Severity of retinopathy of prematurity was associated with a higher risk of cerebral dysfunction in young adults born extremely preterm

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Short title: Severe retinopathy of prematurity and adult outcomes

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ABSTRACT

Aim: This Swedish study evaluated whether the severity of retinopathy of prematurity (ROP) in extremely preterm infants was related to their overall outcome in young adulthood.

Methods: We followed 39 individuals born 1988-93 at less than 28 gestational weeks, included in the Stockholm Neonatal Project. 19 were treated for severe ROP and 20 had no or mild ROP. They were assessed for general cognitive abilities and mental health at 18 years of age and compared with 23 term-born controls. Visual acuity was examined at 21-25 years. They were asked about their education and everyday life.

Results: The 19 individuals with severe, treated ROP had lower visual acuity and higher risk for intellectual deficits, cerebral palsy, and neuropsychiatric diagnoses than those with no or mild ROP and the term controls. Three were visually impaired, none were blind. They were less physically active than the other groups and had more problems finding their way around. However, nine were at university.

Conclusion: Young adults treated for severe ROP had more problems resulting from cerebral dysfunction than those with no or mild ROP and term-born controls. Retinal and brain pathologies in the extremely preterm infant constitute different expressions of neurovascular disease.
Keywords: adult outcome, cerebral dysfunction, cognition, cryo-treatment, retinopathy of prematurity

Key notes:

- Adults born extremely preterm and treated for severe ROP presented more often with cerebral dysfunction including intellectual deficits, cerebral palsy and neuropsychiatric problems, than those with no or mild ROP.
- Preterm born adults had problems to find their way and these problems were most pronounced in the group treated for ROP.
- Brain injury and ROP in the preterm infant have similar aetiologies and may constitute different expressions of neurovascular pathology.

Abbreviations: FSI, Full Scale Index; POI, Perceptual Organisation Index; PSI, Processing Speed Index; ROP, retinopathy of prematurity; SDQ, Strengths and Difficulties Questionnaire; VCI, Verbal Comprehension Index; WISC-III, Wechsler Intelligence Scale for Children, Third Edition
INTRODUCTION

The manifestation of severe retinopathy of prematurity (ROP) in Sweden has gradually changed since the 1950s. The first generations of infants who survived moderately preterm birth had been generously supplied with oxygen, which occasionally led to severe retinal pathology. This meant that ROP was by far the most common cause of blindness in children in the 1960s (1). From the late 1970s, the improved survival of very and extremely preterm infants was associated with blindness from ROP. This was more frequently accompanied by neurodevelopmental impairments, such as cerebral palsy, intellectual disability and autism, when compared with children who were congenitally blind because of a hereditary degenerative retinal disease, Leber’s congenital amaurosis (2, 3). Screening for ROP was introduced in the mid-1980s, as was cryotherapy to prevent detachment of the retina in severe ROP. This treatment completely changed the visual prognosis, reducing the risk of blindness from 5-11 % (4) to around 1% (5) in preterm populations. These days, ROP is recognised as a vascular disease of the immature retina and it affects 70% infants born extremely preterm (6).

Severe ROP has been shown to be associated with impaired cognitive development (7,8) and that was what we found when the cohort that this paper focuses on was 5.5 years of age (9). Specifically, ROP was found to be a predictor of poorer performance on testing of executive functions (10). A relationship between ROP and reduced brain volumes has been demonstrated (7), and the presence of severe ROP may be a predictor of delayed white matter maturation and impaired neurodevelopment, despite favourable visual outcomes (8). In 2019, Morken et al (11) suggested that ROP is a neurovascular disease and part of a spectrum that includes pathological development of the retinal and the cerebral interphase.
Retrograde trans-synaptic degeneration of retinal ganglion cells following a primary lesion in the optic radiation (12) in preterm individuals, illustrates that the retina is an extension of the central nervous system.

It is not just the retina that is vulnerable when infants are born extremely preterm, as the immature brain is also affected. Periventricular white matter injury may affect both motor and visual tracts. The dorsal stream, running from the occipital to the parietal territories, processes information about motion and spatial relationships, and guides movements. Dorsal stream dysfunction has been demonstrated in preterm populations (13). One consequence of such dysfunction is when individuals have problems finding their way around and they need to consciously remember sequences of orientation marks to compensate for that. This problem is not evident in young children, but has been described in teenagers and young adults suffering from cerebral visual impairment (14).

