONH with a green contour line illustrating the margin of the ONH. Bottom-left: a cross-sectional image demonstrates the position of the standard reference plane needed to analyze the dimensions of the cup and rim of the optic nerve head. Bottom-right: Red area demonstrates the cup area. Green demonstrates the non-sloping neural rim tissue and blue the sloping neural rim tissue.

There have been three commercially available generations of HRT. The first generation, HRT 1, relied substantially on operator input. The second generation, HRT 2, had more automated features (Fingeret, 2005). The HRT 3 presents numerous updates to the imaging software. It includes a normative database that has been expanded and diversified as differences in normal ONH morphology in different populations have been described. HRT 1 and 2 included the Moorfields Regression Analysis for glaucoma diagnostics and follow-up. HRT 3 also introduces a Glaucoma Probability Score for the same purpose. In HRT 3 software (used in our study), a scaling error of in the previous version has been corrected, the resolution of the imaging improved, and the image acquisition time shortened. The previous scaling error enlarged horizontal measurements by 4%, affecting the area and volume measurements. (Strouthidis & Garway-Heath, 2008)

HRT can measure ONH topography in a reproducible fashion (Mikelberg et al., 1993; Rohrschneider et al., 1994). Previous studies have found the greatest variability to occur in measurements along the cup border. Factors that influence this variability include age, glaucoma, optical properties of the eye that produce aberrations, misalignment of the study subjects and the scanner, movement of the eye or head during scanning, poor visual acuity, age, high astigmatism, cataract, and pupil size (Artal et al., 2001; Chauhan et al., 1994; Orgül et al., 1996; Sihota et al., 2002; Tan et al., 2004; Zangwill et al., 1997). The short-term and long-term variability of topographic measurements are very similar, suggesting that the imaging device has a robust image alignment algorithms (Chauhan & Macdonald, 1995).

2.2.3 Optical coherence tomography (OCT)

Optical coherence tomography (OCT) works much like ultrasound imaging, but instead of sound, it uses light. Spectral-domain OCT, used in the NFBC Eye Study, uses laser-generated light with an infrared wavelength to measure the tissue. The tissue absorbs some light; some is scattered, and some is reflected back to the device. OCT can form an image of the layers of the tissue by analyzing the return time and the interference spectrum of the light rays from different tissue depths (Podoleanu, 2012). Because OCT can be used to analyze the deeper tissue beneath the surface, it is suitable for imaging the layers of the retina. OCT is a versatile technology with a range of clinical applications. Its ability to investigate the deeper layers of the retina makes it an excellent tool for diagnosing macula diseases (Drexler & Fujimoto, 2008). In addition, its efficacy in finding defects in the RNFL makes it helpful in glaucoma diagnosis. In a Cochrane systematic review, the accuracy of OCT in detecting glaucomatous damage was found to be comparable to that of HRT 3 and scanning laser polarimetry (Michelessi et al., 2015).

Measuring the peripapillary RNFL is a part of glaucoma diagnostics, requiring follow-up with OCT. The OCT used in our study locates the center of the disc of the ONH. Then it scans a 6 x 6 mm area 200 times with A-scans, and subsequently forms a single B-scan. Finally, it measures the average peripapillary RNFL from a circle of 3.4 mm in diameter centered on the ONH. Local RNFL thicknesses can be calculated from four quadrants to 12 sectors if needed. (Figure 3)

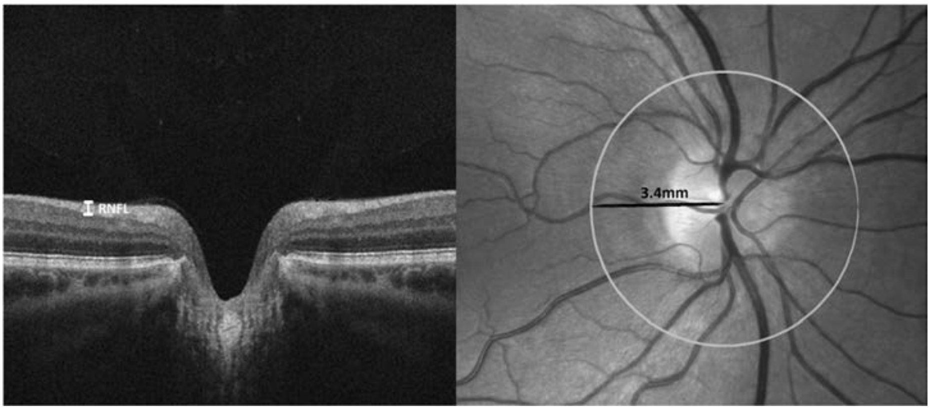

Fig. 3. Demonstration of the peripapillary RNFL thickness measurement with OCT. The left image shows the part of the retina where the device measures the RNFL thickness. The right image demonstrates the peripapillary circle where the RNFL thickness is measured.

The reproducibility of the peripapillary RNFL measurements made using OCT is good (Budenz et al., 2008; Leung et al., 2009; Mwanza et al., 2010). Factors that can affect the quality of the peripapillary RNFL measurements include panphotocoagulation of the retina and glaucomatous damage (Stein et al., 2006; Yazdani et al., 2016). In addition, the oblique configuration of the peripapillary retina in myopia may affect the reliability of the peripapillary RNFL measurements (Hwang et al., 2012). Cataracts can affect the image quality of OCT, but less than other methods of fundus imaging (Van Velthoven et al., 2006). Pupil dilation does not seem to substantially affect the measurements of the RNFL using OCT (Tanga et al., 2015).

2.2.4 Comparison of imaging modalities

Medeiros et al. measured the cup-to-disc ratio (c/d ratio) using HRT 2 and stereophotographs. When incorporated into their predictive model for estimating the risk of conversion from ocular hypertension to glaucoma, they found that the c/d ratio estimates derived from HRT 2 and stereophotographs could be used interchangeably (Medeiros et al., 2007). Another study found that HRT 2 and stereophotographs had a high intercorrelation when measuring the depth of the ONH (Nakagawa et al., 2008). In the Vellore Eye Study, HRT 2 produced significantly smaller optic disc area measurements than stereophotographs (Thomas et al., 2005).

Two studies have evaluated the differences in ONH morphology measured by OCT (StratusOCT 3000; software version 4.0; Carl Zeiss Meditec, Inc.) and HRT 2. Both found that HRT 2 produced smaller cup area measurements and larger rim area measurements than OCT. There was no statistically significant difference between disc area measurements (Nagai-Kusuhara et al., 2008; Naithani et al., 2007). Three studies compared ONH measurements by different versions of OCT and HRT. Although they found good correlation between ONH measurements by different devices, the absolute values different significantly between the devices (Iliev et al., 2006; Kratz et al., 2014; Schuman et al., 2003).

Calvo et al. compared HRT 3 and Cirrus OCT (Optic Disc Cube 200 × 200 scan protocol; software version 6.2) devices and found that the equivalent ONH parameters are different and cannot be used interchangeably (Calvo et al., 2014). Another study came to the same conclusion when it compared the performance of the HRT and Cirrus HD-OCT device performance when measuring the ONH morphology (Sato et al., 2012).

A previous study on the Northern Finland Birth Cohort shows a strong correlation between the c/d ratio, cup volume, and disc area measurements using HRT 3 and Cirrus HD-OCT 4000 (software V.6.0.0; Carl Zeiss Meditech AG, Oberkochen, Germany). The correlations between rim measurements are weaker but also statistically significant. In addition, the average RNFL measurements differ to a statistically significant degree between the instruments (Stoor et al., 2022). The same results regarding the RNFL measurements have been found in another study (Fanihagh et al., 2015).

2.2.5 Standard automated perimetry (SAP) testing

SAP refers to a static threshold perimetry, in which stationary white stimuli are presented at defined points in the visual field against a white background. The stimulus presentation is standardized, as is the recording of the study subject's responses. SAP is used in the diagnosis and follow-up of different glaucoma diseases. Various testing algorithms have been produced to balance the test's reliability, diagnostic accuracy, and duration. The Swedish Interactive Threshold Algorithms (SITA) are widely used because of their shorter test time and good reproducibility (Bengtsson & Heijl, 1998; Sekhar et al., 2000; Sharma et al., 2000; Shirato et al., 1999).

One of the devices used for SAP testing is the Humphrey Field Analyzer (HFA) (Humphrey Instruments, San Leandro, California) includes the SITA Standard algorithm. It uses an isopter of light which is flashed at different intensities 6 degrees apart from each other within the central 24 degrees of the visual field. The task of the study subject is to indicate when the isopter is seen by pressing a button. The result is provided in a variety of maps and values depicting the visual field, its defects, and the reliability of the testing. In addition, the speed at which the task was completed is registered (Bengtsson et al., 1997).

2.2.6 Structure-function analysis (S-F analysis)

A structure-function analysis (S-F analysis) combines structural and functional data to assess any possible pathological changes or progression in the eye. The corresponding structural and functional areas are combined and presented as an S-F map, e.g., the Garway-Heath map (Garway-Heath et al., 2000). The earliest example of an S-F analysis was a combination of histologic analyses and perimetry data (Quigley et al., 1989).

A challenge facing S-F analysis is that changes in structural and functional data do not necessarily occur simultaneously, so any correlation between the two may be seen after a follow-up period of one to six years (Quigley et al., 1992; Tuulonen & Airaksinen, 1991). (Figure 4)

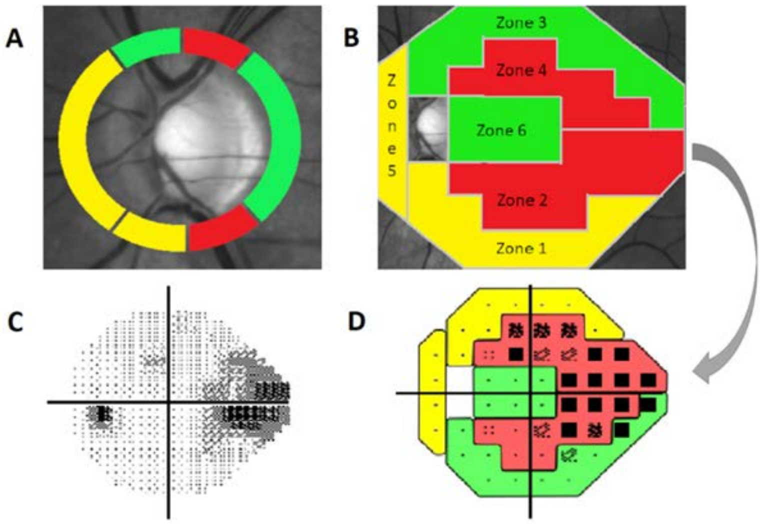

Fig. 4. A combined structure-function map formed using Cirrus FORUM Glaucoma Workplace. A. The six peripapillary RNFL zones. B. Corresponding zones shown on the fundus image. C. Standard automated perimetry result (Humphrey Field Analyzer). Darker areas represent the damaged parts of the visual field. D. Combined structure-function image combines the B image rotated 180 degrees along the horizontal axis and the SAP data. Green = healthy RNFL, yellow = RNFL thickness outside of the 95 percentile of the normal distribution, red = RNFL thickness outside of the 99 percentile of the normal distribution.

Several methods have been developed to improve the S-F analysis when discriminating glaucomatous eyes from healthy ones (Medeiros et al., 2012; Wachtl et al., 2017). However, the diagnostic performance has mostly been tested in selected study populations (Cui et al., 2019; Hood et al., 2019). In a non-selected population, the results are not as good (Karvonen et al., 2022). In addition, anatomical factors such as axial length, ocular torsion, and the angle of the temporal raphe can affect the S-F map (Denniss et al., 2019). The current commercially available algorithms include FORUM Glaucoma Workplace software (Carl Zeiss Meditec Inc., Dublin, CA, USA), Glaucoma Module Premium Edition (Heidelberg Engineering Inc., Franklin, MA, USA), and Topcon Maestro 2 (Topcon Healthcare Solutions, Oakland, NJ, USA).

2.3 Factors affecting the morphology of the ONH or the RNFL

2.3.1 Ante- and perinatal factors

The predecessor of the optic nerve, the optic stalk, forms around the sixth week of gestation. It connects the developing eye and the diencephalon and allows the axons of the retinal ganglion cells to travel down it, thus forming the optic nerve (Graw, 2010; Smith & Czyz, 2022). Provis et al. examined the optic nerves of fetuses after 10 to 33 weeks of gestation. They found an abundance of axons in the earlier stages of gestation; their number diminished and finally stabilized at an estimated 1.1 million axons by around 29 weeks of gestation (Provis et al., 1985). That is approximately the same number of axons found in adult optic nerves (Jonas et al., 1990, 1992; Mikelberg et al., 1989). Another study concluded that approximately 50% of the growth of the ONH had occurred after 20 weeks of gestation, 75% by birth, and 95% during the first year (Rimmer et al., 1993). In the following section, we present several studies that have explored the possible factors that can influence the morphology of the ONH. Moreover, we explore morphological and physiological factors that might reflect the circumstances during the pregnancy and their relation to ONH morphology. We hypothesize that the peak number of axons influences the area of the ONH as they require room to develop. The size of the cup and neuroretinal rim would therefore be associated with the final number of axons left since the axons form the neuroretinal rim after apoptosis.

Gestational age

Åkerblom et al. examined ONH morphology with HRT. They compared 5−16-year-old children born prematurely (≤32 gestational weeks) with children born at term and found that the rim area was smaller in prematurely born children. There were no statistically significant differences regarding disc or cup area (Åkerblom et al., 2018). Another study found that prematurely born children (≤32 gestational weeks) had increased rim volume, but there were no significant differences in the disc area or cup area between preterm children and children born at term when examined at the age of 8−16 years old using HRT (Alshaarawi et al., 2014). Optic disc parameters calculated from the RetCam fundus image showed no statistically significant relationship with number of weeks of gestation (Park et al., 2013). Samarawickrama et al. studied the effect of prematurity (<37 gestational weeks) on the ONH. They found no statistically significant effect on the disc or cup area. They conducted the study on 12-year-old children using OCT for imaging (Samarawickrama et al., 2009). Hackl et al. found that in prematurely born children examined six weeks after birth with RetCam images of the fundus, a low gestational age influenced the form of the ONH: A lower gestational age also correlated with a more vertically oval ONH. They did not study the effect of gestational age on the disc, cup, or rim area/volume (Hackl et al., 2013). Hellström found that children born preterm (≤32 gestational weeks) without known brain lesions had normal optic disc morphology (Hellström, 1999). In another study, Hellström et al. found that the optic disc size correlated negatively with gestational weeks in preterm girls. However, the morphology of the ONH did not differ between prematurely born children and children born at term. Both studies used fundus photographs for their measurements (Hellström et al., 1997). Very preterm children (24−28 weeks of gestation) had significantly smaller disc areas than participants in the reference group. They also had smaller rim areas. The study used fundus photographs (Hellström et al., 2000). Smaller disc areas and rim areas correlated with preterm birth (<32 gestational weeks) in children aged 4−6 years compared with a control group of children born at term. Fundus photographs were used in the study (Wikstrand et al., 2010). The Gutenberg Prematurity Eye Study evaluated the effect of prematurity on RNFL thickness with OCT imaging. Participants were 18−52 years old, and they were divided into four groups: 1) born at term, 2) moderately premature (33−36 gestational weeks), 3) very prematurely born (29−32 gestational weeks), and 4) extremely premature (≤28 gestational weeks). Peripapillary RNFL was thinner in every premature group when compared with the group born at term (Fieß et al., 2022).

Birthweight and length

Optic disc parameters calculated from RetCam fundus images showed no statistically significant relationship with birthweight in a study conducted with 97 prematurely born children (Park et al., 2013). Another study, which used RetCam to image prematurely born children, found that low birthweight correlated with a more vertically oval ONH (Hackl et al., 2013). Samarawickrama et al. studied the effect of low birthweight (≤2499g) and short birth length on ONH from OCT images in 12-year-old children. They found no statistically significant effect on the disc or cup area. Nevertheless, low birthweight and short birth length correlated with a larger cup-to-disc ratio, as well as a larger cup diameter, and smaller vertical disc diameter (Samarawickrama et al., 2009). When subjects with very low birth weight (≤1500g) were compared with the control group of normal birthweight, the subjects with low birthweight had larger cup areas and smaller rim areas. The study used digital fundus photographs (Hellgren et al., 2009). The same results were found in another study that compared children born before 32 weeks with children born at term (Wikstrand et al., 2010). Hellström et al. found that children with a lower birthweight had larger optic disc areas (Hellström et al., 2000). Raffa et al. found that the central macular RNFL was thicker in subjects born at term compared to participants born at 32−36 weeks gestation, but they found the difference only in the right eye. Optic disc variables did not differ between the groups. They conducted the study when the children were eight years old. The RNFL measurements were obtained with OCT and ONH parameters with fundus photographs (Raffa et al., 2016). Preterm birth is also linked to ONH hypoplasia (Tornqvist et al., 2002). A study conducted on full-term infants found no difference in the disc area between the low-weight group (<2500g) and the normal-weight group (Kandasamy et al., 2012). The Gutenberg Prematurity Eye Study found no statistically significant correlation between birthweight and RNFL (Fieß et al., 2022).

