Use of the ISNT rule for optic disc evaluation in 40 to 79 year old patients seen in optometric practice

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Abstract

The purpose this study was to investigate the association between intraocular pressure (IOP) and the outcome of ISNT rule assessment of the optic disc in healthy patients seen in mainstream optometric practice. Consecutive patients over the age of 40 years and with no known general- or ocular pathology were enrolled from 4 optometric practices in Norway and Sweden during a period of 9 months. The sample was stratified by age group (40-49, 50-59, 60-69 and 70-79 years) and ISNT rule outcome (obeyed or broken). Subjects underwent a full optometric examination including stereoscopic assessment of the optic disc with the use of the ISNT rule, followed by measurements of intraocular pressure (IOP), central corneal thickness (CCT) and vertical size of the optic disc. Odds ratio (*OR*) was used to assess the association between IOP and the outcome measure. Stratified and multivariable analyses were employed to investigate the effect of age, gender, CCT, refractive error and disc size on the association. IOP was dichotomized at a cut-off corresponding to the 75th percentile (18 mmHg), whereas numeric covariables were categorized at cut-offs corresponding to the 33rd (ONH 1.6 mm, CCT 545 µm) and 66th percentile (ONH 1.8 mm, CCT 571 µm), respectively. A total of 177 patients (F: 57%, age range 40-79 years) were included. IOP was significantly higher in patients with broken ISNT rule (16.6 vs. 15.5 mmHg, $p = 0.046$), corresponding to a crude *OR* of 2.0 (CI 0.95-4.24). In stratified and multivariable analyses the association between IOP and outcome of the ISNT rule was strengthened in males (*OR* 4.8) and in subjects with small discs (*OR* 2.2), however only the effect modification by gender reached significance. Further research is necessary to understand the possible implications of these findings on the assessment of optic discs with the use of the ISNT rule.

Keywords: Optic disc, ISNT rule, intraocular pressure, gender, age

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Introduction

In normal healthy eyes, the neuroretinal rim of the optic nerve head (ONH) is usually widest in the inferior disc region, followed by the superior, then the nasal, and finally the temporal disc region. The mnemonic ISNT describes this anatomic situation (Jonas, Gusek, & Naumann, 1988), which is a consequence of the distribution of retinal nerve fibres as they exit the eye through the scleral canal (figure 1). Nerve fibres assume an arcuate pattern as they converge towards the ONH, with the inferior and superior poles receiving larger number of nerve fibres than the nasal and temporal regions of the ONH. As macula is located slightly below the centre of the ONH the greatest number of nerve fibres, and therefore widest rim, is normally found at the inferior pole of the disc.

It has been estimated that approximately 80% of normal eyes conform to the ISNT configuration (Harizman et al., 2006; Jonas et al., 1988), with the thinnest rim found in the temporal segment in 96% of eyes and widest rim found in the inferior- or superior segment in 87% of the eyes (Budde, Jonas, Martus, & Grundler, 2000). Therefore, whenever the width of the rim does not follow the ISNT configuration, it is necessary to rule out pathology.

Systematic evaluation of the ONH with the use of the ISNT rule has become a primary screening method for glaucoma in many optometric practices, together with functional tests (visual fields) and measurements of the intraocular pressure (IOP). Elevated IOP is regarded as a major risk factor for alterations in the neuroretinal rim configuration in glaucomatous optic neuropathy. However, the association between IOP and neuroretinal rim configuration is less well documented in normal eyes. Therefore, the purpose of this study was to investigate the association between IOP and the outcome of ISNT rule assessment of the optic disc in healthy patients seen in four different mainstream optometric practices, using standard clinical methods and somewhat different instrumentation. It was expected that the results of the study would provide insight into factors that can influence the likelihood of finding an optic nerve head that does not conform to the ISNT rule when IOP is within the high range of normal.