A review of the outcomes in adults born preterm, found that they remained at higher risk for impaired general cognitive abilities, executive function, attention and neuro-motor abilities well into adulthood. The review also found that there were considerable variations in these outcomes (15). A large proportion of the adults reported self-perceived quality of life issues, which were not evident in their term-born peers (15) However, the review did not focus on potential relationships of these outcomes with the presence and severity of ROP. Saigal presented the life stories of 42 individuals in their thirties who had been born preterm. Many of them had functional deficiencies and 11 were blind or partially sighted due to ROP (16). Despite this, most of them rated their quality of life as good.

Our study focused on the first generation of extremely preterm born individuals to be treated for severe ROP when they reached early adulthood. The aim was to explore whether
or not those who needed treatment for severe ROP in infancy developed cognitive difficulties, mental health problems, difficulties with educational achievement or everyday functioning in adulthood.

**METHODS**

The participants in this study were part of the Stockholm Neonatal Project, which is a longitudinal, population-based prospective study of infants treated in intensive care units in Stockholm between 1988 and 1993. They were all born with very low birth weights of less than 1500g. There were 291 infants included in the study and 92 were diagnosed with ROP, of whom 29 needed cryotherapy (17). At the age of 5.5 years the children were invited to a follow-up study and 182 accepted to participate. To compare their results 125 children of the same age, born healthy at term at the same hospital, were included as a control group. Further assessment of cognition and mental health were carried out when the participants reached 18 years of age, and this comprised of 134 from the original birth cohort and 94 individuals from the control group. A comprehensive report of the follow up at 18 years of age was published in 2015 by Lundequist et al (18).

A further follow-up study was carried out when the participants reached 21-25 years of age and this focused on those born at less than 28 weeks of gestation. There were 28 adults who had been treated for severe ROP stage 3 or more and 42 who had not needed treatment as they had no or mild stage 1-2 ROP. The follow-up study looked at blood pressure, visual and retinal outcomes, and they were interviewed about their educational achievements, physical activity, and their ability to find their way (19). Fifty-five participants
were randomly selected from the original term control group and were invited to also take part. Twenty-one participants with severe, treated ROP and 21 with no or mild ROP together with 23 full term controls agreed to take part in the current study. The most common causes to decline participation were that they could not take the time off from work or studies, or that they did not live in Stockholm. In addition, we had to exclude three extremely preterm participants; two because of syndromes associated with developmental delay and one because of missing data from the 18-year follow-up. All participants provided written informed consent.

The longitudinal study was originally approved by the Ethics Committee at Karolinska Hospital in 2002. The Regional Ethics Board of Stockholm approved the cognitive assessment and continued use of the original database when the subjects reached 18 (2007/46-31/3 and 2009/1229-32), and the study of adult blood pressure and visual outcomes and interviews at 21-25 years (2013/646-31/4). The study procedures followed the Declaration of Helsinki.

**Background data and current health**

Data were collected from the participants’ neonatal and post-neonatal medical files. All preterm participants were interviewed about their current health status. Data on maternal and paternal education were based on the data compiled for the study at 5.5 years.

According to the Swedish Standard Classification of Education grades were applied: zero for no formal school education, one for less than nine years’ education, three for two years of high school, four for completed high school, five for a bachelor degree, six for a Master’s degree and seven for a PhD degree (Table 1).

**Visual assessment and ophthalmological examination**
All participants were seen and interviewed by a research nurse on two consecutive days, and all preterm born participants were seen by a paediatric ophthalmologist for examination of the eyes and assessment of vision.

Best corrected visual acuity was tested with a letter chart and the cover test was performed. All preterm participants had undergone cycloplegic refraction at the age of six years and were subjectively refracted at this follow up. All full-term controls had normal visual acuity and normal ocular alignment at the age of six years and they were not assessed again as adults. All participants were examined with fundus photography. We further investigated 14 of the preterm participants with cryo-treated ROP by using optical coherence tomography and computerised perimetry (21).

**Cognitive measures**

We used data from the follow-up study at 18 years of age. Cognitive levels were evaluated by trained psychologists using the Wechsler Intelligence Scale for Children, Third Edition (WISC-III) short form. WAIS was not an option when the 18 years study was planned, due to its lack of reliable norms for adolescents. WISC-III was chosen instead of WISC IV as it has Swedish norms. The short form has shown satisfactory reliability and validity and the four factor models meet the criteria for comparing the results between preterm and term participants. The factor index has a mean of 100 and a standard deviation (SD) of 15. The test comprises eight subtests, and six were used to calculate a Full Scale index (FSI). The Verbal Comprehension index (VCI), the Perceptual Organisation index (POI), and Processing Speed index (PSI) completed the cognitive measures. (22). In order to analyse the impact of independent variables on cognitive outcome, multiple regression analyses were performed.
using the cognitive test results from the four indexes as dependent variables. Treated ROP, intraventricular haemorrhage grade 3-4, and, or, cystic periventricular leukomalacia, the child’s sex, and maternal education were used as predictors.