Smoking

The Copenhagen Child Cohort 2000 Eye Study showed that at 11−12 years, children whose mothers had smoked during pregnancy had thinner RNFLs than their reference group (Ashina et al., 2017). The same results were presented in another study (Pueyo et al., 2011). Both studies used OCT for imaging. In addition, an extensive study of 1287 participants found a statistically significant correlation between exposure to in-utero smoking and thinner RNFL, even after controlling for alcohol exposure during gestation and passive smoking during childhood (Lee et al., 2022).

Medication and recreational drug use during pregnancy

There is very little knowledge of the possible effects of maternal use of drugs on the optic nerve of a fetus. Most of the speculated associations correlate to ONH hypoplasia, which is discussed later in this chapter. In a large two-part review of the literature on drugs associated with teratogenic mechanisms, there is no mention of the optic nerve. However, the review does not exclude the possibility of an association included with multiple deficits in the infant (Van Gelder et al., 2014).

One study compared 40 infants exposed to cocaine during pregnancy with a control group of 40 nonexposed infants and found no difference in ONH anomalies between the groups (Stafford et al., 1994).

Brain lesions

Hellström found that children born preterm with brain lesion acquired late in gestation had enlarged optic cups, while children with fetal alcohol syndrome (FAS) had smaller optic discs (Hellström, 1999). The same observation of enlarged optic cups in children born preterm with an acquired brain lesion was repeated in another study (Wikstrand et al., 2010). Brain lesions affect the cup and rim areas (Jacobson et al., 1997, 2003). McLoone et al. found no association between disc morphology and the timing of brain injury (McLoone et al., 2006).

Racial variation

Allingham et al. studied 58 newborns with OCT and found racial variation in the vertical disc and cup diameters and cup/disc ratio. Caucasian newborns had a smaller vertical disc diameter, a smaller vertical cup diameter, and a smaller c/d ratio when compared with newborns of African ancestry. (Allingham et al., 2013).

Optic nerve head hypoplasia

Although our study does not focus on ONH hypoplasia, we include a limited literature review as it can be speculated that the same factors associated with ONH hypoplasia can affect the morphology of the ONH and the RNFL with a less extreme severity. ONH hypoplasia is a congenital abnormality in which axons are reduced in one or both optic nerves. The range of symptoms varies from no visual impairment to blindness (Tornqvist et al., 2002). It can be considered the extremely small end of the spectrum in terms of ONH size. Such hypoplasia is associated with FAS, young maternal age, primiparity, and maternal smoking (Chan et al., 1991; Gyllencreutz et al., 2020; Ribeiro et al., 2007; Strömland, 1985, 1987; Tornqvist et al., 2002). Maternal use of various prescription and recreational drugs has been speculated as an etiological factor, but this is based on anecdotal papers (Garcia-Filion & Borchert, 2013; Hoyt & Billson, 1978). McLoone et al. found that premature infants with intraventricular hemorrhage had an increased incidence of optic nerve hypoplasia (McLoone et al., 2006).

Maternal illness

Hypertensive problems during pregnancy have been associated with developmental problems of the brain and neurological problems (Maher et al., 2018; Rees et al., 2008). However, no research on the association between hypertension and the optic nerve has been conducted. There are some studies that have linked gestational cytomegalovirus exposure, pre-eclampsia, twin transfusion syndrome, systemic lupus erythematosus, isolated cases of gestational diabetes, and toxemia to ONH hypoplasia (Burke et al., 1991; Hittner et al., 1976; Tornqvist et al., 2002).

2.3.2 Height, weight, body mass index, blood pressure and ocular dimensions

Due to the extensive literature on the associations between physiological, ocular, and other anatomical factors and the morphology of the ONH and the RNFL, we have structured this section of the literature review around similar eye studies to NFBC Eye Study, that have evaluated this subject. The chosen studies are all population-based except for the African Descent and Glaucoma Evaluation Study (ADAGES), which we chose for broader geographical representation. The study populations are large and include different ethnicities around the world (Figure 5). The studies do not solely focus on the ONH or RNLF morphology. The discussion chapter presents some additional smaller studies relevant to our own results.

We included in this literature review the African American Eye Disease Study (AFEDS), ADAGES, the Beijing Eye Study, the Blue Mountains Eye Study, the Bridlington Eye Assessment Project, the European Prospective Investigation of Cancer (EPIC)-Norfolk Eye Study, the European Eye Epidemiology Consortium (E3), the Handan Eye Study, the Kumejima Study, the Reykjavik Eye Study, the Rotterdam Study, the Tajimi Eye Study, and the Tanjong Pagar Study. A comparison of these studies and our own research is presented in Table 1. The results of all studies, including our own, are presented in Table 2. The following paragraphs will describe these studies' main findings concerning the ONH and the RNFL morphology. Although numerous other papers have been published on this subject, this selection gives a good overall picture on the variety and inconsistency of results found in other extensive population-based studies on the same topic.

Fig. 5. Locations of the eye studies. 1. African American Eye Disease study, 2. African Descent and Glaucoma Study, 3. Beijing Eye Study, 4. Blue Mountains Eye Study, 5. Bridlington Eye Assessment Project, 6. EPIC-Norfolk Eye Study, 7. European Eye Epidemiology Consortium, 8. Handan Eye Study, 9. Kumejima Eye Study, 10. Reykjavik Eye Study, 11. Rotterdam Study, 12. Tajimi Eye Study, 13. Tanjong Pagar Eye Study, 14. NFBC Eye Study.

We excluded the Aravind Comprehensive Eye Study, the Baltimore Eye Study, the Beaver Dam Eye Study, the Coimbra Eye Study, the Framingham Eye Study, the Gutenberg Eye Study, the Los Angeles Latino Eye Study, the Thessaloniki Eye Study, and the Visual Impairment Project Australia as their focus of research was not relevant to our study. In addition, we excluded the Vellore Eye Study because of its comparatively small study population. (Jonas et al., 2003).

AFEDS

AFEDS was a five-year, population-based study designed to assess the African American population in the United States for the prevalence of and risk factors associated with visual impairment, lens opacity, glaucoma, age-related macular degeneration, and diabetic retinopathy. The study population consisted of 6500 African Americans aged over 40 years from Los Angeles County (McKean-Cowdin et al., 2018). The RNFL thickness and the optic nerve head were measured using OCT. A total of 1029 eyes were analyzed. The researchers excluded the eyes with ocular diseases except for mild to moderate diabetic retinopathy, scans with poor signal strength, and scans with poor image quality. The AFEDS found that RNFL thickness had a statistically significant positive correlation with peripapillary vessel density and a negative correlation with the eye's axial length (Nelson et al., 2019).

ADAGES

The main objective of the ADAGES was to study the factors that might explain differences in glaucoma incidence and progression between African and European populations over the age of 18. It included a prospective cohort of 1221 participants (Sample et al., 2009). The researchers have published one study that is of interest to our own research, in which they found statistically significant differences in the following factors between African (AD) and European descendants (ED): In the AD group the mean disc area was 2.06 mm^2 when measured with HRT and 2.47 mm^2 when measured with OCT. By comparison, the areas were 1.77 mm^2 (HRT) and 2.26 mm^2 (OCT) in the ED group. In addition, the cup area was 0.53 mm^2 in the AD group and 0.39 mm^2 in the ED group (HRT). The cup volume was 0.13 mm^3 in the AD group and 0.09 mm^3 in the ED group (HRT). The rim area was 1.53 mm^2 in the AD group (HRT) and 1.38 mm^2 in the ED group (HRT). The rim volume was 0.41 mm^3 in the AD group and 0.38 mm^3 in the ED group (HRT). When measured with HRT, the mean RNFL thickness was 0.26 mm for both groups. The study found statistically significant differences between the groups with the OCT measurements for the following parameters: the cup area was 0.72 mm^2 in the AD group and 0.56 mm^2 in the ED group. When adjusted for age, the global RNFL thickness was 103.69μm in the AD group and 100.6μm in the ED group. However, the difference was statistically insignificant when adjusted for age and disc area. There was no statistically significant difference in the rim area when measured with OCT. The rim area (HRT, OCT) and RNFL thickness (OCT) correlated positively with the disc area in both groups. Age had a negative statistically significant correlation with the rim area and the RNFL thickness and a positive statistically significant correlation with the cup area when the parameters were acquired with OCT, but not when the measurements were made using HRT (Girkin et al., 2010).

The Beijing Eye Study

The Beijing Eye Study is a population-based study conducted in the region of Greater Beijing, including both urban and rural areas. The purpose of the study is to gather and analyze ophthalmological data in a population representative of mainland China. Participants were recruited through house visits, and the eligibility criteria was an age of ≥40 years. A total 5324 individuals were recruited for the study, of whom 4439 took part in an eye examination (Jonas et al., 2009). Wang et al. studied the optic disc size using digital fundus photographs. They found that the mean optic disc area measured 2.65 mm². Highly myopic (refractive error of -8.00D or less) and highly hyperopic (refractive error of +4.00D or more) subjects had larger and smaller disc sizes, respectively. The difference is statistically significant. The disc size was found to be independent of age, and no statistically significant differences existed between genders (Wang et al., 2006). Another study on the same population found that the mean rim area was 1.70 mm² in the group with an intraocular pressure ≤21 mmHg, normal visual fields, and an unremarkable optic nerve head (Xu et al., 2007). The other group included individuals with intraocular pressure greater than 21mmHg. The study excluded eyes with myopia greater than -8 dioptres. In the former group, the rim area had a statistically significant positive correlation with the disc area and myopic refractive error. The associations of rim area with age, IOP (≤21mmHg), gender, diabetes mellitus, arterial hypertension or hypotension, hyperlipidemia, coronary heart disease, and cerebral hemorrhage were statistically insignificant. The mean optic cup area was 0.68 mm² and had a statistically significant correlation with the disc size. The mean rim area was significantly smaller, and the cup area was larger in the latter group. The study found no statistically significant difference in the disc area (Xu et al., 2007). The mean global RNFL thickness was 103.2 µm, calculated from 12 different points located circumferentially along a circle of 3.45 mm in diameter around the optic disc. In a univariate analysis, a thicker RNFL had a statistically significant correlation with younger age, lower BMI, lower prevalence of diabetes mellitus and arterial hypertension, a smaller rim and disc area, a shorter axial length, more hyperopia, and the female gender. In the final multivariate analysis, a thicker RNFL still had a statistically significant correlation with younger age, a larger disc and rim area, a shorter axial length, more hyperopia, a flatter anterior corneal curvature, and the female gender (Wang et al., 2013).

The Blue Mountains Eye Study

This population-based study was conducted in the Blue Mountains region of Australia, focusing on the elderly population (≤49 years). The purpose was to survey vision and common eye diseases in the region (Mitchell et al., 1996). Of the 1952 participants, 1276 had HRT scans eligible to study the morphology of the ONH and its correlations. The mean age was 71.9 years. The mean disc area was

1.91mm², the cup area was 0.46mm², the cup volume was 0.09mm³, the rim area was 1.45mm², the rim volume was 0.38mm³, and the RNFL thickness 230µm. A larger disc area correlated with statistical significance with a larger cup area (r=0.616), a larger rim area (r=0.602), and a thinner RNFL (r=−0.134) (Li et al., 2013).

The Bridlington Eye Assessment Project

This study focused on the elderly population of Bridlington, England. The investigators invited residents over the age of 65 for a comprehensive eye examination. The study was a screening exercise for eye disease. In total, 1246 subjects participated. The study obtained the measurements of the ONH and the RNFL with HRT from 459 participants. The mean age was 73 years. The mean disc area was 1.98 mm², the mean cup area was 0.45 mm², the mean cup volume was 0.09 mm³, the mean rim area was 1.52 mm², the mean rim volume was 0.40mm³, and the mean RNFL thickness was 230 µm. Men were found on average to have a larger cup area and volume than women; women had a larger rim volume. The mean RNFL thickness was greater in women compared with men. The ONH parameters and the mean RNFL thickness correlated with statistical significance with the disc area (r=0.12–0.54), with the mean RNFL having the lowest correlation coefficient and the cup area having the highest (Vernon et al., 2005). In another publication from this eye study, the central corneal thickness (CCT) and the optic disc parameters had no statistically significant correlation (Hawker et al., 2009).

The EPIC-Norfolk Eye Study

The European Prospective Investigation of Cancer was a collaborative study of 10 countries that began in 1989, and EPIC-Norfolk was one of its UK centers. The study later broadened to research topics beside cancer. The original population of the EPIC-Norfolk Eye Study, aged 40–79 years old, was recruited between 1993 and 1997. The third round of health examinations was conducted between 2004 and 2011, including those subjects used in the eye study. In all, 8623 participants aged 40−90 years old and living in Norwich and its surroundings took part in the third round of examinations (Khawaja et al., 2013). The measurements of the ONH and RNFL were acquired using HRT. In a univariate analysis, Khawaja et al. found that men had a significantly larger disc area, cup area, and cup volume than women. Correspondingly, women had a larger rim area, rim volume, and mean RNFL thickness. In a multivariate analysis, height and axial length had a statistically significant positive correlation with the disc area. The study performed a principal components analysis (PCA) to find the components that affect ONH morphology the most. The researchers excluded the optic disc area but included all the other studied ONH and RNFL parameters. They found that 80% of the variance in the ONH data was explained by three PCA-computed factors, which they named cup, rim, and RNFL according to their principal correlations. For these three factors, they chose the cup-to-disc ratio (CDR), the RNFL thickness, and the rim area as the best representatives for the measured data. The CDR had a statistically significant positive correlation with age, height, and IOP, and a negative correlation with body mass index (BMI). The RNFL thickness had a negative association with age and axial length, women had a thicker RNFL, and pseudophakic subjects had a thinner RNFL. Rim area had a negative correlation with age and IOP, a positive correlation with BMI; pseudophakic subjects had smaller rim areas than phakic subjects (Khawaja et al., 2013). A separate EPIC-Norfolk publication studied the RNFL measurements acquired by GDxVCC (scanning laser polarimetry with the variable corneal compensation) and their associations. Age was found to have a statistically significant negative correlation and axial length a positive correlation to RNFL thickness. These associations persisted in a multiple regression model (Khawaja et al., 2013).

The European Eye Epidemiology Consortium (E3)

The E3 consists of 29 research groups from 12 European countries. It aims to collaborate and share data and knowledge in ophthalmic epidemiology research (Delcourt et al., 2015). The E3 includes eight European studies: the Alienor Study, the Coimbra Eye Study, the Montrachet Study, the LIFE Study, the Rotterdam Study I–III, and the Twins UK Study. Researchers have conducted a meta-analysis of factors affecting the thickness of the peripapillary RNFL. The measurements were obtained with different OCT devices and imaging modalities. In this random-effects analysis, the RNFL thickness correlated positively with female gender, spherical equivalent, and smoking. On the other hand, statistically significant negative correlations were found with age, IOP, visual impairment, hypertension, stroke, and dementia (Mauschitz et al., 2018).