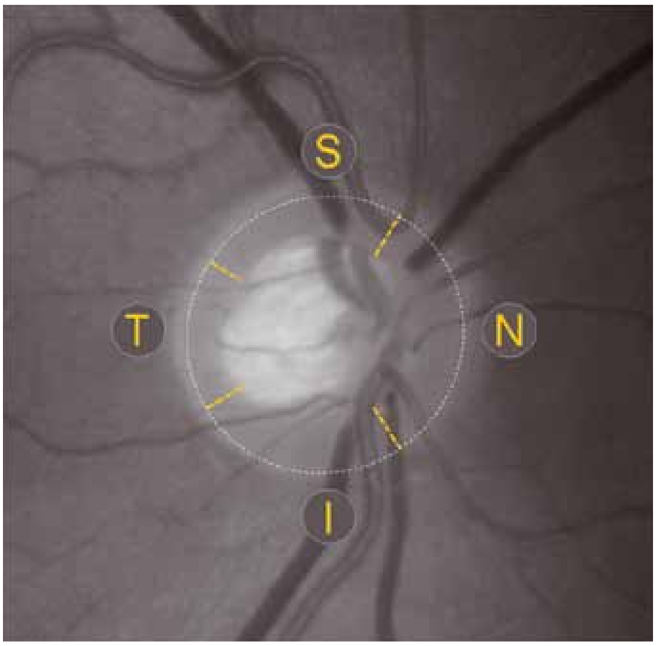


Figure 1. Clinical assessment of the ISNT rule for a normal optic nerve head. Rim width was stereoscopically assessed within four segments (I: inferior; S: superior; N: nasal and T: temporal). In order to obey the ISNT rule the narrowest part of the Inferior sector had to be wider than the narrowest part of the Superior section, which had to be wider than the narrowest part of the Nasal sector, which in turn had to be wider than the narrowest part of the Temporal sector. The central retinal vessel trunk was not considered part of the neuroretinal rim.

Methods

Enrolled into the study, which had a cross-sectional design, were healthy patients of both genders aged 40 years or older, who underwent voluntary eye examinations in private optometric practices in Mosjøen, Bergen and Haugesund in Norway, and in Malmö in Sweden between December 2005 and August 2006. Patients were excluded if their medical- and ocular history included conditions that may influence the relationship between intraocular pressure (IOP) and the neuroretinal rim appearance, such as massive blood loss or shock, diabetes mellitus, retinal ischemia, dysthyroidism, ischemic optic neuropathy, glaucoma and systemic lupus erythematosus. Excluded were also patients with congenital papillary abnormalities (e.g. optic disc drusen, optic disc coloboma, morning glory syndrome, optic hypoplasia and optic pit), a history of vitreous loss from ocular surgery, high myopia and/or astigmatism (> 6 D), unreliable IOP measurements and poor ophthalmoscopic view defined as difficulties determining the scleral ring.

Stratified semi-systematic sampling by age groups (40-49, 50-59, 60-69 and 70-79 years), and ISNT rule outcome (obeyed or broken) was used to ensure statistical power. Consecutive sampling was used for eligible patients with broken ISNT rule whereas systematic sampling of every fifth patient was performed for eligible patients with obeyed ISNT rule. Recruitment aimed at including 20 subjects in each stratum. Recruitment, except exclusion rate, was reported to and monitored by one of the researchers (GBS).

Subjects underwent a full optometric examination including stereoscopic assessment of the optic disc, followed by measurements of IOP and central corneal thickness (CCT) in both eyes. Stereoscopic assessment of the optic disc was performed in undilated eyes using a Volk Super Field NC lens (Volk Optical). The absolute vertical diameter of the optic disc was measured as the product of the height of the slit lamp beam (Topcon SL-7, Topcon, Japan) when aligned inside the scleral ring, and a magnification factor of 1.5. The neuroretinal rim was identified as the tissue between the inner margin of the scleral ring and the outer extension of the excavation defined as the part of the slope with the greatest apparent change of inclination. The width of the neuroretinal rim was ranked within the segments as shown in Figure 1 and compared with the ISNT rule. The assessment was considered as *ISNT rule obeyed* if the ranking of the width was in agreement with the ISNT rule (widest inferiorly followed by superiorly, nasally and temporally) or *ISNT rule broken* in other cases. Optic discs with equal rim width inferiorly and superiorly were assessed as ISNT rule broken.

Measurements of the IOP were obtained using one of three non-contact tonometers: Topcon CT-60 (Topcon, Japan), Topcon CT-80 (Topcon, Japan), or Keeler Pulsair 2000 (Keeler Ltd, UK) in Mosjøen, Malmö/Haugesund and Bergen, respectively. All instruments have shown to be reliable and accurate within a normal range of IOPs (Mackie, Jay, Ackerley, & Walsh, 1996; Ogbuehi, 2006). Patients were instructed to stay relaxed and to breathe normally during all measurements, which were not performed earlier than 2 hours after awakening. Recorded IOP was based on the average of three consecutive measurements (four for Keeler Pulsair 2000). If a trend of decreasing or increasing values was found measurements were continued until a levelling was observed. Recorded IOP was based on the last three or four measurements.