**Mental health screening**

To investigate mental health, the Swedish version of the self-reporting Strengths and Difficulties Questionnaire (SDQ) (22) was completed by the participants when they were 18 years old. The Swedish translation states that the test was designed for adolescents aged 11 to 16 years; Svedin & Priebe (23) found that the scale could be effectively used in 19-year-olds. It comprises five different scales about feelings, behaviour and peer relations, namely: emotional symptoms, conduct problems, hyperactivity/inattention, peer relationship problems, and prosocial behavior. There are five questions for each scale, which provide total values of 0-10 points. The sum of the scores for each scale was analysed as normal, borderline, or abnormal, according to specified norms. When prosocial behaviour was excluded, the other four scales provided an index of mental health.

**Education, physical activity and wayfinding**

All participants were interviewed at 21-25 years of age. They were asked about their education, their physical activity, and their experiences of wayfinding, which is finding their way around in familiar and unfamiliar surroundings.

**RESULTS**

**Background data and neurological and neuropsychiatric status**
The children who needed treatment for ROP had lower gestational ages and birth weights and were more likely to have had chronic lung disease than those who were not treated for ROP. No difference was found in the neonatal cranial ultrasound findings between the two preterm groups with regards to lesions involving the periventricular white matter, namely intraventricular haemorrhage grade 3-4 or cystic periventricular leukomalacia (Table 1).

Of the 19 individuals treated for severe ROP, five had one of the following diagnoses and six had more than one: intellectual disability, cerebral palsy, attention deficit hyperactivity disorder, autism spectrum disorder, hearing deficit, or gender dysphoria.

Four of the 20 individuals with no or mild ROP had one of the following diagnoses: intellectual disability, epilepsy and bipolar disorder, Table 4.

**Visual outcome**

The group treated for ROP had lower visual acuity, larger refractive errors, and more frequently strabismus than those with no or mild ROP and the term controls, Table 2. Thirty-eight eyes in 19 individuals were treated. Visual acuity 0.8 or better was obtained in 21 of the treated eyes. Six individuals who were treated for ROP achieved normal visual acuity in both eyes. Three males with treated ROP were visually impaired, with a visual acuity less than 0.5 in the best eye. No-one was completely blind. We found that 11 had manifest strabismus.

Of the 20 participants with no or mild ROP, 19 had normal visual acuity in each eye. One male participant with mild ROP had subnormal visual acuity and strabismus related to posterior periventricular white matter damage that had been verified by magnetic resonance imaging.
Cognitive outcomes

The cognitive levels measured by the index scores at 18 years differed between the groups and those with treated ROP had the lowest scores (Table 3a). Each group was analysed according to sex and the index values were more favourable in females with severe ROP, no or mild ROP, and the controls. The individual results for the four test indices, FSI, VCI, POI and PSI, varied between 32 and 144. This means that the results ranged from levels consistent with intellectual disability to high levels of ability. When we compared the cognitive results between those treated for ROP and the controls, all the test results were significantly better in the control group: FSI (p< 0.01), VCI (p=0.01), POI (p<0.01) and PSI (p<0.01). The differences between the group with no or mild ROP and the term controls was only significant for POI (p= 0.04).

The regression analyses showed that treated ROP and maternal education were significantly associated with cognitive outcomes, and that sex differences had an impact, but to a lesser degree (Table 3b).

Results of the SDQ assessment

The majority of the participants reported no problems with mental health, except for difficulties with peer relationships. In all three groups most participants evaluated their problems with peer relationship as being substantial, corresponding to a borderline or deviant quality. This affected 16/18 in the treated ROP group, 15/20 in the group with no or mild ROP and 20/23 of the controls.

Education, physical activity, and wayfinding
Problems finding their way around in unfamiliar surroundings were common in the group treated for ROP, and some also had difficulties in familiar surroundings. These issues were present, but less severe, in the group with no or mild ROP. The group treated for severe ROP reported less physical activity than the untreated group and controls. However, nine individuals in the treated group had gone to university and one had been accepted as a member of Mensa at the age of 18 (Table 4).