The Handan Eye Study

This population-based cohort study was conducted in 2006-2007 in Yongnian County, Handan City, China, to explore possible risk factors associated with eye diseases. The participants were aged 30 years or older. They went through a physical and eye examination and answered a questionnaire. A total of 6830 study subjects took part in the study (Liang et al., 2009). The optic disc morphology was assessed using HRT. In all, 2633 study subjects were eligible for the analyses. The mean disc area was 2.28 mm^2, the cup area was 0.47 mm^2, the cup volume was 0.11 mm^3, the rim area was 1.80 mm^2, the rim volume was 0.51 mm^3, and the RNFL thickness was 280 µm. Men had a larger disc area, cup area, and cup volume. The disc area correlated negatively with age, DBP, and hyperopia and positively with axial length. After adjusting for other confounders, the refractive error no longer reached statistical significance. All other ONH parameters had a statistically significant correlation with the mean disc area (r=0.054–0.736) (Zhang et al., 2014). In another publication from the Handan Eye Study, the mean RNFL was measured with OCT in 2638 participants. The average RNFL thickness was 113µm. It was thicker in women than in men. There was a statistically significant negative correlation with age when participants were divided into five different groups: <39, 40–49, 50–59, 60–69, and ≥70 years old. Study subjects who smoked had an increased BMI value, coronary heart disease, a history of cataract surgery, a higher IOP, a lower spherical equivalent, a longer axial length, and thinner RNFLs. Of these, coronary heart disease and smoking were not statistically significant in a multivariate model (Wu et al., 2022).

The Kumejima Study

The Kumejima Study was conducted in 2005-2006 on Kumejima, an island in the Okinawa Prefecture, Japan. All residents aged 40 years or older were invited to participate. Of the 4632 subjects eligible for the study, 3762 took part in the study. They participated in an interview and physical and ophthalmological examinations. The ONH morphology was measured from stereoscopic fundus photographs. Photographs of 2208 subjects were deemed eligible for the analysis. The mean disc area was 2.54mm^2, the mean rim area was 1.67mm^2, and the mean cup area was 0.87mm^2. Age had a statistically significant negative correlation with rim area, and after adjustment for age, men had greater disc and rim areas (Iwase et al., 2017). Another publication from this study included 2474 eyes for analyses of factors affecting the superior and inferior halves of the rim area. Age, IOP, and axial length had a statistically significant negative correlation on both halves, as well as a greater disc area positive effect for both. Only the superior half was affected by blood pressure, male gender, and CCT (Iwase et al., 2020).

The Reykjavik Eye Study

The Reykjavik Eye Study began in 1996, with the data on ocular measurements being gathered five years later, in 2001. The original study population was a random sample from the national population aged 50 years or older. The percentages for each year of birth and gender were equal. The original study population consisted of 1045 participants, of whom 757 were eligible for the latter examination. The ONH morphology was measured with fundus stereophotographs. The mean optic disc area varied from 1.80–1.89mm² in men and 1.77–1.88mm² in women depending on the age group (55–64, 65–74, 75+ year old). In the multivariate model of the study, age, gender, height, and weight did not influence the disc area (Eysteinsson et al., 2005).

The Rotterdam Study

The Rotterdam Study is a prospective cohort study designed to research the health of elderly participants. It started in 1990 and there have been four examination cycles to date, with the participants aged 40, 45, or 55 years and older, depending on the cycle (Ikram et al., 2017). Ramrattan et al. studied 5114 participants in the first cycle who were 55 years of age or older at the time of the study. Fundus stereophotographs were used to measure ONH morphology. The mean disc area was 2.42 mm², the mean rim area was 1.85 mm², and the mean cup area was 0.57 mm². Men had larger disc and rim areas. The disc and rim areas correlated negatively with refractive error. Height correlated positively with the disc area when tested separately for men and women (Ramrattan et al., 1999).

The Tajimi Eye Study

The Tajimi Eye Study is a population-based study of 4000 Japanese subjects aged 40 or older. They were randomly selected from the city of Tajimi in 2000. Some 3021 participants finally participated in the screening examinations. The ONH morphology was acquired with HRT from 2036 study subjects. The mean disc area was 2.06 mm^2, the mean cup area was 0.51 mm^2, the mean cup volume was 0.11 mm^3, the mean rim area was 1.55 mm^2, the mean rim volume was 0.41 mm^3, and the mean RNFL thickness 250 µm. The disc area had a statistically significant correlation with all the other ONH parameters. Age correlated negatively with disc area, rim area, rim volume, and mean RNFL thickness. Men had larger cup areas. Height had a positive correlation with cup-related parameters and a negative correlation with rim-related parameters. The refractive error correlated positively with the disc area and negatively with the rim volume and the RNFL thickness. IOP was positively and CCT negatively correlated with the cup volume (Abe et al., 2009). Another study studied 2634 subjects from the same study population with fundus photographs. The mean disc size was 2.30 mm^2. It had a statistically significant negative correlation with the spherical equivalent (Mataki et al., 2017).

The Tanjong Pagar Study

This study was conducted in Tanjong Pagar district, Singapore, from 1997 to 1998. Two thousand subjects were randomly selected so that 500 participants were represented from each age group: 40–49, 50–59, 60–69, and 70–79 years. Of these, 929 were deemed eligible for the analysis. The ONH morphology was evaluated from fundus photographs. The mean disc area was 2.17 mm^2, the rim area was 1.43 mm^2, and the optic cup area was 0.74 mm^2. Men had statistically significantly larger disc and rim areas than women. Age had a statistically significant correlation with the disc area. In addition, the disc area had a significant positive correlation with the other ONH parameters (Bourne et al., 2008). In the second part of this study, the disc area correlated positively with axial length, myopia, and height. The rim area was negatively associated with IOP and positively associated with height, anterior chamber depth, and axial length. In a multiple variable analysis, the correlation of the disc and rim area with axial length remained statistically significant (Bourne et al., 2008).

Table 1. Overview of the studies reviewed in chapter 2.

Study	n	Type	Study population	Age	ONH imaging	RNFL imaging
Northern Finland Birth Cohort Eye Study	3070	population-based, cross-sectional	Finnish	46–49	HRT	OCT
African American Eye Disease Study	6500	population-based, cross-sectional	African American	>40	OCT	OCT
African Descent and Glaucoma Study	1221	cross-sectional study of a prospective cohort	African, European	>18	HRT, OCT	HRT, OCT
Beijing Eye Study	4439	population-based, cross-sectional	Chinese	≤40	FP	OCT
Blue Mountains Eye Study	3654	population-based, cross-sectional	Australian	≥49	HRT	
Bridlington Eye Assessment Project	459	population-based, cross-sectional	British	≥65	HRT	HRT
EPIC-Norfolk Eye Study	8623	cross-sectional within a population-based prospective cohort study	British	48–92	HRT	HRT, GDx
European Eye Epidemiology Consortium	16084	combination of 8 cross-sectional population-based studies	European	n/a		OCT
Handan Eye Study	6830	population-based, cross-sectional	Chinese	≥30	HRT	HRT, OCT
Kumejima Eye Study	3762	population-based, cross-sectional	Japanese	≥40	SFP	
Reykjavik Eye Study	846	population-based, cross-sectional	Icelandic	≥55	SFP	
Rotterdam Study	5114	population-based, cross-sectional	Dutch	≥55	SFP	
Tajimi Eye Study	3021	population-based, cross-sectional	Japanese	≥40	HRT, FP	HRT
Tanjong Pagar Study	1232	population-based, cross-sectional	Singaporean	40–79	FP	

ONH, optic nerve head; RNFL, retinal nerve fiber layer; HRT, Heidelberg retinal tomograph; OCT, optical coherence tomography; FP, fundus photograph; GDx, scanning laser polarimetry; SFP, stereo fundus photograph

Table 2. Statistically significant correlations affecting disc area and RFNL in the reviewed eye studies in chapter 2 and the present study.

Study	Disc area		Retinal nerve fiber layer	
	Positive correlation or larger disc	Negative correlation or smaller disc	Positive correlation or thicker RNFL	Negative correlation or slimmer RNFL
NFBC Eye Study	myopia	hyperopia	hyperopia, CCT	myopia, cylindrical correction, AOD
African American Eye Disease Study			peripapillary vessel density	axial length
African Descent and Glaucoma Study	African descent	European descent		age
Beijing Eye Study	high myopia	high hyperopia	female gender, hyperopia	age, axial length, myopia
Blue Mountains Eye Study			female gender	
Bridlington Eye Assessment Project			female gender	male gender
EPIC-Norfolk Eye Study	male gender		female gender	age, axial length
European Eye Epidemiology Consortium			female gender, hyperopia, smoking	age, IOP, visual impairment, hypertension,
Handan Eye Study	male gender, axial length	age, DBP	female gender, hyperopia	age, BMI, pseudophakia, IOP, myopia
Kumejima Eye Study	male gender			
Reykjavik Eye Study				

Study	Disc area		Retinal nerve fiber layer	
	Positive correlation or larger disc	Negative correlation or smaller disc	Positive correlation or thicker RNFL	Negative correlation or slimmer RNFL
Rotterdam Study	male gender, height, myopia	female gender, hyperopia		
Tajimi Eye Study	myopia	age, hyperopia		age
Tanjong Pagar Study	male gender, age, axial length, height	female gender		

CCT, central corneal thickness; AOD, anterior chamber angle opening distance; IOP, intraocular pressure; DBP, diastolic blood pressure; BMI, body mass index

2.3.3 Cognition

Cognition is a difficult feature to define precisely. Oxford English Dictionary defines cognition as "The action or faculty of knowing taken in its widest sense, including sensation, perception, conception, etc., as distinguished from feeling and volition." The book "Cognition" by Farmer and Matlin describes it as acquisition, storage, transformation, and use of knowledge (Farmer & Matlin, 2019). Many studies referenced in this thesis leave it undefined (Deary et al., 2007; Roth et al., 2015; Sandsør, 2020). For the present study, we define cognition as the capability to process external and internal stimuli, differentiate the relevant from the irrelevant, and produce a planned response. Storing and retrieving processed information is also part of cognitive capabilities (Kandel et al., 2013).

In recent years, extensive research has been performed features of the ONH or RNFL that might be possible markers for neurodegenerative. Findings associated with mild cognitive impairment (MCI), Alzheimer's disease, Parkinson's disease, and multiple sclerosis have been published (Danesh-Meyer et al., 2006; Deng et al., 2022; Green et al., 2010; Inzelberg et al., 2004; Kesler et al., 2011; Monteiro et al., 2012). These diseases manifest, among other symptoms, as cognitive decline. However, less research has been conducted on the possible association between ONH and RNFL morphology and cognition in a population presumably unaffected by neurodegenerative diseases.

Cognitive testing

Cognitive testing includes a variety of tests that assess different aspects of the cognitive capabilities of the study subjects. Reasons for testing vary from school selection and job recruiting to psychological and medical evaluations (Bestetti et al., 2020; Claesdotter et al., 2017; Wee et al., 2014; Yin Foo et al., 2013). Parts of the tests can include testing for verbal and non-verbal comprehension, reasoning, knowledge, visual-spatial processing, different parts of memory, and processing speed (Yin Foo et al., 2013). In addition, some tests can include psychological parts of cognition in their test, for example, the Cambridge Neuropsychological Test Automated Battery (CANTAB) tests a person's social and emotional recognition, decision making, and response control (Barnett et al., 2016).

Level of education

A person's level of education has been shown to correlate with cognition (Strenze, 2006). Rohde et al. have found that information processing speed predicts fluid intelligence, working memory, and number sense capabilities. In addition, these features significantly correlate with academic achievement (Rohde & Thompson, 2007). A meta-analysis has shown that the Miller Analogies test predicts academic and vocational performance (Kuncel et al., 2004).

Grade point average (GPA)

The grade point average has a high correlation with intelligence. A meta-analysis found that school grades and intelligence tests had a substantial mean correlation of 0.54. The correlation was highest for tests that included both verbal and nonverbal materials. This may indicate that a broad skill set in cognitive abilities is the best predictor of good grades. Grades in mathematics, languages, and social sciences all correlated with intelligence, with mathematics having the highest correlation (Roth et al., 2015). A Norwegian study found similar results. Grade variance is negatively correlated with later educational attainment (Sandsør, 2020). Deary et al. showed that good performance on cognitive ability tests at age 11 correlated positively with all tested school subjects at age 16 (Deary et al., 2007).

Paired associates learning test

The Paired Associates Learning (PAL) test assesses simple visual patterns and visuospatial associative learning. It contains aspects of both a delayed response procedure and a conditional learning task (Égerházi et al., 2007). The test consists of colored boxes displayed on a touch screen. One or more boxes reveal a pattern, after which that pattern is displayed separately, and the participant must choose the box that initially revealed it (Figure 6). The test involves eight stages of increasing difficulty (Barnett et al., 2016). Subjects with mild cognitive impairment (MCI) or mild Alzheimer's disease have impaired performance in the PAL test (Barnett et al., 2016; Blackwell et al., 2004; Égerházi et al., 2007; Fowler et al., 1997, 2002; Junkkila et al., 2012). In combination with other measures, performance in the PAL test predicts progression from MCI to dementia (Mitchell et al., 2009).

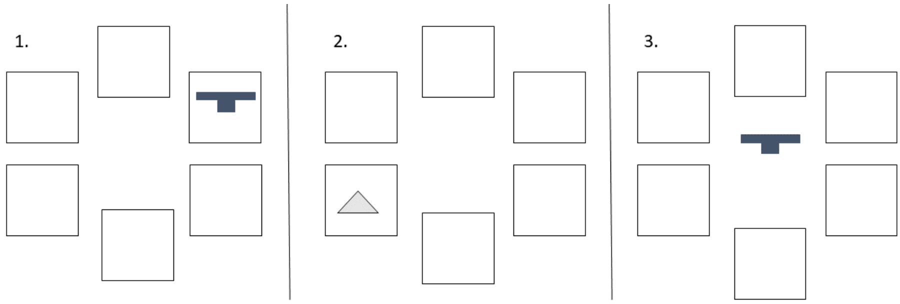

Fig. 6. In the PAL test, shapes are revealed one by one (images 1 and 2). At the end, a shape is shown on the screen and the participant chooses which box showed the shape before.

Standard automatized perimetry testing as a test for cognition

Although not routinely used for evaluating cognitive abilities, performance in the SAP has been linked to cognition: Poorer performance in visual field testing is associated with cognitive decline in glaucoma patients (Diniz-Filho et al., 2017). In addition, cognitive demand negatively correlates with performance in visual field testing (Gangeddula et al., 2017). Visual field test duration has been used as a surrogate for cognition before (Jonas et al., 2013).

Cognition and the RNFL

Interest in the association between cognition and RNFL thickness is based on findings that neurodegenerative processes that affect the brain may also affect the retina. RNFL imaging is faster, cheaper, and more available than, for example, an MRI of the brain (London et al., 2013). In a study of a small sample of 20 healthy subjects aged 60 to 90, a thinner average peripapillary RNLF was associated with poorer performance in two Delis-Kaplan Executive Function System trail-making tests. Tests 2 and 4 measure psychomotor speed/visuomotor tracking and executive function/visuomotor tracking, respectively. Several other tests for cognitive capabilities did not have a statistically significant correlation with the RNFL (Mammadova et al., 2020). The following paragraphs describe larger studies that have evaluated the association between the RNFL and cognition.

Erasmus Rucphen Family (ERF) study

Van Koolwijk et al. studied a sample of 1485 study subjects from a genetically isolated family in the Netherlands. The study assessed cognition with the Dutch Adult Reading Test, the Rey Auditory Verbal Memory Test, the Trail-Making Test, the Stroop Color-Word Test, and Block Design. RNFL thickness was measured with scanning laser polarimetry. Except for the Stroop Color-Word Test, better performance in the tests had a statistically significant correlation with a thicker RNFL. After dividing the participants into three age groups (18–38, 39–52, 53–85), they found that the association was stronger in the younger age groups and diminished in the oldest group. The associations, though significant, were weak and of no predictive value (van Koolwijk et al., 2009).

EPIC-Norfolk Cohort Study

In the EPIC-Norfolk Cohort Study, the findings were the same as the ERF. A better performance in the cognitive tests correlated with a thicker RNFL. Study subjects were 48–89 years old. Tests for cognition were the Mini-Mental State Examination (MMSE), an animal naming task, a letter cancellation task, the Hopkins Verbal Learning Test, the National Adult Reading Test, and the PAL (Khawaja et al., 2016).

LIFE-Adult study

In a large population-based cohort study, poorer performance in cognitive testing across a broad spectrum of neuropsychological tests was correlated with thinner peripapillary RNFL. The participants were 19−80 years old. The tests used were the CERAD-NP Plus test battery (Consortium to Establish a Registry for Alzheimer's Disease), Stroop-Test, Reading the Mind in the Eyes Test, and the Multiple-Choice Vocabulary Intelligence Test. Gender, laterality of the eye, and different RNFL sectors were found to affect the magnitude of the correlation (Girbardt et al., 2021).

