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Morphology of the optic nerve head and factors affecting it in the Northern Finland birth cohort

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Abstract

Purpose: To assess topographic characteristics of the optic nerve head (ONH) and retinal nerve fibre layer (RNFL) and study the effect of ocular and physiological factors on them in a middle-aged population.

Methods: A 1552-person randomised sample from Northern Finland population aged 45–49 was examined. Laser scanning tomography and optical coherency tomography were performed to obtain measurements for ONH and RNFL morphology. Measurements of the RNFL included global thickness and the six zones used in automated structure–function analysis (S–F analysis). Influence of central corneal thickness (CCT), refractive correction, intraocular pressure (IOP), anterior chamber angle, gender, blood pressure, height, weight and body mass index (BMI) on tomographic data was analysed.

Results: The optic disc area had a strong correlation with all other parameters of ONH morphology ($R = 0.261$ to 0.706) as did spherical equivalent ($R = -0.280$ to 0.280). The correlations between ONH and RNFL measurements were weaker ($R = 0.057$ to 0.180). Gender, CCT, anterior chamber angle, blood pressure, height and BMI had statistically significant, yet feeble, correlations with a number of ONH parameters.

Conclusion: Other than spherical equivalent, the studied anatomical and physiological attributes had little predictive value on the ONH morphology. The optic disc area itself had a significant effect on other measurements of ONH tomography and should be taken into consideration when the thresholds for normal ONH morphology are calculated.

KEYWORDS
neuroretinal rim, optic disc, optic nerve head, retinal nerve fibre layer

1 | INTRODUCTION

Understanding the morphology of the normal optic nerve head (ONH) and the retinal nerve fibre layer (RNFL) is essential when diagnosing optic nerve pathologies. Previously, considerable variation in their morphology has been described in different population-based studies (Abe et al., 2009; Bourne et al., 2008; Jonas et al., 2003, Khawaja et al., 2013, Li et al., 2013; Ramrattan et al., 1999; Samarawickrama et al., 2012; Vernon et al., 2005; Wang et al., 2006). Many intraocular, anatomical and physiological correlations of varying effect have been studied between the ONH, RNFL and other measurements of the structure of the eye (Abe et al., 2009; Bourne et al., 2008; Jonas et al., 2003; Khawaja et al., 2013; Li et al., 2013; Ramrattan et al., 1999; Vernon et al., 2005; Xu et al., 2007). Furthermore, racial differences have also been found (Knight et al., 2012; Pilat et al., 2014; Varma et al., 1994).

Automatically generated structure–function analysis (S–F analysis) can be used for glaucoma diagnostics and follow-up. Karvonen et al. studied this as a potential method for systematic glaucoma screening (Karvonen et al., 2021). However, the potential factors affecting the six peripapillary RNFL zones used in the S–F analysis are what is not yet known (Figure 1).

The purpose of this study is to characterise the distribution of the ONH and RNFL parameters and their