Central corneal thickness was measured using two handheld pachymeters: Pachmate DGH55 (DGH Technologies Inc, USA) or Sonogage Plus (Sonogage Inc, USA) in Malmö/Mosjøen/Haugesund and Bergen, respectively. Both instruments use ultrasound technology for thickness measurements. Corneas were anaesthetized with 1-2 drops of Oxibuprocain 0.4 mg/ml (Chauvin) prior to measurements. The average value of five measurements per eye was recorded. Fundus photographs were obtained from selected eyes as part of a different study.

Ocular parameters were analyzed for one eye per subject. Selection was randomized when both eyes were equally classified. In other cases the eye with broken ISNT rule was selected. All data was coded in order to make it anonymous. Group differences were analyzed with Student t-tests, Chi-square tests and Fishers exact test. Odds ratio (*OR*) was used to measure the strength of association between outcome of ISNT rule assessment and IOP. Therefore IOP was dichotomized at a cut-off corresponding to the 75th percentile. Stratification was used to explore the effect of age (40-49, 50-59, 60-69 and 70-79 years), gender (female vs. male), refractive error (myopia vs. emmetropia/hyperopia), CCT, and disk size on the association between ISNT rule outcome and IOP. CCT and disk size were categorized at cut-offs corresponding to the 33rd and 66th percentile, respectively. Adjustment of *OR* and tests of the homogeneity of strata were by Mantel-Haenzel Chi-square methods. Multiple logistic regressions were used to further explore the independent association between ISNT rule and IOP. Effect modification as identified by stratified analyses was forced into models. Statistical significance was set at $p < 0.05$ (two-tailed test). In the multivariate analyses *ORs* and 95% confidence intervals (CIs) were reported (SPSS, version 17).

Results

A total of 177 patients were included in the study. Demographics and recruitment characteristics are displayed in Table 1.

Vertical ONH diameter was larger in patients with broken ISNT rule than patients with obeyed ISNT rule ($p = 0.016$). Age, gender distribution, refractive status, CCT and distribution of practice sites were similar in both groups and did not differ when analyzed for each practice site separately (data available at request).

Table 2 shows main predictor variable and covariables for patients with broken and obeyed ISNT rule. Intraocular pressure was significantly higher in patients with broken ISNT rule than in patients where the ISNT rule was obeyed ($p = 0.046$). Dichotomized analysis showed a similar trend ($p = 0.065$) with a corresponding unadjusted *OR* of 2.0 (CI 0.95-4.24). The distribution of ISNT outcome varied significantly between different age groups ($p = 0.003$), however there was no association between age groups and IOP levels (data not shown). Each age stratum was composed of patients with a broad range of ages. Whereas neither gender nor CCT was significantly associated with the outcome there was a trend ($p = 0.082$) towards a greater proportion of broken ISNT rule in larger discs.

The calculated unweighted absolute risk for having a disc that breaks the ISNT rule is displayed as a function of IOP in Figure 2. There was a positive correlation between IOP and the probability of a broken ISNT rule corresponding to an increase of 0.29 in probability for every 10 mmHg increase in IOP. However, the linear regression must be interpreted with caution as measurement points were based on ratios of broken and obeyed ISNT rule outcomes ranging from 2 to 29 subjects.

Results from stratified analyses are summarized in Figure 3. Overall, the likelihood of having IOP > 18 mmHg was 2 times greater in patients with broken ISNT rule than in patients with obeyed ISNT rule. However, unequal bar heights indicated a modifying effect on the association between IOP and ISNT rule outcome that was strongest for gender and vertical optic disc size (Tarone's test for homogeneity) with significant *ORs* in males (6.4, CI 1.3-31.0) and in patients with ONH ≤ 1.6 mm (4.4, CI 1.4-13.7). *OR* was borderline significant for myopia (5.2, CI