UK Biobank

A total of 32 038 participants from the UK Biobank cohort aged 40–69 had their RNFL thickness measured, and cognition evaluated. The study protocol excluded eyes with disease or vision loss. The RNFL was measured with OCT, and cognition was tested for prospective memory, pair matching, numeric and verbal reasoning, and reaction time. The cognition was tested in 2009–2010 for a baseline, and a repeated assessment was performed in 2012–2013. The participants were divided into quintiles according to the RNFL thickness. Those in the quintile with the thinnest RNFL were 11% more likely to fail one or more cognitive tests than those in the quintile with thickest. The difference was statistically significant even after adjusting for confounding factors. Those in the two thinnest RNFL quintiles were twice as likely to perform poorly in the follow-up tests as those in quintile with the thickest RNFL (Ko et al., 2018).

TwinsUK cohort

In the TwinsUK cohort, a thicker RNFL correlated with better MMSE and reaction time results. The study also suggested that the correlation is partly due to shared genetic factors, but the predictive value of the RNFL thickness for performance in the cognitive tests is low (Jones-Odeh et al., 2016).

Lothian Birth Cohort

The global RNFL did not correlate statistically with cognitive testing in the Lothian Birth Cohort. The study subjects were 72 years old. The study used several cognitive tasks from the Wechsler Adult Intelligence Scale-III (WAIS-III). Considering the IQ of the participants when they were 11 years old, the global RNFL thickness had a statistically significant correlation with the test representing general memory and general speed of cognition. The correlation differed from the previously mentioned studies since a thicker RNFL was associated with poorer test performance (Laude et al., 2013).

Dunedin Multidisciplinary Health and Development Study

Barret-Young et al. measured the mean thickness of the RNFL with OCT using data from the Dunedin Multidisciplinary Health and Development Study (New Zealand) subjects when they were 45 years old. A total of 865 study subjects were included. Cognitive function was tested at ages 7, 9, 11, and 45. The Wechsler Intelligence Scale for Children–Revised (WISC-R) and the WAIS-IV were used to assess IQ. A mean was calculated from the three tests in childhood. In addition, three indexes from the WISC-R and WAIS-IV were used, each representing a different specific cognitive domain: verbal comprehension, perceptual reasoning, and processing speed. Lower IQ in adulthood and childhood was statistically significantly associated with a thinner mean RNFL thickness. However, a decline in IQ was not statistically significantly associated with the RNFL measurements. Of the specific cognitive domains, a reduction in processing speed was correlated with thinner RNFL thickness (Barrett-Young et al., 2022).

The Beijing Eye Study

In the Beijing Eye Study, cognition had a statistically significant negative correlation with RNFL thickness in univariate analysis. However, the correlation lost its significance when other significant factors were included in a multivariate analysis. The RNFL thickness was measured with OCT, and cognition was assessed using the MMSE (Wang et al., 2013). In another study, 78 participants with a mean age of 72 years were tested for cognitive capabilities and deterioration over 25 months. They used the Repeatable Battery for the Assessment of Neuropsychological Status to assess cognitive functioning, and the RNFL thickness was measured with OCT. The cognitive tests focused on five areas: list learning, list recall, story recall, immediate memory, and delayed memory. They found that a reduction of the RNFL thickness was positively associated with a reduction in the results of list recall and delayed memory at follow-up, even after adjusting for age, gender, education, blood glucose, and cholesterol level. In a subgroup of 18 subjects whose cognitive level changed from normal to MCI or from MCI to dementia (defined by the MMSE), the thickness of the RNFL correlated negatively with the change in test scores for list recall, story recall, and delayed memory (Shen et al., 2013).

Cognition and the ONH

The Beijing Eye Study assessed the correlation between ONH morphology and cognition in an unselected population of 4089. The surrogates for cognition were the level of education, and the time it took for respondents to complete a visual field test (frequency-doubling threshold perimetry, program C-20-1.). In univariate analysis, the disc size increased with education level and shorter test times. The results also remained statistically significant in multivariate testing (Jonas et al., 2013).

Women’s Health Initiative Study (WHI)

The Women’s Health Initiative Study, started in 1991 in USA, researches the effect of hormone replacement therapy on women’s health. In addition, WHI has ancillary studies. WHI Sight Exam and WHI Memory Study are relevant to this topic. Vajaranant et al. used a sample of 1636 women who participated in both studies to compare the Modified Mini-Mental State Examination (3MSE) results between groups with normal cup-disc ratio (CDR) and large CDR, defined as greater than 0.6 in either eye. After adjusting for confounding factors, they found that women with large CDR had statistically significantly lower scores in the 3MSE than women with normal CDR (Vajaranant et al., 2019). Another study on the same sample accounted for a known genetic factor affecting the CDR as a confounding factor. The result was the same even after accounting for genetic risk score (Kravets et al., 2022).

3 Aims of the study

The aim of this thesis is to study factors affecting the morphology of the ONH and the RNFL in a randomized 45–49 years old Northern Finland birth cohort. First, it examines whether the similarities shared by the ONH and the CNS manifest as significant associations between ONH and RNFL morphology, on the one hand, and cognitive capabilities of the human mind, on the other. Secondly, it explores possible associations between neonatal and antenatal factors and ONH morphology and produces hypotheses for future research. Finally, it provides information on the effect of physiological and morphometrical measurements on the ONH and RNFL morphologies.

The aims of each scientific article included in this thesis are as follows:

1. To study the association between the morphology of the ONH and the RNFL and cognition. (I)
2. To explore the correlations between maternal factors, measurements of the newborn, and the ONH morphology. (II)
3. To evaluate whether ocular and bodily dimensions or physiological measurements affect the structure of the ONH and RNFL. (III)

4 Materials and methods

4.1 The Northern Finland Birth Cohort

The NFBC is a long-term research program promoting the health of the population. The study began in 1965 to study the risk factors for perinatal problems and morbidity. The cohort is a geographically defined population that comprises 12 231 individuals born in 1966 in the two northernmost provinces of Finland (Oulu and Lapland). It covered 96% of births in the area in that year. Prospective data have been gathered since the 24th week of gestation. Follow-up examinations have been conducted at 1, 14, 31, and 46 years of age (Nordström et al., 2021). Thus, vast amounts of information have been gathered throughout the lives of the cohort. In addition, data on morbidity, mortality, and socioeconomic factors have been obtained from hospitals and national registries (Rantakallio, 1988). No data from one-year or 31-year follow-ups was used in the present study. (Figure 7)

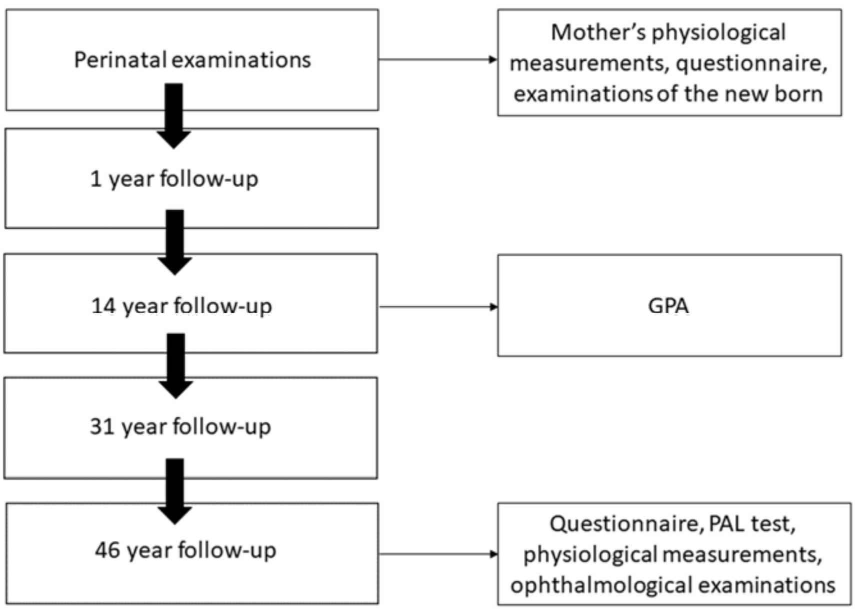

Fig. 7. A flow chart of the NFBC follow-ups. GPA = gradepoint average, PAL test = paired associates learning test.

4.1.1 The 46-year follow-up

The cohort was invited for an extensive examination at the age of 46. This consisted of a postal questionnaire and a clinical health examination, which was conducted at the University of Oulu and Oulu University hospital in 2012-2013. All living members of the cohort with a known address in Finland in 2011 (n=10 321) were contacted through the Digital and Population Data Services Agency. A questionnaire, which had questions on background information, lifestyle, and health behavior was obtained from 67% (n=6868) of the living cohort members. Another questionnaire assessing socioeconomic factors, work-related issues, and mental resources was completed by 66% (n=6774) of the cohort members. The health examinations included physiological, cardiorespiratory, orthopedic, dermatological, and cognitive assessments. In all, 57% of the cohort members took part in the examinations. Smaller samples were evaluated for ophthalmological, gynecological, occupational, dental, and mental health.

4.2 The NFBC Eye Study and the ophthalmological examinations

The NFBC Eye Study was designed to evaluate the efficiency and cost-effectiveness of glaucoma screening in a middle-aged population. The study design (Saarela et al., 2013) and the cross-sectional results on glaucoma screening have already been published (Karvonen et al., 2019, 2022). Because the data used in the present study were gathered during the NFBC Eye Study, its design and data gathering techniques are described in this chapter.

Half of the 10 321 (5155, 50%) NFBC members were randomized to the eye study and half to the control group. Randomization of the population was based on gender, age, and postcode based on the nearest regional post center. There were four age groups depending on the month they were born in: January−March, April−June, July−September, and October-December. For the postcode, there were 13 categories based on the national postal agency’s nearest regional center. Resampling was done using Resampling Stats software (Resampling Stats Inc., Arlington, Virginia, USA). In total, 104 (2 x 4 x 13) strata were assessed by a professional epidemiologist, who was blinded for all factors other than the aforementioned.

Data collection was conducted during 2012-2015 in the Department of Ophthalmology of Oulu University Hospital and seven remote units across Finland.

The examinations were performed during a single visit. A total of 3070 subjects (60%) of the randomized group took part in the examinations.

Numerous ophthalmological examinations were conducted. Those relevant to the present study are listed as follows:

- The morphology of the ONH (optic disc area, neuroretinal rim area and volume, and cup area and volume) was measured with the Heidelberg Retinal Tomograph (HRT) (HRT3, Heidelberg Engineering, Heidelberg, Germany; software version 3.1.2a, Heyex 1.6.2.0).
- The mean RNFL thickness and the six zones of the peripapillary RNFL thickness (Figure 4) were measured with spectral domain optical coherence tomography (OCT) (Cirrus HD-OCT 4000, software version 6.0.0, Carl Zeiss Meditec, Oberkochen, Germany).
- The anterior segment analysis of the same device (Cirrus HD-OCT 4000) was used to assess CCT and the opening of the anterior chamber, which was measured as the angle opening distance between the iris and corneal endothelium 750 μm from the angle closure (AOD).
- Values for refractive correction (spherical equivalent, cylindrical and axial correction of astigmatism) were obtained with an autorefractometer (Nidek AR-360A, Nidek, Gamagori, Japan).
- IOP was measured with the Icare model TA01i (Icare Ltd, Vantaa, Finland).
- The automated perimetry test was performed using the SITA Standard 24-2 test pattern of the Humphrey Field Analyzer II-I (Carl Zeiss Meditec AG, Oberkochen, Germany). The time it took for the participant to complete the test was also recorded.
- The S-F analysis combines the six circumpapillary zones measured with OCT (Cirrus HD-OCT 4000) relative to the visual field test pattern (SITA Standard 24-2). The S-F analysis was created using FORUM Glaucoma Workplace software (Carl Zeiss Meditec AG, Oberkochen, Germany).

4.3 Surrogates for cognition

The grade point average (GPA) of the theoretical school subjects in the 8th grade of comprehensive school was obtained from a questionnaire that was sent to the participants in the year 1980. The grading scale of the Finnish comprehensive school system is between four and 10, with four being the lowest and 10 being the highest grade. The level of education was determined from the questionnaire sent to the cohort members during the 46-year follow-up. For the present study to have large enough groups for statistical analysis, some levels of education were combined to create four categories: no vocational education, vocational course or vocational education, post-secondary education or degree from a university of applied sciences; and a master's degree from a university. The PAL test was done during the same follow-up. The time it took the study subjects to complete the SAP was registered during the eye study.

4.4 Antenatal and perinatal factors

Antenatal data were collected during visits to antenatal clinics by trained staff of local midwives. Measurements of the newborn were taken at maternity hospitals. The blood pressure of the mothers was measured during these visits twice during pregnancy (once during months 2–4 and once during months 5–10), and the data were combined so that the higher value was chosen for the present study. The weight increase during pregnancy was calculated from the data acquired from the antenatal clinics and maternity hospitals. Questionnaires relating to sociodemographic and lifestyle and disease-related factors were collected during visits to the clinics between the 24th and 28th gestational weeks. Data used from the questionnaires in this study include mothers' smoking habits before pregnancy, and amount of smoking during the last three months of pregnancy, and the number of deliveries and miscarriages. Maternal diseases during pregnancy included diabetes, organic heart failure, hypertension, chronic renal disease, fever, placental abruption, thyrotoxicosis, hydrops, albuminuria, urinary infection, chronic pulmonary disease, and bleeding during pregnancy. The use of vitamin or iron supplements, diuretics, antibiotics, analgesics, or sedatives during pregnancy was also assessed. Information on the gender, placental weight, weeks of gestation, birthweight and length, whether the subject is a twin or not, and the mother's age at the time of birth was collected by the maternity hospitals.

4.5 Morphometrical and physiological factors

Systolic (SBP) and diastolic blood pressure (DBP), height, weight, and BMI were measured as part of a clinical examination of overall health during the 46-year follow-up. Systolic and diastolic blood pressure readings were taken three times in the same follow-up, and the mean was calculated and used in the present study.

4.6 Statistical methods

Statistical analyses were conducted using IBM SPSS Statistics (versions 25, 26, and 27 SPSS Inc, Armonk, NY, USA). To assess if the data were normally distributed, they were evaluated in graphical form by a statistician. Table 3 provides a summary of the statistical methods used in the present study.

Table 3. Statistical tests used in the study.

