Antenatal and neonatal factors and morphology of the optic nerve head in the Northern Finland birth cohort

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ABSTRACT.

Purpose: The optic nerve head (ONH) is a part of the brain that can be evaluated through the transparent medium of the eye. The purpose of this study was to explore the possible correlations among the properties of the optic nerve head, maternal factors during pregnancy and neonatal parameters in a randomized sample of a birth cohort.

Methods: The Northern Finland 1966 Birth Cohort has been prospectively monitored since their antenatal period. Data on pregnancy and neonatal period were collected during gestation and right after birth in 1966. A randomized sample of 3070 subjects underwent an ophthalmic assessment at the age of 46–48 years. The examination protocol included scanning laser ophthalmoscopy with the Heidelberg Retina Tomograph. The ophthalmological parameters assessed were the disc area and the neuroretinal rim volume of the ONH.

Results: We found that chronic pulmonary disease of the mother (p = 0.007), the number of gestational weeks (p = 0.030) and the mother’s highest measured systolic blood pressure (p = 0.035) during pregnancy had a statistically significant effect on the disc area. Smaller disc size was associated with pulmonary disease and early gestation. There was a significant difference in rim volume between genders (p < 0.001). Women had larger neuroretinal rim volumes compared to men.

Conclusion: In this population-based study, the vast majority of antenatal and neonatal factors showed no correlation with optic disc area or rim volume. Furthermore, even the factors with statistically significant correlation with ONH morphology had limited predictive value.

Key words: antenatal factors – neonatal factors – neuroretinal rim – optic disc – optic nerve head

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Introduction

The optic nerve head (ONH) is the most distal part of the optic nerve. By 20 weeks of gestation, circa 50% of its growth has occurred, 75% by birth and 95% during the first year of life (Rimmer et al. 1993). During the first and beginning of the second trimester, there is an overproduction of axons in the optic nerve. Subsequently, their number decreases and stabilizes by the end of the second trimester (Provis et al. 1985). Therefore, it may be hypothesized that the size of the optic disc is influenced by the peak number of axons and the size of the cup and neuroretinal rim by the final number of axons left.

Only a few antenatal or perinatal factors affecting the size and shape of the optic nerve head have been established. Birthweight, gender and prematurity have been shown to influence the morphology of the ONH (Hellström et al. 1997; Hellström et al. 2000; Hellgren et al. 2009; Samarawickrama et al. 2009; Hackl et al. 2013; Park et al. 2013; Alshaarawi et al. 2014; Raffa et al. 2016; Akerblom et al. 2018). Brain lesions have been associated with changes in the optic disc morphology (Jacobson et al. 1997; Hellström 1999; Jacobson et al. 2003). Foetal alcohol syndrome has been shown to change ONH morphology (Hellström 1999; Ribeiro Oliveira et al. 2007). Mother’s smoking affects the retinal nerve fibre layer (RNFL) but not the ONH parameters (Pueyo et al. 2011). Racial differences in the
cup-to-disc ratio have been shown to be present at birth (Allingham et al. 2013).

Apart from the findings above, there is limited knowledge on antenatal or neonatal factors affecting the morphology of the ONH. Furthermore, data on the effect of these factors in a randomized, population-based sample are scarce.

The Northern Finland Birth Cohort (NFBC) offers the possibility to assess the significance of antenatal and perinatal factors affecting the ONH in a randomized population with prospective follow-up (Nordström et al. 2021). The purpose of this study is to explore and evaluate the possible correlations among the size of the optic disc, neuroretinal rim volume and the data collected during pregnancy and birthweight, height and gender in a randomized sample of the cohort study population.

Materials and Methods

The Northern Finland Birth Cohort 1966 (NFBC 1966) consists of subjects born in Finland’s two most northern provinces in 1966. It is an unselected and geographically defined population. Qualitative and quantitative data on the cohort have been prospectively collected throughout the years (Rantakallio 1988). The original NFBC study population consisted of 12 058 subjects, covering 96% of the children born in the area.