**DISCUSSION**

The main finding of this study was that individuals who were born extremely preterm and treated for severe ROP had a higher risk of impaired visual and neurocognitive development than preterm individuals with no or mild ROP and term-born controls. Boys were more severely affected than girls. These findings are in accordance with other studies, as described in the review by Morken et al (11). It is noteworthy that the variability within the group treated for ROP was large.

Visual acuity outcomes at adult age were satisfactory in both eyes in six and in one eye in nine of those who had been treated for ROP. Three, however, were visually impaired despite treatment. No-one totally was blind. Therefore, cryotherapy can be considered an effective treatment when severe ROP risks retinal detachment and total blindness, as seen in case one (Figure 1). However, in this group, examination with fundus photography and optical coherence tomography demonstrated major micro-retinal abnormalities, as well as subnormal sensitivity of the visual field function (20). The implications of these findings for future visual function, considering age-related retinal changes, remain unknown. In the current study, the three visually impaired individuals were male, all had intellectual disabilities, one had autism, and another had cerebral palsy. Manifest strabismus, which
indicates brain damage in preterm populations (24), was present in 11/19 in the group treated for ROP and 1/20 in the group with no or mild ROP. These findings are in line with the results of other studies. One highlighted that brain development is negatively related to ROP (25). Another showed that similar mechanisms lead to diminished cortical vascularisation and retinal neuronal and glial vascularisation (26). A third reported that the association between brain disorders and ROP may largely be explained by common risk factors (27).

Extreme preterm birth poses a threat to typical cognitive development. The individual differences in the two preterm groups were large and varied, from scores that indicated severely impaired performance to those that were well above the normal level. The control results were somewhat less dispersed. Individuals treated for ROP had the lowest cognitive scores, a higher incidence of cerebral palsy and neuropsychiatric diagnoses and more difficulties finding their way than preterm individuals with no or mild ROP and the term controls. Two individuals in the group treated for ROP had, after 21 years of age, started hormone treatment because of gender dysphoria. Both had normal intellectual abilities, but had as children been diagnosed with autism spectrum disorder. The group treated for ROP included an extreme outlier, case two, with a Full-Scale index of almost +3 SD (Figure 2). The term controls differed significantly from the group treated for ROP in all cognitive measures, but only in perceptual organisation when compared with the preterm group with no or mild ROP. However, no substantial differences in self-rated mental health were evident between the groups.
Stability of cognitive results from childhood to the age of 26 years was supported by the Bavarian Longitudinal Study (28). They concluded that there was no longitudinal change in the cognitive differences between individuals born preterm and the term controls. This supports that our use of data from the 18 years follow-up can be considered reliable.

Problems with wayfinding were reported in both preterm groups, but they were greater in the group treated for ROP. These problems cannot be explained by loss of visual input. Chaminade et al (29) used functional magnetic resonance imaging to demonstrate dorsal stream abnormalities in healthy adults born preterm. Such processing disorders may explain problems with wayfinding among individuals born preterm who have normal visual acuity and normal cognitive levels. It is important to recognise such difficulties and to identify and apply individually adapted strategies to deal with them.

Individuals in the group treated for ROP reported taking part in significantly less physical activity than both other groups. This may be because their cognitive visual dysfunction made it difficult to judge depth and distance, combined with problems with integrating body movements. In addition, neuromotor difficulties and problems with wayfinding may also have contributed.

Although most of the treated individuals had limited intellectual resources for academic studies, nine of the 19 chose to go to university and three had pursued a vocational education. Of the term controls, 14 of the 20 had started university studies. However, a limitation of our study was that some participants were still too young to evaluate the results of education and the possibilities for independent living. Another limitation was that mental health was not screened again at the age of 21-25 years. We chose to present the mental data from the study at 18 years as a background level when entering adult life. The
large variation in overall outcome in the group treated for ROP was multifactorial. One important cause, besides the better outcome for females, was how the infants were selected for the cryotherapy treatment. The decisions to provide treatment were made by different ophthalmologists at a time when there was limited experience of the natural evolution of ROP. This may explain why unnecessary treatment was provided some cases.

The final architecture of the retinal vessel tree after acute ROP provides predictive information concerning visual outcome, but may also provide information concerning risks of adverse neurodevelopment. Future systemic therapeutic improvements in the neonatal care of extremely preterm infants may prevent severe ROP from arising and thus reduce the risk of visual impairment. This will also prove beneficial for brain maturation.