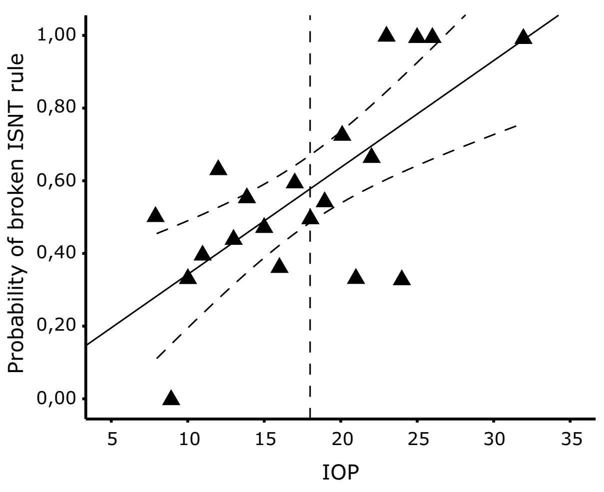
Table 1
Demographics and recruitment characteristics

	Study sample	ISNT rule outcome		
		Broken	*Obeyed*	
Variable	*N* = 177	*n* = 93	*n* = 84	*p*-value
Age (years) [mean (SD)]	56.9 (10.1)	56.2 (10.6)	57.7 (9.4)	0.338 a
Range	40-79	40-79	42-79	
Females [*n* (%)]	101 (57.1)	51 (54.8)	50 (59.5)	0.529 b
Refractive error [mean (SD)]				
Sphere (DS)	0.08 (1.98)	0.20 (1.92)	-0.05 (2.05)	0.410 a
Cylinder † (DC)	-0.88 (0.87)	-0.81 (0.76)	-0.96 (0.99)	0.311 a
Sph. equiv. (D)	-0.26 (2.04)	-0.11 (2.01)	-0.42 (2.08)	0.325 a
CCT (µm) [mean (SD)]	557.9 (32.8)	557.7 (31.5)	558.1 (34.3)	0.927 a
Range	473-648	479-633	473-648	
ONH (mm) [mean (SD)]	1.7 (0.2)	1.7 (0.2)	1.6 (0.2)	0.016 a
Range	1.2-2.3	1.3-2.2	1.2-2.3	
Practice site [*n* (%)]				
Mosjøen, Norway	29 (16.4)	13 (14.0)	16 (19.0)	0.423 b
Bergen, Norway	31 (17.5)	18 (19.3)	13 (15.5)	
Haugesund, Norway	67 (37.9)	32 (34.4)	35 (41.7)	
Malmö, Sweden	50 (28.2)	30 (32.3)	20 (23.8)	

† Based on 135 cases with astigmatism. CCT: Central corneal thickness; ONH: Vertical optic nerve head diameter; a: Student *t*-test; b: Chi-square test.

1.0-25.9), however the modifying effect of refractive error was less marked.

Multiple adjustments for covariables are presented in Table 3. Adjusting for demographic and ocular covariables resulted in a strengthening of the association between IOP and ISNT rule outcome (*OR* 2.8). Effect modifications identified in stratified analyses were confirmed in the logistic regression although significance was not reached and wide CI indicated some instability of the data. When interactions were included in the model the association between IOP and ISNT rule outcome was no longer statistically significant (*OR* 0.7). The estimated strength of association between broken ISNT rule and IOP > 18 mmHg corresponded to an *OR* of 4.8 in males (product of not rounded values of *ORs* [IOP × Male × (Interaction IOP × Gender)]) and an *OR* of 2.3 in subjects with ONH < 1.6 mm. (product of not rounded values of *ORs* [IOP × (ONH < 1.6) × (Interaction IOP × ONH ≤ 1.6)]) However, it should be noted that the model does not take into account the interacting effect of an association between gender and optic disc size. When this was done in an extended model, interactions were strengthened (IOP × Gender: $p = 0.035$; IOP × ONH < 1.6 $p = 0.065$, data available at request), although with wide CIs. For details see Table 3.



Figur 2. Scatter plot of the correlation between unweighted estimates of absolute risk for broken ISNT rule vs. intraocular pressure (IOP). Filled triangles represent ratios between subjects with broken and obeyed ISNT rule outcomes (n ranges between 2 and 29). The solid line represents calculated linear regression ($y = 0.048 + 0.029 \times IOP$, $p = 0.001$, $r^2 = 0.492$). Curved broken lines represent the confidence interval for the mean, and the vertical broken line is the cut-off value (75th percentile) for IOP that was used for the dichotomized data analysis.