Antenatal data were collected during visits to antenatal clinics and using a questionnaire sent to the mothers in the 1960s (Nordström et al. 2021). The antenatal parameters evaluated in the present study included mother’s smoking before pregnancy and amount of smoking during the last 3 months of pregnancy, weight increase during pregnancy, number of deliveries and miscarriages and the highest systolic and diastolic blood pressure during pregnancy. Blood pressure was measured 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. The effect of general health during pregnancy was also studied. The factors 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. In addition, information on the gender, placental weight, gestational weeks, birthweight and height and whether the subject is a twin or not, and the mother’s age at the time of birth was collected by the maternity homes and antenatal clinics.

In 2012, when the cohort was 46 years old, 10 300 subjects living in Finland received an invitation to an extensive clinical examination of overall health. The NFBC eye study is a randomized prospective cohort study investigating the ocular health of the NFBC. Half of the cohort (n = 5155) were randomized to the eye screening group. Randomization was based on gender, postcode and the month of birth. Randomization was performed using Resampling Stats Software (Resampling Stats Inc., Arlington, Virginia, USA) (Saarela et al. 2013). Altogether, 3070 randomized subjects took part in the eye examination protocol. The study was conducted following the principles of the Declaration of Helsinki and was approved by the Ethical Committee of Northern Ostrobothnia Hospital District.

Ocular pathologies affecting the ONH, retina and visual fields were evaluated in a masked fashion by two ophthalmologists. There was particular interest in the evaluation of glaucomatous damage. All eyes with glaucoma suspect findings and their fellow eyes were re-evaluated for glaucomatous damage by glaucoma specialists unaware of the results of the previous assessments. The evaluation protocol has been described previously (Saarela et al. 2013; Karvonen et al. 2019). Glaucomatous damage was not an exclusion criterion for this nonselected, randomized population.

The eye examination protocol included an assessment of the ONH. The topographic ONH parameters evaluated in the present analysis include the disc area and the rim volume. The parameters were analysed as continuous variables, and they were also divided into three groups: the smallest 5%, the largest 5% and the group in-between. The parameters were obtained using the Heidelberg Retinal Tomograph (HRT3, Heidelberg Engineering, Heidelberg, Germany; software version 3.1.2a, Heyex 1.6.2.0). It uses confocal laser scanning imaging to measure the topography of the posterior fundus (Rohrschneider et al. 1994). The ONH parameters are calculated from the topography image by the device. The left eye of the participants was chosen for the analyses.

We tested for Pearson’s correlation coefficient between the optic nerve head parameters and 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, increase in mother’s weight during pregnancy, number of deliveries and gestational week. We used an independent T-test to test the following dichotomous variables in relation to the disc area and rim volume: smoking before pregnancy, gender, birthweight over or under 2500 g, hydrops, albuminuria, urinary infection, vitamin or iron supplements, diuretics, antibiotics, analgesics or sedatives, bleeding during pregnancy and chronic pulmonary disease. Smoking during the last 3 months of pregnancy and miscarriages were variables with multiple groups. We used analysis of variance (ANOVA) to test their relationship to the disc area and rim volume. Threshold p < 0.05 was chosen for statistical significance.

ANOVA was used to test the grouped ONH parameters, mother’s age and weight increase during pregnancy, the number of deliveries, birthweight and -length, placental weight, gestational week and the highest systolic and diastolic blood pressure. In addition, the Chi-square test of independence was used to test the association among the grouped ONH parameters, gender, mother’s chronic pulmonary disease, hydrops, albuminuria, urinary infection, vitamin or iron supplements, diuretics, antibiotics, analgesics or sedatives, bleeding during pregnancy, birthweight over or under 2500 g and smoking habits before and at the end of the pregnancy and miscarriages.

The number of diabetic mothers, mothers with organic heart failure, thyrotoxicosis, hypertension, chronic renal disease, fever, placental abruption or mothers treated for a threat of miscarriage were too low for statistical
analysis. The number of subjects born as twins was also too low.

Results
The differences between the mean disc area and rim volume were 0.0009 mm² and 0.0007 mm³ when the study population including glaucoma cases was compared to the study population without glaucoma cases found in the NFBC Eye Study. This is due to low number of glaucoma cases (left eye cases n = 21). The mean rim volume of the subjects with glaucoma was 0.37 mm³ and the rim volume of the study population was 0.47 mm³. No other diseases of the ONH were found.

Smoking before or at the end of the pregnancy did not have a statistically significant correlation with the optic disc area or the rim volume of the study subjects. Mother’s weight gain or age, highest diastolic blood pressure or the number of deliveries or miscarriages did not significantly correlate with the study participants’ optic disc area or rim volume. (Table 1 & 2).