**CONCLUSION**

Young adults born extremely preterm and treated for severe ROP presented more often with cerebral dysfunction including intellectual deficits, cerebral palsy, neuro-psychiatric problems, and wayfinding problems than those born extremely preterm with no or mild ROP.

**ABBREVIATIONS**

BCVA, best corrected visual acuity; D, diopters; FSI, Full Scale Index; IVH, intraventricular haemorrhage; n.s., not significant; PVL, periventricular leukomalacia; POI, Perceptual Organisation Index; PSI, Processing Speed Index; ROP, retinopathy of prematurity; SDQ, Strengths and Difficulties Questionnaire; VCI, Verbal Comprehension Index; WAIS, Wechsler Adult Intelligence Scale; WISC-III, Wechsler Intelligence Scale for Children, Third Edition
**FUNDING**

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**CONFLICTS OF INTEREST**

The authors have no conflicts of interest to declare.

**ACKNOWLEDGEMENTS**

We thank the study participants, Ann-Charlotte Smedler, principal investigator, and Aiko Lundequist, data collection coordinator, for their essential contributions to the 18-year follow-up study, Lena Swartling for technical assistance.

**REFERENCES**


Figure 1. Case one. Adult fundus photographs of a male born at a gestational age of 24+3, with a birth weight of 675g, who needed mechanical ventilation for 67 days. He developed ROP stage 3+ in the right eye and stage 4 in the left eye and was treated under general anaesthesia with cryo x 2 in the right eye and cryo x 3 plus cerclage in the left eye. The first treatment was performed at a gestational age of 38 weeks. He developed cerebral palsy and intellectual disability. His best corrected visual acuity as an adult was 0.05 in the right eye, but it was not measurable in the left eye. He had high myopia, esotropia and nystagmus. Fundus photographs demonstrate severe dragging of the vessels in the temporal direction from the small optic discs, ectopic maculae and scarring after cryo-treatment in zone 1 in
both eyes. He lives with his parents, and is looked after by them. He depends on a guide to find his way around. In this case treatment inhibited retinal detachment and protected him from total blindness.

Figure 2. Case two. Adult fundus photographs of a male, born at a gestational age of 26+1, with a birth weight of 870g, who needed mechanical ventilation for six hours and had an uneventful neonatal period, except for chronic lung disease. His best corrected visual acuity was 1.25 in the right eye and 1.6 in the left eye. Stereo acuity was normal. Fundus photographs demonstrate normal vessel arcades and there are no signs of retinal pathology in zone 1. In the retinal periphery there is scarring after cryo-treatment that was performed late, six weeks after term-equivalent age, because of ROP grade 3+. Optic coherence tomography demonstrated normal distribution of retinal nerve fibres. At 18 years of age he had a superior IQ level and was accepted as a member of Mensa. He has no problems with wayfinding and is a successful university student. In retrospect, treatment may have been uncalled for in this case.
Table 1 Perinatal and neonatal characteristics plus parental educational

<table>
<thead>
<tr>
<th></th>
<th>Severe, treated ROP n=19</th>
<th>No or mild ROP n=20</th>
<th>Term-born controls n=23</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males/females n</td>
<td>9/9</td>
<td>10/10</td>
<td>13/10</td>
</tr>
<tr>
<td>Gestational age weeks, median (range)</td>
<td>25 (24-27)</td>
<td>26 (25-27)</td>
<td>39 (37-42)</td>
</tr>
<tr>
<td>Small for gestational age, n</td>
<td>0</td>
<td>1</td>
<td>0</td>
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<tr>
<td>Chronic lung disease, n</td>
<td>3</td>
<td>6</td>
<td>0</td>
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<tr>
<td>IVH grade 3-4 and/or PVL, n</td>
<td>6</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Cerebral palsy, n</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Paternal education</td>
<td>5 (2-6)</td>
<td>4 (2-6)</td>
<td>4 (2-6)</td>
</tr>
<tr>
<td>Maternal education</td>
<td>5 (2-6)</td>
<td>5 (2-7)</td>
<td>4 (2-6)</td>
</tr>
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Intraventricular haemorrhage (IVH) grade 3-4 and periventricular leukomalacia (PVL) were combined to indicate brain injury with periventricular tissue involvement.
Table 2  Visual data presented as median and range values