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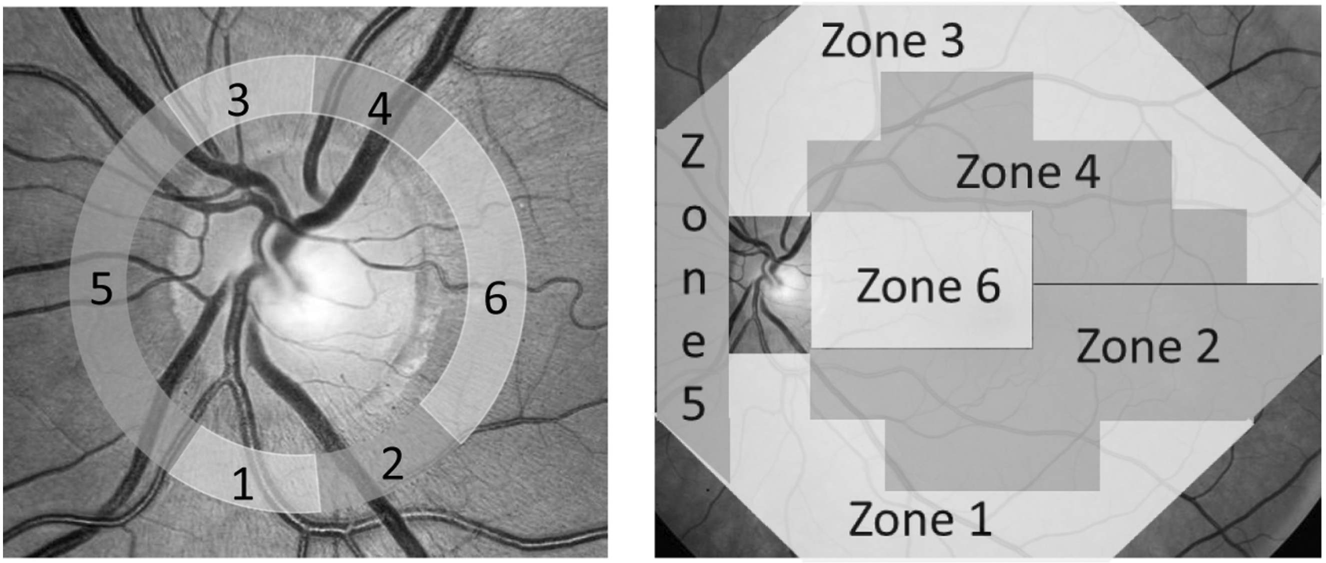

FIGURE 1 The six peripapillary zones of RNFL used in S–F analysis.

associations with other ocular measurements, morphometrics and physiological attributes, in a randomised middle-aged population from Northern Finland.

2 | MATERIALS AND METHODS

2.1 | Study population

The Northern Finland Birth Cohort (NFBC) is a prospectively monitored birth cohort. It consists of subjects born in the two most northern provinces of Finland in the year 1966. When the study subjects were 46 years old, they were sent a questionnaire and an invitation to an extensive clinical examination of overall health. At the same time, the NFBC Eye Study was conducted; the details of the study protocol have been published in detail before (Saarela et al., 2013). Of the 10 321 NFBC participants living in Finland in 2011, 50% (5155) were randomised to the NFBC Eye Study. Of those, the participation rate was 60% (3070). The right eye of the subjects was chosen for the present analysis. The NFBC Eye Study was approved by the Ethics Committee of the Northern Ostrobothnia Hospital District.

2.2 | Ophthalmological parameters

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 1, image on the left) were measured with spectral domain optical coherence tomography (OCT) (Cirrus HD-OCT 4000, software version 6.0.0, Carl Zeiss Meditec). The anterior segment analysis of the same device was used to assess central corneal thickness (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 750). Values for refractive correction (spherical equivalent, cylindrical and axial correction of astigmatism) were obtained with an autorefractometer (Nidek AR-360A). IOP was measured with Icare model TA01i (Icare Ltd). The S–F analysis combining the six circumpapillary OCT zones relative to the visual field test pattern (Figure 1) was formed using FORUM Glaucoma Workplace software (Carl Zeiss Meditec AG).

2.3 | Morphometrics and physiological measurements

Systolic (SBP) and diastolic blood pressure (DBP), BMI, height and weight were measured as part of the clinical examination of overall health. Systolic and diastolic blood pressure were measured three times and the mean was calculated and used in the present study.

2.4 | Statistics

The right eye of the study subjects was chosen for the analyses. The distribution of the parameters used in our study was inspected graphically. The measurements of the optic cup area and volume, cylindrical and 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. A p-value <0.050 was chosen as the threshold for statistical significance for the analyses shown in Tables 2 and 3. Because the ONH and RNFL parameters have a high and significant correlation between each other, correction for multiple testing was not used. For the analyses done for Table 1, a Bonferroni correction of $\alpha/5$ i.e. $p<0.010$ was used because of 5 hypotheses tested: difference of ONH morphology between genders (disc area, rim area, cup area, rim volume, cup volume and RNFL thickness), difference of anterior segment parameters between genders

TABLE 1 Statistics of the studied parameters and difference between genders.