Parameter	Disc area	Rim area	Rim vol.	Cup area[1]	Cup vol.[1]	RNFL thickn.
SAP duration[1]	Spearm. cc		Spearm. cc			Spearm. cc
PAL test[1]	Spearm. cc		Spearm. cc			Spearm. cc
GPA	Pears. cc		Pears. cc			Pears. cc
Level of education	ANOVA		ANOVA			ANOVA
Birth length	Pears. cc	Pears. cc	Pears. cc			
Birthweight	Pears. cc	Pears. cc	Pears. cc			
Gestational weeks	Pears. cc	Pears. cc	Pears. cc			
Number of deliveries	Pears. cc	Pears. cc	Pears. cc			
Placental weight	Pears. cc	Pears. cc	Pears. cc			
Mother's weight increase	Pears. cc	Pears. cc	Pears. cc			
Mother's age	Pears. cc	Pears. cc	Pears. cc			
Highest SBP	Pears. cc	Pears. cc	Pears. cc			
Highest DBP	Pears. cc	Pears. cc	Pears. cc			
Gender	Ind. T test		Ind. T test			
Pulmonary disease	Ind. T test		Ind. T test			
Smoking before pregnancy	Ind. T test		Ind. T test			
Hydrops	Ind. T test		Ind. T test			
Albuminuria	Ind. T test		Ind. T test			
Urinary infection	Ind. T test		Ind. T test			
Vitamin or iron suppl.	Ind. T test		Ind. T test			
Diuretics	Ind. T test		Ind. T test			
Antibiotics	Ind. T test		Ind. T test			
Analgetics or sedative	Ind. T test		Ind. T test			
Bleeding	Ind. T test		Ind. T test			
Birthweight <2500g or ≥2500g	Ind. T test		Ind. T test			

Parameter	Disc area	Rim area	Rim vol.	Cup area[1]	Cup vol.[1]	RNFL thickn.
Smoking at end of the pregrancy	ANOVA		ANOVA			
Miscarriages	ANOVA		ANOVA			
CCT	Pears. cc	Pears. cc	Pears. cc	Spearm. Cc	Spearm. cc	Pears. cc
Spherical equivalent	Pears. cc	Pears. cc	Pears. cc	Spearm. Cc	Spearm. cc	Pears. cc
Cylindrical power[1]	Spearm. cc	Spearm. cc	Spearm. cc	Spearm. cc	Spearm. cc	Spearm. cc
Axis of astigmatism[1]	Spearm. cc	Spearm. cc	Spearm. cc	Spearm. cc	Spearm. cc	Spearm. cc
Intraocular pressure	Pears. cc	Pears. cc	Pears. cc	Spearm. cc	Spearm. cc	Pears. cc
Angle opening of AC	Pears. cc	Pears. cc	Pears. cc	Spearm. cc	Spearm. cc	Pears. cc
SBP	Pears. cc	Pears. cc	Pears. cc	Spearm. cc	Spearm. cc	Pears. cc
DBP	Pears. cc	Pears. cc	Pears. cc	Spearm. cc	Spearm. cc	Pears. cc
Weight	Pears. cc	Pears. cc	Pears. cc	Spearm. cc	Spearm. cc	Pears. cc
Height	Pears. cc	Pears. cc	Pears. cc	Spearm. cc	Spearm. cc	Pears. cc
BMI	Pears. cc	Pears. cc	Pears. cc	Spearm. cc	Spearm. cc	Pears. cc
Grouped cylindr. power	ANOVA	ANOVA	ANOVA	K-W-H-test	K-W-H-test	ANOVA
Gender	Ind. T test	Ind. T test	Ind. T test	M-W-U-test	M-W-U-test	Ind. T test

avg., average; RNFL, retinal nerve fiber layer; thickn., thickness; cc, correlation coefficient; SAP, standardized automated; perimetry; PAL, paired associates learning; GPA, gradepoint average; CCT, central corneal thickness; BMI, bodymass index; ANOVA, analysis of variance; ind., indirect; K-W-H, Kruskal-Wallis-H; Mann-Whitney-U; SBP, systolic blood pressure; DBP, diastolic blood pressure; suppl., supplements; AC, anterior chamber

[1]non-normal distribution

4.6.1 Analyses between the ONH morphology and cognition

To explore associations between ONH morphology and cognition, the number of study subjects would have been low if only those with all the analyzed variables were included. Thus, we used those study subjects with the necessary data for each individual per analysis (Tables 4−5). The left eye of each cohort member was chosen for analysis. Because the results are interpreted as explorative findings, a p-value of 0.05 was chosen as the threshold for statistical significance despite multiple tests. We chose the optic disc area, the rim volume, and the average RNFL thickness to represent ONH morphology. All of them were normally distributed. The time it took to accomplish the SAP, the errors in the PAL test, and the GPA represented cognition. Of these, the duration of the SAP and the errors in the PAL test were not normally distributed. Pearson's correlation coefficient was used to study the correlation between the normally distributed parameters: the optic disc area, the rim volume, the average thickness of the RNFL, and the GPA. Spearman's correlation coefficient was calculated when both or one of the following factors were not normally distributed: the correlations between the ONH parameters, the average RNFL thickness, the total errors in the PAL test, and the duration of the SAP. Spearman's correlation coefficient was also used to evaluate the correlation between the GPA, the total errors, and the duration of the SAP. Analysis of variance (ANOVA) was used to assess the correlation between the ONH parameters, the average RNFL thickness, and the level of education. ANOVA was also calculated to explore the relationship between the total errors in the PAL test, the GPA, the duration of the SAP, and the level of education. An unpaired T-test was used to study the difference between genders when comparing the ONH parameters, the average thickness of the RNFL, the total errors in the PAL test, the GPA, and the duration of the SAP. The difference between the level of education between genders was tested using the Chi-Square test of independence.

4.6.2 Analyses between the ONH morphology, antenatal and perinatal factors

The right eye of the study subjects was chosen for the analyses. Because the results are interpreted as explorative findings, a p-value of 0.05 was chosen as the threshold for statistical significance despite multiple tests. For the analyses performed to explore associations between ONH morphology, and antenatal and perinatal factors, we again used all the study subjects that had the necessary data per each analysis to maximize the number of participants (Tables 6−12). The ONH parameters included in these analyses were the disc area and the rim volume. Pearson's correlation coefficient was used to test for associations between the ONH parameters, mother's age at the time of birth, birth length of the child, birthweight of the child, placental weight, highest systolic and diastolic blood pressure during pregnancy, the increase of mother's weight during pregnancy, number of deliveries, and weeks of gestation. An independent T-test was used to test the following dichotomous variables in relation to the disc area and the rim volume: smoking before pregnancy, gender, birthweight over or under 2500g, hydrops, albuminuria, urinary infection, the use of vitamin or iron supplements, diuretics, antibiotics, analgesics or sedatives, bleeding during pregnancy, and chronic pulmonary disease. For variables with multiple groups, ANOVA was used to test their relationship to the disc area and the rim volume. These variables were smoking during the last three months of pregnancy and multiple groups of miscarriages.

In this study, we also wanted to explore the possible effects of perinatal factors on the extremities of ONH morphology. Thus, we divided the ONH parameters into three groups: the smallest 5%, the largest 5%, and the group in between. ANOVA was then used to test for differences in the mother's age and her weight increase during pregnancy, the number of deliveries, weight and length at birth, placental weight, weeks of gestation, and the highest systolic and diastolic blood pressure between the three groups. In addition, the Chi-square test of independence was used to test the associations between the grouped ONH parameters, mother's chronic pulmonary disease, hydrops, albuminuria, urinary infection, the use of vitamin or iron supplements, diuretics, antibiotics, analgesics or sedatives, bleeding during pregnancy, birthweight over or under 2500g, smoking habits before and at the end of the pregnancy, and miscarriages. Crosstabulation was used for analyses between the grouped ONH parameters and gender.

4.6.3 Analyses between the ONH morphology, morphometrics, and physiological factors

The right eye of the study subjects was chosen for this analysis. For this part of the present study, we included the cohort members who had all the data required for all the analyses, since the number of these study subjects was sufficiently high. The measurements of the optic cup area and volume, the cylindrical correction, and the axis of cylindrical refractive correction were not normally distributed, and non-parametric tests were used to test their associations with each other and other parameters. This subject has been more thoroughly researched than the previous two parts of the present study, i.e., this part is not as explorative. Therefore, we used corrections for multiple testing in the analyses when appropriate. A Bonferroni correction of $\alpha/5$ i.e. $p<0.010$ was used for the following analyses in Table 14 because of five hypotheses tested: 1) difference of ONH morphology between genders (disc area, rim area, cup area, rim volume, cup volume, and RNFL thickness; 2) the difference of anterior segment parameters between genders (spherical equivalent, cylindrical power, axis of astigmatism, and chamber angle opening); 3) the difference of parameters related to intraocular pressure between genders (IOP, CCT); 4) the difference of blood pressure between genders (SBP, DBP); 5) the difference in height/weight between genders (height, weight, BMI). A p-value<0.050 was chosen as the threshold for statistical significance for the analyses shown in Tables 15, 16 and 17 because the ONH and RNFL parameters have a high and significant correlation with each other, so correction for multiple testing was not used. A Bonferroni correction of $\alpha/4$ i.e., $p<0.013$, was used for the following analyses in Tables 18 and 19 due to the four hypotheses tested: 1) the association between anterior segment parameters and ONH morphology; 2) the association between parameters related to intraocular pressure and ONH morphology; 3) the association between blood pressure and ONH morphology; 4) the association between height/weight and ONH morphology.

Pearson's correlation coefficient was used to calculate correlations between the following continuous parameters: ONH morphology, RNFL variables, and morphometric and physiological measurements. Spearman's correlation coefficient was used as a non-parametric test with the non-normally distributed parameters mentioned before. The t-test was used to test for differences in the ONH parameters, the average RNFL thickness, morphometrical measurements, and the physiological factors between genders, while the Mann-Whitney-U-test was used instead with the non-normally distributed parameters.

The cylindrical power of the refractive correction was divided into three groups: the smallest 5%, those in the central 5%-95%, and the largest 5%. Axes of astigmatic refractive corrections were also divided into three groups based on the direction of astigmatism: 1) with-the-rule astigmatism; 2) against-the-rule astigmatism; 3) no astigmatism. The group with with-the-rule astigmatism had a cylindrical correction of at least +0.75D between 80 and 100 degrees. Against-the-rule astigmatism was defined as the cylindrical correction of at least +0.75D between 0 and 10 or between 170 and 180 degrees. The third group did not have any cylindrical correction in any direction. To establish a clear difference between the groups, the subjects who had mild astigmatism of 0.25−0.50 were not included in this analysis. Analysis of variance (ANOVA) was used to test differences in ONH morphology and average RNFL thickness between these groups. The Kruskal-Wallis-H-test was used instead with the non-normally distributed parameters mentioned before. For a thorough assessment of the effect of astigmatism on the ONH morphology, a multiple linear regression analysis was conducted, in which the power of the cylindrical correction and the axis of the correction were analyzed in relation to the ONH parameters.

4.7 Ethical approval

The NFBC Eye Study follows the tenets of the Declaration of Helsinki. Written informed consent was obtained from all cohort members participating in the 46-year follow-up. The ethical approval for the study was given by the Ethical Committee of the Northern Ostrobothnian Hospital District (94/2011).

5 Results

5.1 Characteristics of the NFBC Eye Study population (I-III)

A total of 10 321 members of the cohort were alive and living in Finland in 2011. They were randomized into the NFBC eye examination group and the control group. Of the 5155 members randomized into the Eye Study group, 3070 (60%) participated in the actual examinations. Measurements of sufficient quality were obtained from 3039 participants (59%). In 18 subjects, only one eye was examined because of ocular morbidity, which restricted examinations.

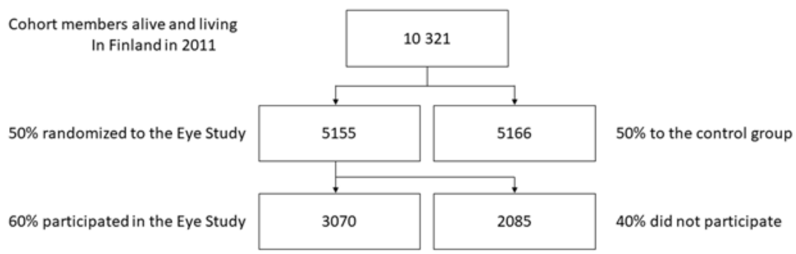

Fig. 8. Participation and randomization of the NFBC Eye Study population.

5.2 Morphology of the ONH, average RNFL, and cognition (I)

Of the 3070 members of the cohort who took part in the ophthalmological examinations, the level of education was acquired from 2585 subjects, the PAL test results from 2484 subjects, the SAP test time from 3041 subjects, the disc area from 2970 subjects, the rim volume from 2970 subjects, and the average RNFL thickness from 2960 subjects. In addition, the GPA from 8th grade from the previous follow-up had been recorded for 2670 study subjects. We present the study variables in detail in Table 4. For the analyses done to explore associations between the ONH morphology and cognition, we used all the study subjects that had the required data per analysis, i.e., we did not form a population that would have had all the data required for all the analyses for this part of the present study. However, this probably would not have substantially diminished our study population since the number of subjects for each study parameter was high (2484−3041).

Table 4. Study variables of the analyses between ONH morphology and cognition. Republished with permission from the article I © Taylor & Francis.

Study variables	N	Min.	Max.	Mean	Std. Deviation
Participants	3068				
Level of education	2585	1	4		
Total errors in PAL test	2484	0	116	13	12
Disc area [mm^2]	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 [µm]	2960	20	141	90	9
SAP test time [mm:ss]	3041	3:40	13:34	4:45	0:39
School grade point average	2670	5.0	9.9	7.7	1.0

PAL, paired associates learning; RNFL, retinal nerve fiber layer; SAP, standard automated perimetry

5.2.1 ONH and cognition

The disc area had a statistically significant correlation with the SAP test time and the GPA but not with the total errors in the PAL test. The correlation coefficients were low for the statistically significant results (R=-0.065–-0.084). The results were the same when tested separately for men. For women, only the GPA correlated with statistical significance with the disc area. The rim volume had a statistically significant correlation with the SAP test time, the total error in the PAL test, and the GPA. However, the correlation coefficients were low even for the statistically significant results (R=-0.056–0.072). When tested separately for men, only the GPA had a statistically significant correlation with the rim volume. Only the SAP test time and rim volume correlated with statistical significance for women. We present the results between the ONH parameters and the continuous parameters cognition in Table 5.

Table 5. Correlations between ONH morphology and the surrogates for cognition. Republished with permission from article I © Taylor & Francis.

ONH and RNFL variables	SAP test time	Total errors in PAL test	Gradepoint average
Disc area [mm^2]			
All subjects (N=2970)	p<0.001, R=-0.065	p=0.932, R=-0.002	p<0.001, R=-0.084
Men (N=1334)	p=0.001, R=-0.093	p=0.298, R=-0.033	p=0.012, R=-0.073
Women (N=1636)	p=0.181, R=-0.033	p=0.673, R=0.011	p=0.001, R=-0.085
Rim volume [mm^3]			
All subjects (N=2970)	p=0.011, R=-0.047	p=0.006, R=-0.056	p<0.001, R=0.072
Men (N=1334)	p=0.283, R=-0.030	p=0.303, R=-0.032	p=0.004, R=0.082
Women (N=1636)	p=0.001, R=-0.085	p=0.074, R=-0.048	p=0.331, R=0.025
Average RNFL thickness [μm]			
All subjects (N=2943)	p=0.012, R=-0.047	p=0.845, R=-0.004	p=0.936, R=0.002
Men (N=1330)	p=0.015, R=-0.067	p=0.613, R=0.016	p=0.351, R=-0.027
Women (N=1613)	p=0.153, R=-0.036	p=0.688, R=-0.011	p=0.624, R=0.013

ONH, optic nerve head; SAP, standard automated perimetry; PAL, paired associates learning test.

The disc area of the subjects with vocational courses or education was significantly larger than that of subjects with post-secondary education or degree from university of applied sciences, i.e., subjects with a lower level of education had slightly larger disc areas. We found no differences in the disc areas between the other levels of education. The same results applied when tested separately for men. Women’s level of education did not influence the disc areas to a statistically significant degree. The rim volume of the subjects with a master's degree from a university was significantly larger than the rim volume of the subjects with no vocational education, vocational course, or vocational education. We found no statistically significant differences when the same analysis was performed separately for men. The female study subjects with a master's degree from a university had on average a larger rim volume than women with no vocational education. (Figure 9)

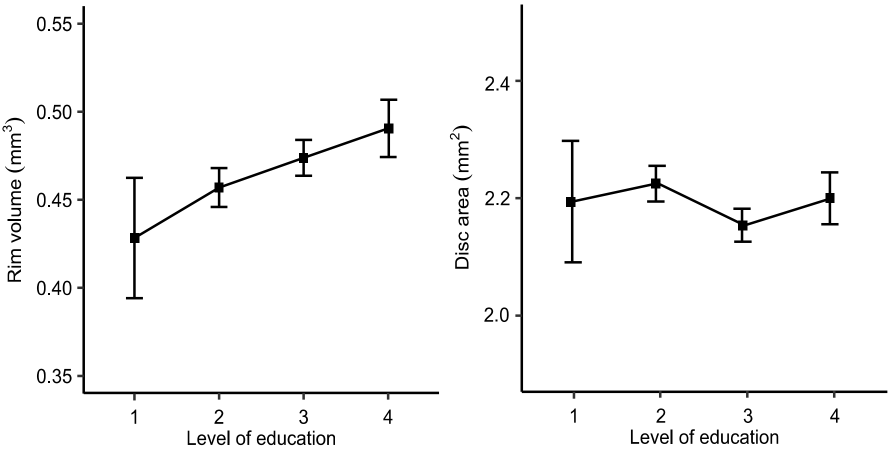

Fig. 9. Rim volume, disc area and the level of education. 1=no vocational education, 2=vocational course or vocational education, 3=post-secondary education or degree from university of applied sciences, 4=master's degree from a university. Edited with permission from the article I © Taylor & Francis.

5.2.2 The average RNFL thickness and cognition

The average RNFL thickness displayed a statistically significant correlation with the duration of the SAP test. We found the same result in men but not in women when we tested separately for genders. The correlations were negative, meaning the participants with the thicker RNFL accomplished the SAP test faster. The GPA and total errors in the PAL test did not correlate statistically with the RNFL (Table 5). The average RNFL thickness did not differ with statistical significance between the different levels of education, and the results were the same when tested separately for men and women.