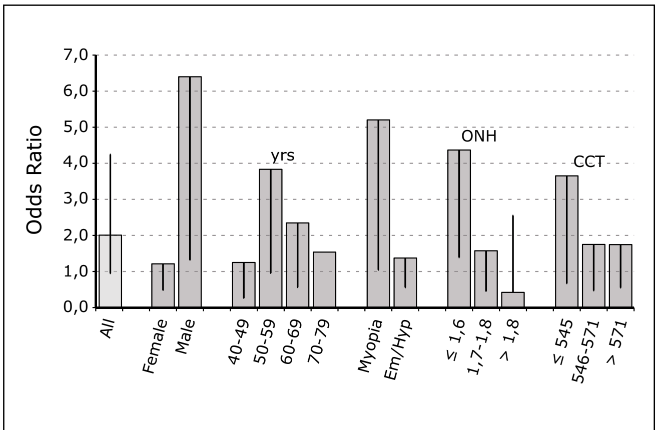
Discussion

The purpose of the study was to investigate the association between IOP and the outcome of ISNT rule assessments of the optic disc in healthy patients seen in four mainstream optometric practices using standard clinical methods and somewhat different instrumentation. Patients with broken ISNT rule were associated with significantly higher IOP and a trend towards 2 times greater likelihood of having IOPs above 18 mmHg when compared with patients with obeyed ISNT rule. Although this association was strengthened in both stratified analyses and

Table 2
Main outcome and covariables

	Study sample	ISNT rule outcome		
		Broken	*Obeyed*	
Variable	*N = 177*	*n* = 93	*n* = 84	*p*-value
IOP (mmHg) † [mean (SD)]	16.0 (3.7)	16.5 (4.0)	15.5 (3.1)	0.046 a
Range	8.0-32.0	8.0-32.0	8.0-24.0	
IOP ≤ 18 mmHg [*n* (%)]	139 (78.5)	68 (73.1)	71 (84.5)	0.065 b
IOP > 18 mmHg	38 (21.5)	25 (26.9)	13 (15.5)	
Gender [*n* (%)]				
Females	101 (57.1)	51 (54.8)	50 (59.5)	0.529 b
Males	76 (42.9)	42 (45.2)	34 (40.5)	
Age groups [*n* (%)]				
40-49 years	50 (28.2)	29 (31.2)	21 (25.0)	0.003 b
50-59 years	62 (35.0)	36 (38.7)	26 (31.0)	
60-69 years	42 (23.7)	12 (12.9)	30 (35.7)	
70-79 years	23 (13.0)	16 (17.2)	7 (8.3)	
Spherical equivalence [*n* (%)]				
Myopia	80 (45.2)	41 (44.1)	39 (46.4)	0.755 b
Emmetropia/Hyperopia	97 (54.8)	52 (55.9)	45 (53.6)	
ONH †† [*n* (%)]				
ONH ≤ 1.6 mm	85 (48.0)	38 (40.9)	47 (56.0)	0.082 b
ONH 1.7-1.8 mm	59 (33.3)	33 (35.5)	26 (31.0)	
ONH > 1.8 mm	33 (18.6)	22 (23.7)	11 (13.1)	
CCT †† [*n* (%)]				
CCT ≤ 545 μm	59 (33.3)	29 (31.2)	30 (35.7)	0.457 b
CCT 546-571 μm	61 (34.5)	36 (38.7)	25 (29.8)	
CCT > 571 μm	57 (32.2)	28 (30.1)	29 (34.5)	

Group differences for IOP (main predictor) and dichotomized values of covariables (underneath stippled line). IOP: Intraocular pressure; ONH: Vertical optic nerve head diameter; CCT: Central corneal thickness; † Cut-off corresponding to the 75th percentile; †† Cut-offs corresponding to the 33rd and 66th percentile, respectively; a: Student *t*-test; b: Chi-square test.