Table 1. Correlation and distribution of maternal factors, neonatal measurements and disc area.

| Pearson’s correlation coefficient | N    | R     | p     |
|----------------------------------|------|-------|-------|
| Birth length                     | 2939 | 0.046 | 0.012 |
| Birthweight                      | 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 1. Correlation and distribution of maternal factors, neonatal measurements and disc area.

| t-test | N    | mean | 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 |       |
| No bleeding                        | 793  | 2.195 | 0.363 |
| Bleeding during pregnancy          | 30   | 2.114 |       |
| Birthweight > 2500 g               | 2888 | 2.180 | 0.764 |
| Birthweight < 2500 g               | 80   | 2.196 |       |

ANOVA

|          | N  | mean  | p     |
|----------|----|-------|-------|
| Did not smoke at end of the pregnancy | 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 miscarriage                        | 2413 | 2.180 | 0.458 |
| 1 miscarriage                        | 352  | 2.199 |       |
| 2 miscarriages                        | 100  | 2.203 |       |
| 3 or more miscarriages               | 39   | 2.078 |       |

Factors written in bold are the ones in which statistically significant difference was found (p < 0.05). The italic entries are used to highlight the compared groups in t-tests, for example: female vs. male. In tables showing the results of anova-test the italics are used to highlight the place where new comparison of groups starts, for example in Table 1: did not smoke at the end of the pregnancy, 0 miscarriage.

correlation between the study subjects’ birth length (R = 0.046, p = 0.012, Pearson’s correlation coefficient) and the optic disc area. Nevertheless, the correlation was not statistically significant when tested separately for men (R = 0.046, p = 0.142) and women (R = 0.042, p = 0.088). Birth length
Table 2. Correlation and distribution of rim volume, maternal and neonatal factors

| Pearson’s correlation coefficient | N | R | p   |
|----------------------------------|---|---|-----|
| Birth length                     | 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 |

**ANOVA**

| Did not smoke at end of the pregnancy | N  | mean  | p   |
|--------------------------------------|----|-------|-----|
| N                                    | 2557 | 0.467 | 0.964 |
| 1–5 cigarettes or 1–3 pipefils       | 167  | 0.466 |     |
| 6–10 cigarettes or 4–8 pipefils      | 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 miscarriage                       | 2413 | 0.465 | 0.384 |
| 1 miscarriage                       | 351  | 0.467 |     |
| 2 miscarriages                      | 100  | 0.483 |     |
| 3 or more miscarriages              | 39   | 0.440 |     |

Factors written in bold are the ones in which statistically significant difference was found (p < 0.050). The italic entries are used to highlight the compared groups in t-tests, for example: female vs male. In tables showing the results of anova-test the italics are used to highlight the place where new comparison of groups starts, for example in Table 1: did not smoke at the end of the pregnancy, 0 miscarriage.

and rim volume did not have a statistically significant correlation (R = 0.025, p = 0.169). Gestational weeks had a statistically significant correlation with the optic disc area (R = 0.031, p = 0.030) but not with the rim volume (R = 0.029, p = 0.117). The highest systolic blood pressure correlated positively with the disc area (R = 0.040, p = 0.035) but not with the rim volume (R = 0.019, p = 0.327). (Table 1 & 2, Fig. 1).

Women were overrepresented in the largest 5% group of rim volume and men in the smallest 5% group of rim volume. The difference was statistically significant (p < 0.001) (Table 3). The subjects whose mother had chronic pulmonary disease were overrepresented in the smallest 5% group of disc area (p = 0.020) (Table 4). None of the infant's other attributes or maternal factors had a statistically significant correlation with the grouped ONH parameters (the smallest 5%, the largest 5% and the group in-between) (Table 5).

**Discussion**

We found that excluding mother’s chronic pulmonary disease and highest measured blood pressure during pregnancy, none of the studied diseases, physiological measurements of the mother, previous miscarriages or deliveries, drugs or supplements used during pregnancy had a significant effect on the optic nerve head in a randomized birth cohort population. There was a difference in the rim volume between genders. The gestational weeks correlated positively with the disc area. Nevertheless, the measured differences and correlations were negligible at best.