5.2.3 Correlation between the cognitive function parameters

The association between the total errors in the PAL test and the level of education was statistically significant. The study subjects with a master's degree made fewer errors in the PAL test than their counterparts with lower levels of education. The correlation between the total number of errors in the PAL test and the duration of the SAP was also statistically significant. A longer SAP duration was associated with more errors in the PAL test. The time it took to accomplish the SAP differed with statistical significance between the different levels of education. Faster completion of the SAP correlated with a higher education level when not including people with no vocational education. There was a statistically significant negative correlation between the GPA and the total errors in the PAL test, meaning that the study participants with a higher GPA made fewer errors in the PAL test. We found a statistically significant positive correlation between GPA and the level of education. Participants with a higher GPA tended to have a higher level of education, except when comparing study subjects with no vocational education to study subjects with vocational courses or vocational education.

5.2.4 Difference between genders

We found a statistically significant difference between men and women regarding rim volume, average RNFL thickness, and total number of errors in the PAL test, the GPA, the duration of the SAP, and the distribution of the level of education. Men had less rim volume, and their average RNFL thickness was thinner. Men had a lower GPA. Men completed the SAP test faster but made more errors in the PAL test and had a lower level of education than women.

5.3 Morphology of the ONH and perinatal factors (II)

We chose the right eye of each study subject for our analysis. The number of mothers with diabetes, mothers with organic heart failure, thyreotoxicosis, hypertension, chronic renal disease, fever, or placental abruption, or those undergoing treatment for a threat of miscarriage was too low for statistical analysis. The number of subjects born as twins was also too low.

5.3.1 ONH parameters as continuous variables

Of the continuous perinatal factors, the disc area had a statistically significant correlation with birth length and weeks of gestation. The correlations were weak and positive, meaning that higher birth length and gestational age correlated with larger disc areas. Birthweight, number of deliveries, placental weight, and the mother’s weight increase or highest diastolic blood pressure, and mother’s age did not influence the disc area significantly. The gender of the newborn did not influence the disc area to a statistically significant degree. The disc area was also positively correlated with the mother's highest systolic blood pressure measured during pregnancy. Study subjects whose mothers had a pulmonary disease had smaller disc areas than subjects whose mothers did not. The difference was statistically significant. No other recorded disease, use of vitamin or iron supplements, diuretics, antibiotics, analgesics, or sedatives during pregnancy influenced the optic disc area to a statistically significant degree. Bleeding during pregnancy, smoking at the end of the pregnancy, previous miscarriages, or birthweight under 2500g did not significantly affect the disc area. We tested the same variables in relation to the rim volume, and only gender had a statistically significant influence on it. Women had larger rim volumes. (Tables 6−11)

Table 6. Correlations between continuous maternal and neonatal factors and disc area. Republished with permission from article II © John Wiley & Sons.

Maternal and neonatal factors	Pearson's correlation coefficient		
	N	R	p
Birth length	2939	0.046	0.012
Birth weight	2968	0.035	0.054
Gestational weeks	2867	0.031	0.030
Number of deliveries	894	0,018	0,592
Placental weight	2593	0.013	0.521
Mother's weight increase during pregnancy	651	-0.016	0.686
Mother's age	2939	0,004	0,809
Highest systolic blood pressure during pregnancy	2741	0.040	0.035
Highest diastolic blood pressure during pregnancy	2740	0.000	0.984

Table 7. Correlations between grouped maternal factors and disc area. Republished with permission from article II © John Wiley & Sons.

Grouped maternal factors	Anova		
	N	mean [mm^2]	p
Did not smoke at end of the pregrancy	2558	2.180	0.290
1–5 cigarettes or 1–3 pipefuls	167	2.196	
6–10 cigarettes or 4–8 pipefuls	71	2.069	
11–15 cigarettes	20	2.249	
16–20 cigarettes	18	2.309	
more than 20 cig or more than 8 pipes	5	2.276	
0 miscarriages	2413	2.180	0.458
1 miscarriage	352	2.199	
2 miscarriages	100	2.203	
3 or more miscarriages	39	2.078	

Table 8. Correlations between dichotomous maternal and neonatal factors and disc area. Republished with permission from article II © John Wiley & Sons.

Dichotomous maternal and neonatal factors	t-test		
	N	mean [mm^2]	p
Female	1645	2.168	0.085
Male	1336	2.198	
No Pulmonary disease	2574	2.184	0.007
Pulmonary disease	62	2.020	
No smoking before pregnancy	2364	2.184	0.501
Smoking before pregnancy	533	2.169	
No hydrops	1909	2.187	0.194
Hydrops during pregnancy	852	2.162	
No albuminuria	2525	2.171	0.772
Albuminuria during pregnancy	226	2.181	
No urinary infection	769	2.191	0.337
Urinary infection during pregnancy	60	2.130	
No vitamin or iron supplements	67	2.155	0.567
Vitamin of iron supplements during pregnancy	768	2.189	
No diuretics	709	2.190	0.868
Diuretics during pregnancy	112	2.181	
No antibiotics	740	2.195	0.392
Antibiotics during pregnancy	80	2.147	
No analgetics or sedatives	767	2.196	0.137
Analgetics or sedative during pregnancy	53	2.096	

Dichotomous maternal and neonatal factors	t-test		
	N	mean [mm²]	p
No bleeding	793	2.195	0.363
Bleeding during precnancy	30	2.114	
Birthweight ≥2500g	2888	2.180	0.764
Birthweight <2500g	80	2.196	

Table 9. Correlations between continuous maternal and neonatal factors and rim volume. Republished with permission from article II © John Wiley & Sons.

Continuous maternal and neonatal factors	Pearson's correlation coefficient		
	N	R	p
Birthlength	2938	-0.025	0.169
Birthweight	2967	-0.006	0.733
Gestational weeks	2866	0.029	0.117
Number of deliveries	893	-0.008	0.808
Placental weight	2592	-0.013	0.511
Mother's weight increase during pregnancy	650	0.012	0.751
Mother's age	2938	-0,007	0,698
Highest systolic blood pressure during pregnancy	2738	-0.019	0.327
Highest diastolic blood pressure during pregnancy	2739	0.020	0.307

Table 10. Correlations between grouped maternal factors and rim volume. Republished with permission from article II © John Wiley & Sons.

Grouped maternal factors	Anova		
	N	mean [mm³]	p
Did not smoke at end of the pregrancy	2557	0.467	0.964
1–5 cigarettes or 1–3 pipefuls	167	0.466	
6–10 cigarettes or 4–8 pipefuls	71	0.448	
11–15 cigarettes	20	0.473	
16–20 cigarettes	18	0.477	
more than 20 cig or more than 8 pipes	5	0.476	
0 miscarriages	2413	0.465	0.384
1 miscarriage	351	0.467	
2 miscarriages	100	0.483	
3 or more miscarriages	39	0.440	

Table 11. Correlations between dichotomous maternal and neonatal factors and rim volume. Republished with permission from article II © John Wiley & Sons.

Dichotomous maternal and neonatal factors	t-test		
	N	mean [mm^3]	p
Female	1644	0.482	<0.001
Male	1336	0.445	
No Pulmonary disease	2573	0.464	0.876
Pulmonary disease	62	0.461	
No smoking before pregnancy	2364	0.467	0.394
Smoking before pregnancy	533	0.461	
No hydrops	1908	0.466	0.588
Hydrops during pregnancy	852	0.462	
No albuminuria	2524	0.470	0.658
Albuminuria during pregnancy	226	0.465	
No urinary infection	768	0.472	0.780
Urinary infection during pregnancy	60	0.466	
No vitamin or iron supplements	67	0.456	0.461
Vitamin of iron supplements during pregnancy	767	0.472	
No diuretics	709	0.470	0.477
Diuretics during pregnancy	111	0.482	
No antibiotics	739	0.472	0.541
Antibiotics during pregnancy	80	0.460	
No analgetics or sedatives	767	0.472	0.947
Analgetics or sedative during pregnancy	52	0.470	
No bleeding	793	0.473	0.690
Bleeding during precnancy	29	0.460	
Birthweight ≥2500g	2887	0.466	0.360
Birthweight <2500g	80	0.449	

5.3.2 ONH parameters as grouped variables and perinatal factors

The results did not differ substantially between ONH parameters as continuous variables and those tested as grouped variable in relation to the perinatal factors. Women were overrepresented in the largest 5% group of rim volume and men in the smallest 5% group of rim volume (Table 12). The difference was statistically significant. The cohort members whose mothers had a chronic pulmonary disease were overrepresented in the smallest 5% group of disc area (Table 13). None of the other measurements of the newborn or the maternal factors had a statistically significant correlation with the grouped ONH parameters.

Table 12. Crosstabulation between rim volume as a grouped parameter and gender. Republished with permission from article II © John Wiley & Sons.

Rim volume groups	female	male	total
Smallest 5%			
Count	70 (4%)	87 (7%)	157 (5%)
Expected Count	87 (5%)	70 (5%)	157 (5%)
5–95%			
Count	1466 (89%)	1206 (90%)	2672 (90%)
Expected Count	1474 (90%)	1197 (90%)	2672 (90%)
Largest 5%			
Count	109 (7%)	43 (3%)	152 (5%)
Expected Count	84 (5%)	68 (5%)	152 (5%)
Total			
Count	1645	1336	2981
Expected Count	1645	1336	2981

p<0.001

Table 13. Crosstabulation between disc area as a grouped parameter and mother's chronic pulmonary disease. Republished with permission from article II © John Wiley & Sons.

Disc area groups	Chronic pulmonary disease	No chronic pulmonary disease	Total
Smallest 5%			
Count	6 (10%)	124 (5%)	130 (5%)
Expected Count	3 (5%)	127 (5%)	130 (5%)
5–95%			
Count	54 (87%)	2317 (90%)	2371 (90%)
Expected Count	56 (90%)	2315 (90%)	26721(90%)
Largest 5%			
Count	2 (3%)	133 (5%)	136 (5%)
Expected Count	3 (5%)	133 (5%)	136 (5%)
Total			
Count	62	2574	2636
Expected Count	62	2574	2636

p=0.020

5.4 The ONH morphology, the average thickness of the RNFL, physiological and morphometrical factors (III)

In total,1552 right eyes of the participants had all the data required for the analysis. Eight (0.5%) eyes had glaucomatous damage. As the number of glaucomatous eyes was low, and we wanted to perform the analyses on a non-selected population, we included these eyes with glaucomatous damage in the analyses. We present the key statistics of the parameters and the difference between genders in Table 14. Of the statistically significant findings, men had smaller rim volumes (men 0.45 mm^3 vs. women 0.48 mm^3, difference 6%), thicker CCT (538 µm vs. 533 µm, 1%), larger spherical equivalent (-1.0D vs. -1.6D), larger anterior chamber angle opening (974 µm vs. 869 µm, 12%), higher SBP (131 mmHg vs. 121 mmHg, 8%) and DBP (87 mmHg vs. 83mmHg, 5%), more weight (88kg vs. 72kg, 22%), more height (179cm vs. 165cm, 8%), and higher BMI (27.5 vs. 26.3, 55%).

Table 14. Study parameters (III) and their difference between genders. Republished with permission from article III © John Wiley & Sons.

Study variables	All			Men (n=635)	Women (n=917)	
	N	Mean	SD	Mean	Mean	p
Disc area [mm^2]	1552	2.18	0.48	2.20	2.17	0.196
Rim area [mm^2]	1552	1.73	0.34	1.72	1.73	0.441
Rim volume [mm^3]	1552	0.47	0.16	0.45	0.48	<0.001
Cup area [mm^2]	1552	0.41	0.45	0.43	0.38	0,013
Cup volume [mm^3]	1552	0.06	0.12	0.07	0.06	0,037
RNFL thickness [µm]	1552	92	10	91	92	0.072
CCT (µm)	1552	535	35	538	533	0.005
Spherical equivalent	1552	-1.36	2.47	-1.03	-1.59	<0.001
Cylindrical power[1]	1552	0.50	0.50	0.50	0.50	0.588
Axis of astigmatism[1]	1552	89	56	87	89	0.435
IOP (mmHg)	1552	15	3	15	15	0.447
AOD (µm)	1552	912	326	974	869	<0.001
Systolic BP (mmHg)	1552	125	16	131	121	<0.001
Diastolic BP (mmHg)	1552	84	11	87	83	<0.001
Weight (kg)	1552	78.3	17.4	88	71.64	<0.001
Height (cm)	1552	170.6	9.0	178.7	165.1	<0.001
BMI (kg/m^2)	1552	26.8	5.0	27.5	26.3	<0.001

RNFL, retinal nerve fiber layer; CCT, central corneal thickness; IOP, intraocular pressure; AOD, anterior chamber angle distance; opening; BP, blood pressure; BMI, body mass index

[1]median, interquartile change and non-parametric test used because of non-normal distribution

As expected, the optic disc area was strongly associated with ONH morphology parameters (rim area, rim volume, cup area, cup volume, cup volume) (r=0.261−0.706). All the correlations were positive. The average RNFL thickness correlated significantly and positively with all the other parameters of the ONH morphology except cup area. However, when compared to the disc area, the associations were considerably weaker (r=0.051−0.092). (Table 15)

Table 15. Correlations between ONH and RNFL parameters. Republished with permission from article III © John Wiley & Sons.

RNFL variables	Disc area		Average RNFL thickness	
	r	p	r	p
Rim area	0.706	<0.001	0.08	0.026
Rim volume	0.261	<0.001	0.09	<0.001
Cup area[1]	0.706	<0.001	0.034	0.181
Cup volume[1]	0.597	<0.001	0.051	0.044
Disc area			0.057	0.026

ONH, optic nerve head; RNFL, retina nerve fiber layer

[1]Spearman's correlation coefficient used instead of Pearson's because of non-normal distribution

All six RNFL zones (Figure 4) correlated strongly and positively with the average RNFL thickness (R=0.40−0.71). The correlations with the ONH morphology were considerably weaker. The disc area, cup area, and cup volume correlated significantly with zones 1, 5, and 6. The correlations were positive, except with zone 6, where they were negative. The rim area and volume had a statistically significant positive correlation with zones 2, 4, and 6. The rim volume also had a statistically significant negative correlation with zone 5. The results are presented in detail in Tables 16 and 17.

Table 16. Correlations between ONH morphology and RNFL zones. Republished with permission from article III © John Wiley & Sons.

RNFL Zones	Disc area		Rim area		Rim volume	
	Pears. cc	p	Pears. cc	p	Pears. cc	p
RNFL Zone 1	0.07	0.006	0.03	0.227	0.00	0.918
RNFL Zone 2	0.04	0.163	0.06	0.012	0.13	<0.001
RNFL Zone 3	0.02	0.46	0.05	0.058	0.05	0.054

RNFL Zones	Disc area		Rim area		Rim volume	
	Pears. cc	p	Pears. cc	p	Pears. cc	p
RNFL Zone 4	0.05	0.066	0.07	0.01	0.12	<0.001
RNFL Zone 5	0.13	<0.001	0.05	0.066	-0.08	0.003
RNFL Zone 6	-0.06	0.021	0.06	0.029	0.18	<0.001

RNFL, retinal nerve fiber layer; Pears, cc., Pearson's correlation coefficient

Table 17. Correlation between ONH morphology, average RNFL thickness and RNFL zones. Republished with permission from article III © John Wiley & Sons.

RNFL Zones	Cup area[1]		Cup volume[1]		Average RNFL thickn.	
	Spearm. cc	p	Spearm. cc	p	Pears. cc	p
RNFL Zone 1	0.08	0.003	0.09	0.001	0.61	<0.001
RNFL Zone 2	0.00	0.995	0.02	0.540	0.71	<0.001
RNFL Zone 3	-0.01	0.642	-0.01	0.602	0.53	<0.001
RNFL Zone 4	0.01	0.763	0.01	0.612	0.64	<0.001
RNFL Zone 5	0.18	<0.001	0.18	<0.001	0.70	<0.001
RNFL Zone 6	-0.11	<0.001	-0.09	0.001	0.40	<0.001

RNFL, retinal nerve fiber layer; Spearm. cc., Spearman's correlation coefficient; Pears.cc., Pearson's correlation coefficient

[1]non-normal distribution

CCT had a statistically significant but weak correlation with all the other ONH parameters except the disc area. A thicker CCT was correlated with a larger rim area and volume and a thicker average RNFL. A thicker CCT correlated with a smaller cup area and volume. The spherical equivalent had a statistically significant association with all the ONH parameters and the average RNFL thickness. As the spherical equivalent increased, the disc area, rim area, and rim volume showed a tendency to decrease (Figure 10).