Figur 3. Bar graph of odds ratios (ORs) for having an IOP > 18 mmHg when the ISNT rule is broken compared with when it is obeyed. ORs provide a measurement of strength of association between IOP and outcome of ISNT rule assessment of the optic disc. Leftmost bar shows unadjusted OR followed by ORs stratified for gender, age group, refractive error, vertical disc size (ONH), and central corneal thickness (CCT). Whiskers indicate 95% confidence interval.

multivariable analyses, its independent effect was not significant when the effect modifying interactions of gender and optic disc size were adjusted for in multivariable analyses. These interactions were manifested as a trend towards an increased likelihood for broken ISNT rule in men with IOP > 18 mmHg and in subjects with optic disc size < 1.6 mm and IOP > 18 mmHg. Taking into account the relationship between these interactions (IOP in common) both effect modifications were strengthened, however, only the interaction related to gender reached significance (i.e. men with IOP > 18 mmHg). To the best of our knowledge this is the first reported study on the association between intraocular pressure and the outcome of ISNT rule assessment of optic discs in healthy patients seen in optometric practice.

We set out to investigate the relationship between IOP and ISNT rule outcome in order to achieve a better understanding of factors that may influence the likelihood of identifying an optic nerve head that does not follow the ISNT rule when IOP is within a normal high range. The target population was patients seen in optometric practices in Scandinavia and the study sample was recruited from four optometric practices in Norway and Swe-

Table 3
Results of logistic regression analyses

Variable	Main predictor + covariables		Main predictor + covariables + interactions	
	OR	95% CI	*OR*	95% CI
IOP > 18 mmHg (ref: IOP ≤ 18 mmHg)	2.8 *	1.2-6.7	0.7	0.1-4.5
Male (ref: Female)	1.1	0.6-2.1	0.8	0.4-1.7
Age group (ref: 40-49 years)				
50-59 years	0.9	0.4-2.1	1.0	0.4-2.2
60-69 years	0.2 **	0.1-0.5	0.2 **	0.1-0.5
70-79 years	1.7	0.5-5.1	1.5	0.5-4.8
Myopia (ref: Emmetropia/Hypermetropia)	1.0	0.5-2.1	1.0	0.5-1.9
ONH (ref: 1.7-1.8 mm)				
≤ 1.6 mm	0.6	0.3-1.3	0.5	0.2-1.2
> 1.8 mm	1.9	0.7-5.0	2.6	0.9-8.0
CCT (ref: 546-571 μm)				
≤ 545 μm	0.5	0.2-1.2	0.5	0.2-1.2
> 571 μm	0.6	0.3-1.3	0.6	0.3-1.5
Interaction IOP × Gender			7.8	0.9-70.4
Interaction IOP × ONH				
IOP × ONH ≤ 1.6 mm			5.7	0.7-46.2
IOP × ONH > 1.8 mm			0.3	0.0-5.0

Independent associations with and without interactions. * $p < 0.05$; ** $p < 0.01$.

den. Stratified semi-systematic sampling was performed in order to achieve equal distribution of cases with broken and obeyed ISNT rule outcomes within age strata which were thought to be a main influencing factor. This was however not completely achieved and the independent effect of age group 60-69 years can probably be explained by an under-recruitment of patients with broken ISNT rule in this age group (Table 2).

The main finding of this study is the influencing effects of gender and optic disc size on the association between IOP and ISNT rule outcome with a stronger association found for males and for optic discs < 1.6 mm. It would suggest that the likelihood of finding a disc that does not conform to the ISNT rule in an eye with IOP in the normal high range would be greater in men and in eyes with a small disc (< 1.6 mm). Morphological studies have shown that both neuroretinal rim size (Caprioli & Miller, 1987; Jonas et al., 1988; Varma et al., 1994) and shape (Budde et al., 2000) are correlated with the optic disc area. A small disc is associated with less neuroretinal rim area and a smaller proportion of inferior (and superior) rim area relative to the total rim area (Budde et al., 2000). However, small discs are also associated with smaller normal cup/disc ratios than large optic discs (Crowston, Hopley, Healey, Lee, & Mitchell, 2004; Garway-Heath, Ruben, Viswanathan, & Hitchings, 1998; Jonas et al., 1988). Assessment of the neuroretinal rim width and comparison between the quadrants may be more precise in a small disc where distances between the assessed elements are shorter than the corresponding distances in a large disc. As a consequence, the reduced misclassification would help to strengthen the measured correlation found between IOP and neuroretinal rim area (Jonas, Grundler, & Gonzales-Cortes, 1998). However, optic disc size would not have an independent effect on the outcome, which is in agreement with the reported data on optic disc size (Table 3) and with the literature that shows that optic disc size is not a predictor of early glaucomatous changes of the neuroretinal rim (Jonas, Fernandez, & Naumann, 1991).