We found that women had slightly larger rim volumes than men. Many studies have researched the differences in optic nerve head morphology between genders with varied results. In some studies, men’s disc areas and rim areas were larger, but the difference was insignificant in other studies (Jonas et al. 1988; Ramrattan et al. 1999; Bourne et al. 2008). Abe et al. found that gender had no statistically significant effect on the rim volume (Abe et al. 2009).

A novel finding in this study was the smaller disc area of study subjects whose mothers had a chronic pulmonary disease during pregnancy. Intrauterine hypoxia has been shown to decrease neuron count of the developing foetus (Lawrence et al. 2019). This may affect the peak number of axon of the optic nerve. Also, a novel finding was the correlation between the highest systolic blood pressure and the ONH disc area. Study participants
whose mother had higher highest measured systolic blood pressure had larger ONH disc areas. Neurodevelopment of the foetus may be affected by hypertension through a variety of biological mechanisms, e.g. via angiogenetic and inflammatory pathways. (Scime et al. 2021). Yet, stronger results on hypertension’s effect on ONH development are needed before more detailed hypothesizing on the underlying mechanisms is warranted.

We also found that subjects born taller had larger disc areas, but when tested separately for genders, the test yielded insignificant results. This result could imply that gender affects the birth length and the optic disc area in

Fig. 1. The statistically significant correlations between the ONH disc area and birth length, gestational weeks and highest systolic blood pressure during pregnancy. *Scale = number of cases are represented by each symbol.
In the present study, the number of gestational weeks had a positive correlation with disc area. This could be because the ONH has less time for developing in subjects born prematurely. However, the correlation was feeble and explained only 0.1% ($R^2 = 0.001$) of the variation of the disc area. Mixed results have been published before. Akerblom et al. found that the rim area of the ONH was smaller in prematurely born children than in children born at term (Akerblom et al. 2018). Alshaarawi et al. described larger rim volumes, smaller and deeper cups and increased height variation in the ONH in preterm children (Alshaarawi et al. 2014). One study showed that the child’s smaller birthweight and earlier delivery correlated with more oval optic nerve heads in premature children (Hackl et al. 2013). In very low birthweight (<1500 g) children, the optic cup area was larger, the optic rim was smaller and the optic rim/optic disc ratio smaller (Hellgren et al. 2009). In one study, the association between birthweight and optic disc morphology was insignificant in premature infants (Park et al. 2013). Low birthweight has been shown to correlate with the decreased vertical diameter of the optic nerve head (Samarawickrama et al. 2009). These results combined would imply that birthweight has only minor effect on ONH morphology.
Despite the statistically significant correlation with ONH morphology, the correlations were weak at best for all factors tested. The low correlations may be explained by the complex, multifactorial nature of ONH development during different stages of the foetal period. ONH morphology may be influenced by numerous genetic and physiological and pathological environmental factors affecting growth and ocular and neural development. In conclusion, in our study population, the measured maternal factors and infants’ attributes did not have a clinically significant effect on ONH morphology and it would seem that the development of the optic nerve head is well protected during pregnancy.

### Table 5. Results among grouped ONH parameters, neonatal measurements and maternal factors.

|                      | Disc area          | Rim volume         |
|----------------------|--------------------|--------------------|
|                      | p                  | p                 |
| Birth length (cm)    | 0.735              | 0.543              |
| Birthweight (g)      | 0.899              | 0.646              |
| Gestational weeks    | 0.179              | 0.756              |
| Number of deliveries | 0.812              | 0.934              |
| Placental weight (g) | 0.271              | 0.517              |
| Mother’s weight      | 0.099              | 0.294              |
| Mother’s age         | 0.741              | 0.504              |
| Highest SBP during pregnancy | 0.329 | 0.359 |
| Highest DBP during pregnancy | 0.719 | 0.546 |

Factors written in bold are the ones in which statistically significant difference was found (p < 0.050). The italic entries are used to highlight the compared groups in *t*-tests, for example: female vs male. In tables showing the results of anova-test the italics are used to highlight the place where new comparison of groups starts, for example in Table 1: *did not smoke at the end of the pregnancy,* 0 miscarriage.

* μ = mean, μ (<5%) = smallest 5%, μ (>5%) = largest 5%, μ (5–95%) = group in-between, SBP/DBP = systolic/diastolic blood pressure.

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