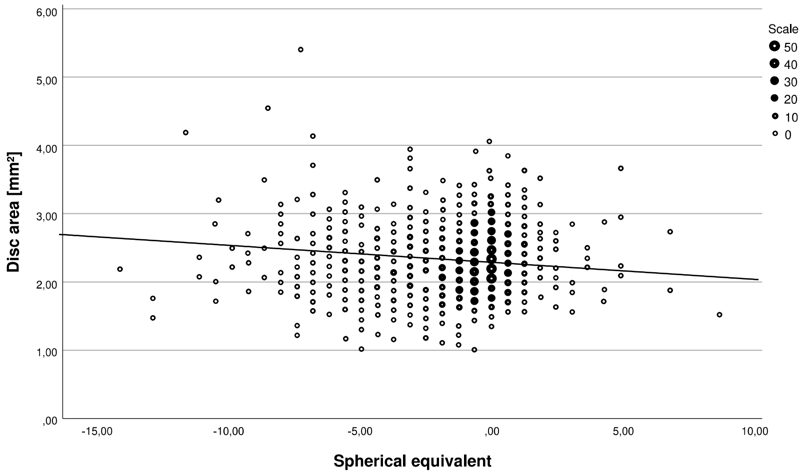

Fig. 10. Correlation between spherical equivalent and disc area. Republished with permission from article III © John Wiley and Sons.

We found the opposite effect between the spherical equivalent, cup area, volume, on the one hand and the average RNFL thickness, on the other. The power of the cylindrical correction of astigmatism had a statistically significant negative correlation with the average RNFL thickness (Table 18 and 19). Because astigmatism consists of the power and axis of astigmatism, we also performed a multivariate linear regression analysis. It showed that the cylindrical correction remained correlated to statistically significantly degree with the average RNFL thickness, and the axis of the correction had a statistically insignificant correlation with the average RNFL thickness. All the other correlations between continuous and grouped cylindrical and axial corrections and ONH morphology and RNFL thickness were not found to be statistically significant.

Table 18. Correlations between anatomical and physiological factors, and ONH and RNFL morphology. Republished with permission from article III © John Wiley & Sons.

Variables	Disc area		Rim area		Rim volume	
	Pears. cc	p	Pears. cc	p	Pears. cc	p
CCT (μm)	0.02	0.427	0.07	0.004	0.07	0.007
Spherical equivalent	-0.12	<0.001	-0.22	<0.001	-0.28	<0.001
Cylindrical power[1]	0.05	0.066	-0.01	0.732	0.05	0.065
Axis of astigmatism[1]	-0.04	0.162	-0.02	0.365	0.01	0.759
IOP (mmHg)	0.05	0.07	0.01	0.667	-0.02	0.338
AOD (μm)	-0.01	0.602	0.04	0.141	0.06	0.030
SBP (mmHg)	0.03	0.276	-0.05	0.071	-0.08	0.003
DBP (mmHg)	0.04	0.09	-0.03	0.311	-0.04	0.103
Weight (kg)	0.00	0.979	-0.01	0.827	-0.03	0.232
Height (cm)	0.02	0.477	-0.01	0.782	-0.07	0.004
BMI (kg/m^2)	-0.02	0.537	0.00	0.938	0.01	0.658

Pears. cc., Pearson's correlation coefficient; CCT, central corneal thickness; IOP, intraocular pressure; AOD, anterior chamber angle opening distance; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index

[1]non-normal distribution, Spearman's correlation coefficient used

Table 19. Correlations between anatomical and physiological factors, and ONH and RNFL morphology. Republished with permission from article III © John Wiley & Sons.

Variables	Cup area[1]		Cup volume[1]		Average RNFL thickness	
	Spearm. cc	p	Spearm. cc	p	Pears. cc	p
CCT (μm)	-0.07	0.007	-0.07	0.008	0.08	0.001
Spherical equivalent	0.07	0.006	0.08	0.002	0.28	<0.001
Cylindrical power[1]	0.03	0.241	0.02	0.361	-0.12	<0.001
Axis of astigmatism[1]	-0.05	0.145	-0.03	0.186	0.00	0.930
IOP (mmHg)	0.05	0.071	0.04	0.1	-0.03	0.275
AOD (μm)	-0.07	0.009	-0.08	0.001	-0.17	<0.001
SBP (mmHg)	0.09	0.001	0.09	0.001	-0.03	0.184
DBP (mmHg)	0.08	0.002	0.08	0.002	-0.03	0.282
Weight (kg)	-0.03	0.245	-0.04	0.095	-0.01	0.809

Variables	Cup area[1]		Cup volume[1]		Average RNFL thickness	
	Spearm. cc	p	Spearm. cc	p	Pears. cc	p
Height (cm)	0.03	0.176	0.03	0.268	-0.01	0.833
BMI (kg/m^2)	-0.04	0.092	-0.06	0.028	0.00	0.903

Spearm. cc., Spearman's correlation coefficient; Pears. cc., Pearson's correlation coefficient; RNFL, retinal nerve fiber layer; IOP, intraocular pressure; AOD, anterior chamber angle opening distance; SBP systolic blood pressure, DBP, diastolic blood pressure; BMI, body mass index

[1]non- normal distribution; Spearman's correlation coefficient used

The AOD had a statistically significant negative association with cup area, cup volume, and average RNFL thickness. However, the associations were weak. We found no statistical significance between the AOD, the disc area, or the rim parameters. IOP did not correlate to a statistically significant degree with the ONH parameters or the average RNFL thickness in our study population. SBP and DBP had a statistically significant correlation between the cup area and volume. The correlations were positive but weak. SBP correlated negatively with rim volume, and the effect was weak. All other correlations between BP and ONH morphology were statistically insignificant. Taller participants had marginally smaller rim volumes. We found no other significant effect between the study subjects' height/weight/BMI or ONH morphology. (Tables 18 and 19)

Finally, we performed a multivariate linear regression analysis to see if the results differed from the univariate analyses. The spherical equivalent remained statistically significant, but its association was weak (beta=-0.03). The anterior chamber angle had a statistically significant association, which we did not find in univariate analysis. However, the effect was not substantial (beta<0.01).

5.5 The effect of the statistically significant results (I-III)

We found a substantial number of statistically significant correlations but also performed multiple analyses. Therefore, this chapter is dedicated to exploring the quality and quantity of those results. We report R^2 when the association is between continuous variables. Between grouped variables, we report the absolute and relative changes. The results are presented in Table 20. Most of the found correlations are weak, explaining less than 1% of the variation in ONH morphology or average RNFL thickness. The spherical equivalent had the largest effect of the studied variables, not including correlations between the ONH morphology factors themselves, explaining up to 8% of the variation in ONH morphology seen in our study population. We found the most considerable difference (15%) in ONH morphology in the rim volume between study subjects with a master's degree from a university and subjects with no vocational education.

Table 20. The effect of the statistically significant results.

Variables	Disc area	Rim area	Rim vol.	Cup area	Cup vol	RNFL thickn.
Cont. variables, pos. correlation	R^2	R^2	R^2	R^2	R^2	R^2
Gradepoint average	–	n/t	0.005	n/t	n/t	–
Birth length	0.002	n/t	–	n/t	n/t	n/t
Gestational weeks	0.001	n/t	–	n/t	n/t	n/t
Highest SBP during pregnancy	0.002	n/t	–	n/t	n/t	n/t
Central corneal thickness	–	0.005	0.005	–	–	0.006
Spherical equivalent	–	–	–	0.005	0.006	0.078
Systolic blood pressure	–	–	–	0.008	0.008	–
Diastolic blood pressure	–	–	–	0.006	0.006	–
Cont. variables, neg.correlation	R^2	R^2	R^2	R^2	R^2	R^2
SAP test time	0.004	n/t	–	n/t	n/t	0.002
Gradepoint average	0.007	n/t	–	n/t	n/t	–
Spherical equivalent	0.014	0.048	0.078	–	–	–
Systolic blood pressure	–	–	0.006	–	–	–
Height	–	–	0.005	–	–	–
Central corneal thickness	–	–	–	0.005	0.005	–
Ant. chamber angle opening	–	–	–	0.005	0.006	0.029
Cylindrical power	–	–	–	–	–	0.014
Grouped variables, max. difference between groups						
Level of education	3 %	n/t	15 %	n/t	n/t	–
Pulmonary disease	8 %	n/t	–	n/t	n/t	n/t
Gender	–	–	7 %	–	–	–

n/t, not tested; -, not statistically significant result; vol., volume, RNFL, retinal nerve fiber layer; thickn., thickness; cont. continuous; pos., positive; correl., correlation; GPA, SBP, systolic blood pressure; neg. negative; max., maximum; SAP, standard automatic perimetry; ant., anterior

6 Discussion

6.1 Cognition and ONH morphology

Why should this topic be explored? Firstly, it is fundamental research. Secondly, the results may support the hypothesis that biomarkers for cognitive decline or neurodegenerative diseases can be found in the eye. Furthermore, should an association between cognition and ONH morphology exist, it could be considered when diagnosing diseases of the ONH. Finally, we can turn this thought around: are there anatomical or functional properties of the eye that support higher cognitive capabilities? Many cognitive tests rely on visual input. Therefore, if some anatomical or functional attributes of the eye enhance visual input, this may support better cognition. We base the biological theory for a possible association between cognition and ocular properties on the embryological, anatomical, and immunological similarities between the ONH and the CNS represented in the literature review in the present study.

Cognition is a complex and multifactorial mental process involving information acquisition, storage, manipulation, and retrieval. We were able to use extensive cognitive tests in the present study. We tested subjects for psychomotor speed (SAP), short-term memory (PAL), long-term memory, and linguistic and mathematical cognitive function (GPA and level of education). Almost all of the cognitive surrogates correlated with each other. Furthermore, the correlations indicate that a better performance in one surrogate is associated with a better performance in another. The correlation coefficients varied from weak to moderate ($|R|=0.080-0.137$). Correlations are expected since a higher cognitive capacity in one test probably supports better performance in others. However, since cognition encapsulates a broad spectrum of skills, it is unsurprising that the correlations are not one-to-one. The most interesting finding was the correlation between the duration of the SAP and other surrogates for cognition. Does a higher cognitive level support better performance in this test of psychomotor speed, or does more accurate and faster processing of simple visual input enable skills in other cognitive domains? We speculate that the process goes both ways. In previous studies, cognitive decline and demand were correlated with poorer performance in the SAP (Diniz-Filho et al., 2017; Gangeddula et al., 2017). Our study provides information on this topic in a population unaffected by neurodegenerative diseases.

In our study, a larger disc area correlated to a statistically significant degree with faster performance in the SAP ($p=0.037$, $R=-0.038$). Jonas et al. had a similar result for a similar quantity in the Beijing Eye Study ($p<0.001$, $R=-0.050$) (Jonas et al., 2013). However, in the present study, a larger disc also correlated with a lower GPA ($p<0.001$, $R=-0.084$), and the only statistically significant difference in the level of education was between a vocational course or vocational education and post-secondary education or a degree from the university of applied sciences; cohort members with vocational course or education actually had a larger disc area (0.07 mm^2, $p=0.005$). By contrast, in the Beijing Eye Study, a larger disc area was correlated with a higher level of education. The Beijing Eye Study used different levels of education, from illiteracy to college or more, which could explain the difference in results. Based on our own findings, the disc area does not seem to correlate consistently with cognition, and this association can be largely ignored in clinical work.

The rim volume can be regarded as a more functional part of the ONH than the disc area since it is an accumulation of the retinal ganglion cells' axons. Our study is the first to explore a possible association between rim volume and cognition. In our study population, a larger rim volume was correlated with faster SAP performance, fewer PAL test errors, and a higher GPA. The highest R^2 was 0.005 between the rim volume and GPA, meaning that only a minor part of the variance of GPA is explained by the variance of the rim volume. When we tested the correlations separately between genders, only the association between the rim volume and GPA in men and the association between the rim volume and the SAP duration in women remained statistically significant. This is probably because the correlations are weak, so a large population must be studied to find statistically significant ones.

Finally, in our study, a thicker RNFL correlated with faster performance in the SAP. We found the same result with the male population but not with female participants. Again, although the correlation was statistically significant, it was weak. Numerous other studies have presented similar results. Mammadova et al. performed multiple testing between average thickness of the RNFL, RNFL thickness in different quadrants, and cognitive tests and found that a worse performance in some tests correlated with a thinner RNFL. However, the majority of the tests did not have a statistically significant association with the RNFL, and no correction for multiple testing (130 analyses) was used (Mammadova et al., 2020). The ERF study showed that a better performance in most cognitive tests correlated with a thicker RNFL. The R^2 in univariate analyses ranged from 0.012

to 0.028, i.e., stronger than in our study. The ERF study population's age ranged from 18 to 85, and they found that the correlation was more pronounced in the age groups under 40, which might explain the stronger correlations in their study compared with ours. Interestingly, the correlation was also statistically significant in the one cognitive test that did not require visual input: Rey's Auditory Verbal Learning Test (van Koolwijk et al., 2009). Khawaja et al. also found a statistically significant positive correlation between the cognitive tests and RNFL thickness. However, they concluded that the thickness of the RNFL explained less than one percent of the variability in the test scores (Khawaja et al., 2016).

The LIFE-Adult Study also found that some cognitive tests correlated with peripapillary RNFL thickness. The correlation coefficients in the statistically significant associations were of the same caliber as those in our study, ranging from 0.002 to 0.045 (Girbardt et al., 2021). The study population in the UK Biobank cohort was divided into quintiles based on the RNFL thickness. Participants in the quintile with the thinnest RNFL failed often more likely in the cognitive tests than their counterparts in the thickest quintile. The two thinnest quintiles also performed more poorly in the follow-up tests than the thickest quintile (Ko et al., 2018).

The Dunedin Multidisciplinary Health and Development Study results stand out from the other studies in this field. The correlation coefficients were substantially stronger between RNFL thickness and cognitive tests: 0.202 at the age of 45 years. This study was also conducted on a birth cohort. The main difference compared with our study was that they used a different cognitive test: the WAIS (Barrett-Young et al., 2022). In the Lothian Birth Cohort, the associations were the opposite: a thicker RNFL correlated with poorer performance in the same cognitive test. The study population was older (72 years) than in our study (Laude et al., 2013). Finally, in another study, two groups were analyzed for 25 months. In the group that showed no cognitive decline during that period, a thicker superior quadrant of the peripapillary RNFL correlated with better performance in list recall (R=0.279) and delayed memory test (R=0.294). The correlation was inverse in the group that showed cognitive decline (R=-0.670 and R=-0.493 for the same tests) and was found only in the inferior quadrant (Shen et al., 2013).

Based on our study, the association between ONH morphology, the RNFL thickness, and cognition is weak, and can be ignored in clinical work. When the other reviewed studies are considered, people with a higher cognition seem to have a slightly thicker RNFL, which can serve as an extra reserve against glaucoma. However, the study designs, the cognitive tests, the volume of correlations, and even the direction of correlations vary. More studies on different populations, especially younger ones where the RNFL is intact from neurodegenerative processes, are needed to affirm the correlation. Furthermore, a longitudinal study could show if the RNFL thickness and cognitive capabilities show a similar trend of inclination or decline. If there is such an association, it may be that properties of the ONH and RNFL reflect circumstances in the CNS, as seen in the results of cognitive tests. These tests rely largely on visual input. We speculate that greater RNFL thickness, a larger disc area, or rim volume could provide a higher capacity for visual input to the CNS and improve the results in cognitive tests.

Finally, the association between the performance speed in the SAP and other cognitive tests is significant. It corresponds to our practical clinical work experience and the literature reviewed earlier in this dissertation. This finding strengthens the idea that cognitive capacity, which might diminish due to age or neurodegenerative disease, should be considered when interpreting visual field test results in clinical work.

6.2 Perinatal factors and ONH morphology

Our study is the most extensive exploration of the association between perinatal factors and ONH morphology in a randomized study population. A novel finding of our analysis was that subjects whose mothers had chronic pulmonary disease had smaller disc areas. Unfortunately, no further information on chronic pulmonary disease was available. Chronic intrauterine hypoxia has been shown to decrease neuronal density in an animal model (Lawrence et al., 2019). We can speculate that this may affect the peak number of axons during the development of the ONH, which could in turn affect the final disc area, as we suggested earlier. However, we do not know if the participants' mothers' pulmonary disease was severe enough to cause intrauterine hypoxia.