	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)[a]	1552	0.41	0.45	0.43	0.38	0.013
Cup volume (mm^3)[a]	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[a]	1552	0.50	0.50	0.50	0.50	0.588
Axis of astigmatism[a]	1552	89	56	87	89	0.435
IOP (mmHg)	1552	15	3	15	15	0.447
AOD 750 (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**

Note: *p*-values marked in bold were statistically significant ($p<0.010$).

Abbreviations: AOD, anterior chamber opening; BMI, body mass index; BP, blood pressure; CCT, central corneal thickness; IOP, intraocular pressure; RNFL, retinal nerve fibrefiber layer.

[a]Median, interquartile change and non-parametric test used because of non-normal distribution.

TABLE 2 Correlations between ONH and RNFL parameters.

	Disc area		Avg. 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[a]	0.706	**<0.001**	0.034	0.181
Cup volume[a]	0.597	**<0.001**	0.051	**0.044**
Disc area			0.057	**0.026**

Note: Statistically significant findings are marked in bold ($p<0.050$).

Abbreviations: ONH, optic nerve head; RNFL, retina nerve fibre layer.

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

(spherical equivalent, cylindrical power, axis of astigmatism and chamber angle opening), difference of parameters related to intraocular pressure between genders (IOP, CCT) and difference of blood pressure between genders (SBP, DBP) and difference of height/weight between genders (height, weight, BMI). For the analyses done for Table 4, a Bonferroni correction of α/4 was i.e. $p<0.013$ was used because of 4 hypotheses tested: association between anterior segment parameters and ONH morphology, association between parameters related to intraocular pressure and ONH morphology, association between blood pressure and ONH morphology and association between height/weight and ONH morphology.

Pearson's correlation coefficient was used to calculate correlations between continuous parameters: ONH morphology, RNFL variables, and morphometric and physiological measurements. Spearman's correlation coefficient was used as a non-parametric test with the aforementioned non-normally distributed parameters. The *t*-test was used to test for differences between genders, and the Mann–Whitney-*U*-test was used instead with non-normally distributed parameters (Table 1).

Cylindrical refractive correction was divided into three groups: the smallest 5%, 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 and (3) no astigmatism. The group of with-the-rule astigmatism had cylindrical correction of at least +0.75D between 80 and 100 degrees. Against-the-rule astigmatism was defined as cylindrical correction of at least +0.75D between 0 and 10 or 170 and 180 degrees. The third group did not have any cylindrical correction in any direction. 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 aforementioned non-normally distributed parameters.

Multivariate linear regression analysis was performed to study the association between astigmatism (cylindrical power and axis of astigmatism), the ONH morphology and the average RNFL thickness. The same analysis was performed to analyse which factors contributed most to the optic disc area. The factors included CCT, spherical equivalent, cylindrical power, axis of astigmatism, IOP, anterior chamber angle opening, SBP, DBP, weight, height and BMI.

TABLE 3 Correlations between ONH morphology and RNFL zones.

	Disc area		Rim area		Rim volume		Cup area[a]		Cup volume[a]	
	Pearson's cc	*p*	Pears. cc	*p*	Pears. cc	*p*	Spearman's cc	*p*	Spearm. cc	*p*
RNFL Zone 1	0.07	**0.006**	0.03	0.227	0.00	0.918	0.08	**0.003**	0.09	**0.001**
RNFL Zone 2	0.04	0.163	0.06	**0.012**	0.13	**<0.001**	0.00	0.995	0.02	0.540
RNFL Zone 3	0.02	0.46	0.05	0.058	0.05	0.054	−0.01	0.642	−0.01	0.602
RNFL Zone 4	0.05	0.066	0.07	**0.01**	0.12	**<0.001**	0.01	0.763	0.01	0.612
RNFL Zone 5	0.13	**<0.001**	0.05	0.066	−0.08	**0.003**	0.18	**<0.001**	0.18	**<0.001**
RNFL Zone 6	−0.06	**0.021**	0.06	**0.029**	0.18	**<0.001**	−0.11	**<0.001**	−0.09	**0.001**

Note: Statistically significant findings are marked in bold ($p<0.050$).