Optic disc morphology is not influenced by gender. A few population studies with large numbers of subjects have found slightly larger disc- and neuralretinal rim areas in Caucasian males compared with females (Ramrattan, Wolfs, Jonas, Hofman, & de Jong, 1999; Varma et al., 1994). However, gender differences in axial length are believed to account for these reported differences in disc- and rim area (Bourne et al., 2008a, 2008b). Furthermore, IOP has been shown to correlate negatively with neuroretinal rim area in patients with normal-tension glaucoma (Jonas et al., 1998). Although findings in this study (Figure 2) may indicate that it is reasonable to believe that a similar association exists in normal healthy eyes, we are not aware of any studies that have evaluated the optic disc morphology explicitly related to IOP in normal eyes, nor the influence of gender on this effect. Population-based studies have found no association between gender and the prevalence of glaucoma (Klein et al., 1992; Tielsch et al., 1991), or are inconclusive on the role of gender as a risk factor (Bengtsson, 1981; Kahn et al., 1977; Leske, Connell, Schachat, & Hyman, 1994; Mason et al., 1989; Mitchell, Smith, Attebo, & Healey, 1996). Likewise, in the reported study male gender had no independent effect on the outcome.

Clinic-based studies are vulnerable to selection bias. In this study stratified semi-systematic sampling failed to provide unbiased age groups and one must therefore consider the possibility that the interactions found between IOP, gender and optic disc size are the result of skewed sampling of these variables in the study sample. There was, however, an approximately equal distribution of males and females in the sample and univariate analyses of the associations between gender and the main predictor (p = 0.392, data available at request) and outcome variables (p = 0.529) did not indicate over- or under sampling within the study groups.

With regard to optic disc size, it is possible that the slight overweight of cases with broken ISNT rule in large optic discs (> 1.8 mm) in comparison with small optic discs (≤ 1.6 mm) seen in Table 2, is misclassification due to thinner and more equal rim widths of the vertical segments normally found in large discs. However, because disc size was not related to IOP in univariate analysis (p = 0.821, data available at request) and the effect of the skewed sampling opposed the direction of the effect of the interaction (Table 3), selection bias is not a probable explanation of the interaction seen between optic disc size and IOP. However, one should bear in mind that vertical disc diameter is only a proxy measure of the disc area and as such does not take into account variability in the shape of the disc.

Another source of selection bias is inclusion of patients with early glaucoma since only those who had known glaucoma were excluded. Because of the associated thinning of the neuroretinal rim in glaucoma an overrepresentation of early glaucoma in the group with broken ISNT rule is possible. This could have strengthened the measured relationship to IOP. However, since neither gender nor disc size is a risk factor for glaucoma it is not a likely explanation of the findings in the reported study.

Clinic-based studies are also vulnerable to information bias. In particular, observer related bias that occurs when the clinician modifies measurements according to his knowledge of influencing factors. However, because the sequence of measurements was the same throughout the whole study with assessments of optic discs performed before measurements of IOP using non-contact tonometry, data is less likely to be affected by the observer. Likewise, we find it reasonable to assume that the observers were naive to the effect modifying properties of gender and disc size at the time of data collection.

Other limitations to our study include its cross-sectional design, which precludes causal interpretations of the results, and no confirmed agreement between practice sites for predictor and outcome measurements. Although observers were trained together in the assessment of the optic nerve head, differential misclassification may have occurred as a result of different recruitment rates or undilated stereoscopic examination with the risk of misclassification in patients with poor ophthalmoscopic view. Likewise, the use of different tonometers at the four sites may have biased the results. However, intraocular pressure did not differ significantly between sites (p = 0.806, data available at request).

In conclusion, this study has for the first time reported on the association between intraocular pressure and the outcome of ISNT rule assessment of optic discs in healthy patients seen in mainstream optometric practice. Patients with optic discs that did not obey the ISNT rule were associated with higher IOP than patients with discs that conformed to the rule. Although this association was weak when covariables were adjusted for; there was a trend towards an effect modification with a strengthening of the association in males and in subjects with small optic disc diameters. Further research is necessary to understand the possible implications of these findings on the assessment of optic discs with the use of the ISNT rule.

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