Another novel finding was the association between the highest measured SBP during pregnancy and the disc area. A larger disc area was associated with a higher SBP. An earlier study has shown that hypertension during pregnancy can affect the blood flow, oxygenation, and nutritional delivery through the placenta to the fetus, thus disrupting the development of the fetal brain (Rees et al., 2008). In addition, many neurological problems have been linked to hypertension during pregnancy (Maher et al., 2018). How a larger disc area relates to these problems is beyond the scope of the present study. We were also further restricted from studying this subject since the number of mothers with diagnosed arterial hypertension was too low for reliable analyses.

Birth length had a statistically significant correlation with the disc area, but the correlation coefficient was weak. Samarawickrama et al. found no association between the two (Samarawickrama et al., 2009). All the other studies have focused on the association between birth weight and ONH morphology. In our study, the birth weight did not influence the disc area or rim volume. There was also no difference in ONH morphology when we compared study subjects whose birth weight was under 2500g to the rest of the participants. Previous studies have had mixed results. This variation is probably due to different study designs with differing ages of the participants, gestational ages, and grouping of the variables. Our study differs from previous research in that our subjects were adults when the ONH morphology was imaged.

In our study, weeks of gestation explained a minor portion of the disc area variation (0.1%, R^2=0.001). The association could be because the ONH had less time to develop during pregnancy. We speculate that the effect is weak because the ONH continues to mature after (preterm) birth. Mixed results from different study designs have been published before, as reported in the materials and methods section and presented in Table 21. The variation in the results is probably due to the small effect of gestational age on ONH morphology. Thus, it may easily change when the study population, the age of the population, the study design, or the imaging devices used are different.

Table 21. Associations between gestational age and ONH morphology.

Studies	Imaging	Age at examination	Result
II	HRT	46–48 y	Positive correlation between gestational weeks and disc area
Åkerblom et al. (2018)	HRT	5–16 y	Prematurely born (≤32 weeks) had smaller rim area than children born full term
Alshaarawi et al. (2014)	HRT	8–16 y	Prematurely born (≤32 weeks) had larger rim volume than children born full term
Park et al. (2013)	RetCam	36 wks[1]	No statistically significant findings
Samarawickrama et al. (2009)	OCT	12 y	No statistically significant findings
Hackl et al. (2013)	RetCam	5–6 wks[2]	Lower gestational age correlated with a more vertically oval ONH
Hellström et al. (1997)	Fundus photographs	3–9 y	No difference between premature (24−32) and full-term groups

Studies	Imaging	Age at examination	Result
Hellström et al. (2000)	Fundus photographs	5–9 y	Disc area correlated negatively with gestational weeks in preterm girls (24−28 weeks)
Wikstrand et al. (2010)	Fundus photographs	4–6 y	Prematurely born (≤32 weeks) had smaller disc and rim areas than children born full term
Fiess et al. (2022)	OCT	18–52 y	Prematurely born had thinner RNFL (<36 weeks) than those born full term

y, years; HRT, Heidelberg retinal tomography; OCT, optical coherence tomography; RNFL, retinal nerve fiber layer

[1]postmenstrual weeks; [2]weeks after birth

In conclusion, the perinatal factors explored in this study had a limited effect on the ONH morphology. This is further highlighted by the lack of any new associations found when we grouped the disc area or rim volume to "the extremes" (smallest and largest 5%) and the middle-ground. The low correlations may be explained by the complex, multifactorial nature of ONH development during different stages of the fetal period. ONH morphology may be influenced by numerous genetic, physiological, and pathological environmental factors that affect growth as well as ocular and neural development. Furthermore, it seems that the development of the ONH is well−protected during pregnancy from possible adverse effects studied in the present study.

6.3 Physiological and morphometrical factors and the morphology of the ONH and thickness of the RNFL

Many studies have been published on this topic. One presumed the interest is to identify factors that should be considered when interpreting the appearance and characteristics of the ONH or RNFL. Another aim is to improve diagnostic accuracy. We present the statistically significant findings of the studies reviewed in Chapter 2 in Table 2. In addition, we analyze the findings of our own study in below.

In our study, a larger disc area correlated with a larger rim area, rim volume, and cup volume. Similar results have previously been published in other studies (Iwase et al., 2017; Jonas et al. 2003; Li et al., 2013; Vernon et al., 2005; Zhang et al., 2014). Interestingly, the correlations are strongest between the disc area and the rim area (R^2=0.50) and weakest between the disc area and the rim volume (R^2=0.07). We think the difference arises from the disc area restricting the rim's area. By comparison, the volume of the rim can grow without restriction in a vertical direction. The positive correlation between the disc area and the thickness of the RNFL was substantially weaker (R^2=0.003). The disc area correlates with the rim area/volume, an accumulation of axons forming the RNFL. Thus, a positive correlation was expected. In addition, the RNFL measured at 3.4 mm from the center of the disc. A larger disc means that the measuring point of the RNFL is closer to the disc edge and has not spread as much when compared to a smaller disc. This could also affect the RNFL measurement. Other studies have had varied results, showing positive and negative correlations (Li et al., 2013; Vernon et al., 2005; Zhang et al., 2014). Based on our study population, disc size should be considered when interpreting other ONH morphological values.

Gender significantly influenced the rim volume of the ONH parameters in our study. Women had a 7% larger volume than men. None of the other ONH or RNFL variables differed between genders. Again, interestingly, the rim area did not differ between genders, although its volume did. Varying results have been published before. Some studies found no significant difference between genders when comparing ONH morphology (Gundersen et al., 1998; Jonas et al. 2003; Kashiwagi et al., 2000; Varma et al., 1994). The Bridlington Eye Study found that women had a larger rim volume and a smaller cup area and volume (Vernon et al., 2005). The Tanjong Pagar Study and the Rotterdam Study found that disc area and neural rim area were larger in men than in women (Bourne et al., 2008; Ramrattan et al., 1999). The Handan Eye Study found significant differences in disc area, cup area, and volume between genders (Zhang et al., 2014). Because the differences vary considerably between study populations, no consistent effect can be determined. If the effect of gender on ONH morphology would be accounted for, it should be calculated separately for the population at hand, based on the results for that population.

A thicker CCT correlated positively with male gender, rim area, rim volume, and RNFL and inversely with the cup parameters. However, the associations had limited predictive value (R^2 <0.006). We found no statistically significant association between CCT and disc area. Two other studies have found an inverse correlation between CCT and the disc area (Insull et al., 2010; Pakravan et al., 2007). Another found no significant effect between the two (Carbonaro et al., 2014). None of the reviewed eye studies from Chapter 2 presented a statistically significant association between CCT and ONH morphology. Pakravan et al. hypothesized that the association between CCT and optic disc size could be based on the fact that both fill "a scleral pothole." This does not seem plausible, however, as the ONH and sclera develop from different embryological tissues than the cornea

(Hoar, 1982; Zavala et al., 2013). Based on the previous studies and the present one, the association between CCT and ONH morphology can be said to be weak in a randomized population.

A wider anterior chamber angle was associated with male gender, smaller cup parameters, and thinner RNFL, yet the correlations are relatively low ($R^2 < 0.03$). In the Beijing Eye Study, a narrow anterior chamber angle correlated with large optic discs (Xu et al., 2008). In the Tanjong Pagar Study, anterior chamber depth correlated with the rim but not the disc area (Bourne et al., 2008). A narrow anterior chamber angle is associated with an elevated risk of angle closure glaucoma (Sun et al., 2017). However, in our population, it does not predict changes in the ONH morphology or RNFL related to glaucomatous damage.

The effects of SBP and DBP on ONH morphology and RNFL thickness were found to be of limited predictive value. SBP and DBP had a minor association with the cup parameters and SBP also with the rim volume. A larger cup volume and area correlated with higher SBP and DBP. A smaller rim volume correlated with higher SBP. A smaller disc area correlated with a higher DBP in the Handan Eye Study (Zhang et al., 2014). No significant associations between BP and ONH morphology were found in the Tajimi Study (Abe et al., 2009). Previous studies have found that high blood pressure correlates with a thinner RNFL (Huang et al., 2023; Sahin et al., 2015). High blood pressure can affect the circulation in the terminal capillaries, cause pathological changes in the vessels and disturb the autoregulation of blood flow (Martinez-Quinones et al., 2018). This could damage the RNFL. In our study, the thickness of the RNFL did not correlate with SBP or DBP, but a smaller rim volume or a larger cup area/volume can be a secondary sign of RNFL thinning. The observed effect was small, which could be due to the relatively young age of our population: In effect, the years of high blood pressure would be fewer.

In our study, population height had a minor negative correlation with rim volume. It predicted less than one percent ($R^2=0.005$) of the variance in the rim volume. We found no other effects between the morphometrics of the study subjects and their ONH morphology or average RNFL thickness. The Rotterdam Study found a weak positive association between height and disc area and no association between height and cup area or cup-to-disc area; the Tajimi Study found that increasing height correlated positively but weakly with cup-related parameters and negatively with rim-related parameters (Abe et al., 2009; Ramrattan et al., 1999). The differences between the studies might, to some degree, be attributed to racial differences. The brain has been shown to correlate with height to a certain extent

(Jäncke et al., 2019). Thus, we were interested in studying the association between morphometrics and ONH morphology. Based on our study and the two referred studies, we conclude that height, weight, and BMI can be ignored when interpreting the morphology of the ONH or RNFL.

The present study is the first to evaluate the correlations between parameters of astigmatism and ONH morphology measured by HRT. We found only a minor effect between astigmatism and average RNFL thickness. Greater astigmatism was correlated with thinner RNFL, although the effect was relatively weak (R^2=0.01). The direction of astigmatism did not influence ONH morphology or RNFL thickness. Liu et al. found that subjects with a high degree of with-the-rule astigmatism had a larger disc area and rim area, as well a thinner RNFL in the temporal quadrant in highly myopic subjects. They used OCT to measure the ONH and RNFL (Liu et al., 2012). Another study has shown that corneal astigmatism is significantly correlated with an increasingly elongated optic disc shape using optic disc photographs (Jonas et al., 1997). Based on these studies as well as our own research, it is not possible to assess with certainty if there is an actual anatomical correlation between the astigmatic shape of the cornea and ONH or RNFL anatomy, or there is distortion of the acquired measurements. However, based on our study, it appears astigmatism does not influence the measurements (or the anatomy) of the ONH or RNFL to a degree that it needs to be considered when interpreting the results.

In our study population, the spherical equivalent had a relatively strong positive correlation (R^2=0.08) with RNFL thickness. The same kind of results have been published in several other eye studies (Mauschitz et al., 2018; Wang et al., 2013; Wu et al., 2022; Zhao et al., 2014). These results are further emphasized if we include those that evaluated the association between axial length and RNFL thickness because the axial length and spherical equivalent are strongly correlated (Girkin et al., 2010; Khawaja et al., 2013; Klein et al., 2009). We conclude that the association between spherical equivalent and RNFL thickness exists because the RNFL is spread over a larger area in a larger, i.e., myopic, eye. Thus, the RNFL becomes thinner.

In our study population, the spherical equivalent correlated negatively with disc size and rim parameters. Similar results have been published before (Ramrattan et al., 1999; Zhang et al., 2014). Other studies have found no association between the studied ONH parameters and refraction (Bowd et al., 2002; Gundersen et al., 1998; Kashiwagi et al., 2000; Varma et al., 1994). Myopic eyes are larger in all dimensions, which could be why there is more space for the optic nerve head to grow (Atchison et al., 2004). A larger ONH is more easily suspected of having glaucomatous damage (Jonas et al., 2001, 2004; Sommer, 1996). However, a larger rim volume could provide a better reserve against such damage.

6.4 Strengths of the study

Using data from the NFBC, a prospective cohort, is a major strength of this study. A prospective cohort is a time-consuming and expensive study design. Thus, the NFBC provides a rare opportunity in ophthalmological research. A prospective cohort is less prone to bias and can provide more reliable data on the factors being studied. Due to the prospective design of the cohort, combined with its considerable size, it represents the population (in this case, the middle-aged Finnish population) well.

For studies concerning the association between cognition and ONH morphology, the strengths are the multiple surrogates that can be used for cognition and the age of the studied population. Cognition is a broad concept, and we used many tests to represent it in our study. The level of education is a good surrogate for cognition since the subjects have had similar educational opportunities (OECD, 2015; Pekkarinen et al., 2009). In addition, they were of age when usually no neurodegenerative diseases are found, but the vast majority have completed their education. This provides an excellent time frame for this part of our study.

Data have been collected for the cohort from the prenatal period, providing a unique opportunity to study factors from that stage of development in relation to ONH morphology. Furthermore, the data on maternal factors are more extensive than in previous studies of the same nature. Additionally, the data are probably more reliable since they have been collected prospectively. Our study provides the most extensive research on the association between perinatal factors and ONH morphology thus far.

For the third part of this paper, strengths include the large number of cases that we consider to provide a good representation of the population of the Northern Finnish aged 40-50 years. Moreover, with the extensive eye examination data acquired from the NFBC Eye Study, we were able to conduct unique research on the association between astigmatism and ONH morphology measured with HRT 3.

6.5 Limitations of the study

The cross-sectional nature of the study reduces the possibility of making causal deductions between the studied factors. Sixty percent of the NFBC Eye Study population took part in the examinations. In the present study, we were not able to correct the refractive magnification effect in imaging with HRT 3. This allows for a better comparison with previous studies that used HRT 1 and HRT 2. However, it might still be considered a limitation if we want to think that the results represent actual anatomical ONH morphology. We did not correct for multiple testing in parts 1 and 2 of the present study. These parts are exploratory. However, we have taken this into account in the conclusions we have drawn from the results.

There was a long period between the ages when the study population's GPA and ONH morphologies were studied. We used multiple other surrogates for cognition to compensate for this. Results for the SAP duration and the PAL test are from the same age as the eye examinations. We used all the study subjects that had the necessary data for each individual analysis. This could cause bias as the study population varied between the analyses.

The time between the perinatal data recording and the NFBC Eye Study can be considered a limitation. However, the ONH size remains stable except in subjects with high myopia (Fledelius & Goldschmidt, 2010). In this part of our research, the study population varied between the analyses to maximize the number of subjects for each analysis. Nevertheless, the variance was much smaller in this part than in the analyses conducted between the association of ONH morphology and cognition. We decided to use this method for the first two parts of the study because they represent a more explorative form of research than the third part of our study.

6.6 Summary and future prospectives

The association between cognition and ONH morphology or RNFL thickness varies between populations, intelligence tests, imaging modalities, RNFL quadrants, and age groups. Our study adds to previous studies showing that the associations are weak in a relatively healthy but mature population. This may be because the ocular structures have had time to develop beyond potential childhood challenges and have not yet been affected by neurodegeneration. Based on this, it might be more meaningful in the future to focus on early signs of cognitive decline in the ocular structures. Other interesting subjects for research include the effect that ophthalmological diseases may have on developing or deteriorating cognition.

Perinatal factors do not significantly impact ONH or RNFL morphology in our study population. This may indicate that with time, the structures overcome the possible adversities they have met during the fetal period, childhood, and adolescence. It may also mean that these structures are well protected during pregnancy and childhood. However, more research is still needed on this subject. In the future, the same kind of study should be conducted on younger populations, preferably repeatedly in infancy, childhood, and adolescence.

Height, weight, physiological factors, and ocular dimension generally have limited predictive value in terms of ONH and RNFL morphological variations. Therefore, the clinician does not need to consider them when diagnosing diseases affecting the ONH or RNFL. Automated diagnostic methods are being developed for glaucoma, e.g. S-F-analysis. Computerized analyses have the additional capacity to consider smaller effects. In the future, it may be beneficial to use certain diagnostic algorithms to help analyze structures in greater depth or devise further functional tests.

When a large amount of data has been gathered from a cohort, it is relatively easy to conduct any analysis after the actual data collection, making it a meaningful resource to explore. Producing reference values for specific populations is valuable. However, this kind of research produces multiple tests, and all the confounding factors that arise can be difficult to manage. Thus, we should be careful not to emphasize statistically significant findings with minor effects. Interpretation of the results is the key to this kind of research, and we hope it has been accomplished satisfactorily in this dissertation.

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Original publications are not included in the electronic version of the dissertation.

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