Abbreviations: cc, correlation coefficient; RNFL, retinal nerve fibre layer.

[a]Spearman's correlation coefficient calculated because of non-normal distribution of cup parameters.

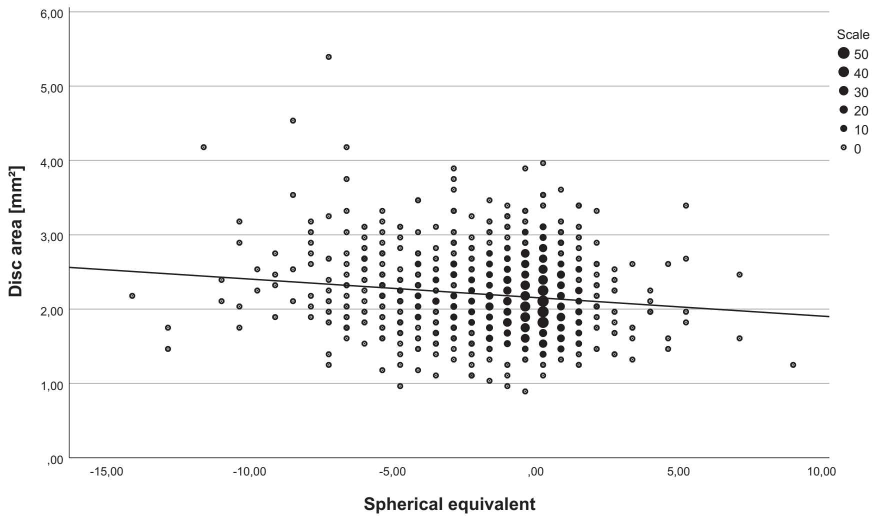

FIGURE 2 The correlation between the ONH disc area and the spherical equivalent.

3 | RESULTS

One thousand five hundred fifty-two eyes had all the data required for the present study. Eight (0.5%) of them had been diagnosed with glaucomatous damage. Key statistics of the parameters and the difference between genders are presented in Table 1. A statistically significant difference between genders was found in the following parameters: rim volume, CCT, spherical equivalent, height of the anterior chamber angle, systolic and diastolic blood pressure, height, weight and BMI.

The optic disc area had a strong correlation with the other ONH morphology parameters (r = 0.261–0.706). The average RNFL thickness correlated significantly to all other parameters of the ONH morphology (r = 0.051–0.092) except cup area (Table 2). All six RNFL zones correlated strongly with average RNFL thickness as expected. The correlations with the ONH morphology were considerably weaker. The results are presented in detail in Table 3.

CCT had a statistically significant, but feeble correlations with all the other ONH parameters except the disc area. The association was positive between CCT, the rim parameters and the average RNFL thickness rim area. The association was negative between CCT and the cup parameters. Disc area, rim area and rim volume had a decreasing tendency as the spherical equivalent shifted towards hyperopia (Figure 2). The opposite effect was found between spherical equivalent and cup area, cup volume and average RNFL thickness. The cylindrical correction of astigmatism had a statistically significant negative correlation with the average RNFL thickness. In the univariate analyses, all the other correlations between continuous and grouped cylindrical and axial corrections and ONH morphology and RNFL thickness were not statistically significant (Table 4).

We also performed a multivariate linear regression analysis between astigmatism (cylindrical power, axis of astigmatism), the ONH morphology and the average thickness of RNFL. The cylindrical correction had a statistically significant correlation ($p<0.001$) with the average RNFL thickness, and the axis of the correction did not have a statistically insignificant correlation with the average RNFL thickness. The parameters of the ONH morphology did not have a statistically significant correlation with astigmatism.

Anterior chamber opening had a statistically significant negative, yet feeble, correlation with cup area, cup volume and average RNFL thickness. No statistical significance was found between anterior chamber opening

TABLE 4 Correlations between anatomical and physiological factors, and ONH and RNFL morphology.

	Disc area		Rim area		Rim volume		Cup area[a]		Cup volume[a]		Avg. RNFL thickn.	
	Pears. Cc	*p*	Pears. cc	*p*	Pears. Cc	*p*	Spearm. cc	*p*	Spearm. cc	*p*	Pears. cc	*p*
CCT (μm)	0.02	0.427	0.07	**0.004**	0.07	**0.007**	−0.07	**0.007**	−0.07	**0.008**	0.08	**0.001**
Sph. equiv.	−0.12	**<0.001**	−0.22	**<0.001**	−0.28	**<0.001**	0.07	**0.006**	0.08	**0.002**	0.28	**<0.001**
Cyl. pow[a]	0.05	0.066	−0.01	0.732	0.05	0.065	0.03	0.241	0.02	0.361	−0.12	**<0.001**
Axe. astigm[a]	−0.04	0.162	−0.02	0.365	0.01	0.759	−0.05	0.145	−0.03	0.186	0.00	0.930
IOP (mmHg)	0.05	0.070	0.01	0.667	−0.02	0.338	0.05	0.071	0.04	0.100	−0.03	0.275
AOD750 (μm)	−0.01	0.602	0.04	0.141	0.06	0.030	−0.07	**0.009**	−0.08	**0.001**	−0.17	**<0.001**
SBP (mmHg)	0.03	0.276	−0.05	0.071	−0.08	**0.003**	0.09	**0.001**	0.09	**0.001**	−0.03	0.184
DBP (mmHg)	0.04	0.090	−0.03	0.311	−0.04	0.103	0.08	**0.002**	0.08	**0.002**	−0.03	0.282
Weight (kg)	0.00	0.979	−0.01	0.827	−0.03	0.232	−0.03	0.245	−0.04	0.095	−0.01	0.809
Height (cm)	0.02	0.477	−0.01	0.782	−0.07	**0.004**	0.03	0.176	0.03	0.268	−0.01	0.833
BMI (kg/m^2)	−0.02	0.537	0.00	0.938	0.01	0.658	−0.04	0.092	−0.06	0.028	0.00	0.903

Note: Statistically significant correlations marked in bold (p<0.013).

Abbreviations: AOD, anterior chamber opening; BMI, body mass index; cc, correlation coefficient; CCT, central corneal thickness; DBP, diastolic blood pressure; IOP, intraocular pressure; Pears, Pearson's; RNFL, retinal nerve fibrefiber layer; SBP, systolic blood pressure; Spearm, Spearman's.

[a]Spearman's correlation coefficient calculated because of non-normal distribution of cup parameters.

and disc area or rim parameters. Surprisingly, IOP did not show a statistically significant effect on ONH morphology in our study. SBP and DBP had a statistically significant, though relatively weak, positive correlation with the cup area the cup volume. Also, SBP correlated negatively with rim volume. No other statistically significant correlations were found between BP and ONH morphology. Taller participants had marginally smaller rim volume. No other significant effect was found between the morphometrics of the study subjects and ONH morphology (Table 4).

A multivariate linear regression analysis was performed to analyse which factors contributed most to the optic disc area. The spherical equivalent remained statistically significant, but its association was weak ($\beta = -0.03$). The anterior chamber angle also had statistically significant association, but with very weak effect ($\beta < 0.01$).

4 | DISCUSSION

In our study, a larger disc area correlated to a larger rim area, rim volume, cup area and cup volume. The correlations were 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). 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). The positive correlation between the disc area and the RNFL thickness was substantially weaker (R^2 = 0.003). Other studies have had varied results showing both 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 taken into consideration when interpreting other values of ONH morphology.

Gender had a significant influence on the rim volume of the ONH parameters. 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 larger rim volume and 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, the effect of gender on ONH morphology should be taken into consideration, for example, when creating reference databases for detecting glaucomatous damage.

Thicker CCT correlated positively with male gender, rim area, rim volume, and RNFL and inversely with the cup parameters. However, the effect on all parameters was feeble (R^2<0.006) and may be insignificant in clinical practice. No significant effect was found between CCT and disc area. Two studies found an inverse correlation between CCT and optic disc area (Insull et al., 2010;

Pakravan et al., 2007). Another study found no significant effect between the two (Carbonaro et al., 2014). A wider anterior chamber angle was associated with male gender, smaller cup parameters and thinner RNFL, yet the correlations were 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).

The effects of systolic and diastolic BP on ONH morphology and RNFL thickness were of limited predictive value. Both SBP and DBP had a minor association with the cup parameters and SBP also with the rim volume. No significant associations between BP and ONH morphology were found in the Tajimi Study (Abe et al., 2009). A negative correlation between autoregulatory responses in ONH blood flow in animal and human testing during changes in BP has been described (Chiquet et al., 2014; Liang et al., 2010). In our study, population height had a minor correlation with rim volume. No other effects were found between morphometrics of the study subjects and their ONH morphology or average RNFL thickness. The Rotterdam Study found a feeble positive association between height and disc area and no association between height and cup area and cup-to-disc area, and the Tajimi Study found that increasing height correlated positively with cup-related parameters and negatively with rim-related parameters (Abe et al., 2009; Ramrattan et al., 1999). The differences between the studies might be to some degree attributed to racial differences. To summarise, in our study population CCT, anterior chamber angle, systolic and diastolic blood pressure, and morphometrics had only minor effect on ONH morphology and average RNFL thickness.

The ONH morphology had a marginal effect on the six RNFL zones used in the S–F analysis. The strongest correlation was found between rim volume, cup volume, and cup area and zone 6, with an R^2 value of 0.032 meaning that approximately 3% of the RNFL thickness of the zone 6 was explained by one of the previously mentioned factors. To our knowledge, our study is the first to explore potential factors affecting the six RNFL zones used in the S–F analysis. Identifying factors that affect the zones could improve the performance of the S–F analysis that has been shown to produce variable results in screening and diagnosing glaucoma (Karvonen et al., 2021; Nilforushan et al., 2012; Wu et al., 2015).

To our knowledge, 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. The direction of astigmatism did not influence ONH morphology or RNFL thickness. Liu et al. found that subjects with high with-the-rule astigmatism had a larger disc area, and rim area and thinner RNFL thickness in the temporal quadrant in high myopes. They used OCT for the measurements of the ONH and RNFL (Liu et al., 2012). Another study showed that the amount of corneal astigmatism was significantly correlated with an increasingly elongated optic disc shape using optic disc photographs (Jonas et al., 1997). In our study population, spherical equivalent had a negative correlation with disc size and rim parameters. Similar results have been published before (Ramrattan et al., 1999; Zhang et al., 2014). Other studies found no association between studied ONH parameters and refraction (Bowd et al., 2002; Gundersen et al., 1998; Kashiwagi et al., 2000; Varma et al., 1994). More studies are needed to establish whether the amount and direction of cylindrical correction should be considered when interpreting the morphology of the ONH or RNFL.

Strengths of our study are the large number of cases and fairly good participation rate of 60%. The study population can be considered to represent the population of Northern Finnish people of 45–50 years old. The cross-sectional nature of our study limits the possibility of deducing causal relationships. The possibility for correcting for refractive magnification effect in imaging with the HRT3 was not used in the present study. This allows for better comparison with the results of previous studies.

In conclusion, our study presents the measurements of ONH morphology obtained with the HRT and RFNL with the OCT in a middle-aged population from Northern Finland. Optic disc size influenced other ONH parameters substantially. Other ocular factors, physiological measurements and morphometrics had a considerably weaker effect on ONH morphology and RNFL and can be largely ignored in clinical work. Also, novel research on the RNFL zones used in S–F analysis was conducted and the correlations between the zones and ONH morphology appeared to be feeble. When the findings of the present study are taken into consideration in calculating the thresholds for normal ONH morphology, they have the potential to improve the diagnostic value of ONH imaging.

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