<table>
<thead>
<tr>
<th></th>
<th>Severe, treated ROP n=19</th>
<th>No or mild ROP n=20</th>
<th>Term-born controls n=23</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCVA right eye</td>
<td>0.65 (0.05 - 1.25)</td>
<td>1.0 (0.65 - 2.0)</td>
<td>Normal at 6 years</td>
</tr>
<tr>
<td>BCVA left eye</td>
<td>0.8 (nm - 1.6)</td>
<td>1.0 (0.3 – 1.3)</td>
<td>Normal at 6 years</td>
</tr>
<tr>
<td>Refraction right eye</td>
<td>+3.5D (-18D - +1.5D)</td>
<td>0 (-6.75D - +4.75D)</td>
<td>Normal at 6 years</td>
</tr>
<tr>
<td>Refraction left eye</td>
<td>-1.75 (-20D - +2D)</td>
<td>0 (-7.75D - +4.75D)</td>
<td>Normal at 6 years</td>
</tr>
<tr>
<td>Manifest strabismus</td>
<td>11</td>
<td>1</td>
<td>0 at 6 years</td>
</tr>
<tr>
<td>Nystagmus</td>
<td>3</td>
<td>1</td>
<td>0 at 6 years</td>
</tr>
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</table>

BCVA, best corrected visual acuity nm, not measurable; D, dioptres
Table 3a Intellectual levels at 18 years of age. Results from WISC-III short form; Full-scale Index (FSI), Verbal Comprehension Index (VCI), Perceptual Organisation Index (POI) and Processing Speed index (PSI). Median values and score ranges are given.

<table>
<thead>
<tr>
<th>WISC-III short form at 18 years</th>
<th>Severe, treated ROP n= 18</th>
<th>Female n=9</th>
<th>Male n=9</th>
<th>No or mild ROP n=20</th>
<th>Female n=10</th>
<th>Male n=20</th>
<th>Term controls n=23</th>
<th>Female n=10</th>
<th>Male n=13</th>
</tr>
</thead>
<tbody>
<tr>
<td>FSI</td>
<td>78.5 (48-144)*</td>
<td>84.0 (61-95)</td>
<td>70.0 (48-144)</td>
<td>96.0 (52-124)</td>
<td>98.5</td>
<td>80.0</td>
<td>103.0 (76-127)</td>
<td>110.5</td>
<td>98.0</td>
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<tr>
<td>VCI</td>
<td>89.5 (60-139)*</td>
<td>94.0 (60-104)</td>
<td>87.0 (60-139)</td>
<td>95.0 (65-123)</td>
<td>100.0</td>
<td>91.5</td>
<td>101.0 (68-125)</td>
<td>106.0</td>
<td>97.0</td>
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<tr>
<td>POI</td>
<td>69.5 (32-139)*</td>
<td>74.0 (67-97)</td>
<td>55.0 (32-139)</td>
<td>94.0 (38-124)</td>
<td>99.0</td>
<td>74.5</td>
<td>105.0 (71-123)</td>
<td>106.0</td>
<td>100.0</td>
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<tr>
<td>PSI</td>
<td>81.0 (47-129)*</td>
<td>88.0 (74-118)</td>
<td>65.0 (47-129)</td>
<td>97.0 (56-120)</td>
<td>101.5</td>
<td>81.0</td>
<td>103.0 (68-141)</td>
<td>110.5</td>
<td>100.0</td>
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</table>

*One 18 year score was missing

Testing of significant differences between groups and sexes: p-levels (Mann-Whitney test):

Controls/ severe, treated ROP FSI: (p<0.01), VIQ (p=0.01), POI (p<0.01), PSI (p=0.01).

Controls/no or mild ROP: POI (p= 0.04)

No or mild ROP / severe, treated ROP3: FSI (p= 0.01); POI (p= 0.01); PSI (p= 0.03)

Control females/males: no significant difference

No or mild ROP females/males: FSI (p = 0.04); POI (p= 0.01), PSI (p= 0.01)

Severe, treated ROP females/males: POI (p= 0.02); PSI (p= 0.03)
Tabell 3b

Regression analyses of the impact from the independent factors: treated ROP, maternal education, sex and IVH/PV on the dependent cognitive factors in WISC-III.

<table>
<thead>
<tr>
<th>Test</th>
<th>Treated ROP</th>
<th>Mo education</th>
<th>Sex</th>
<th>IVH/PVL</th>
</tr>
</thead>
<tbody>
<tr>
<td>FSI</td>
<td>19% (p=&lt;0.01)</td>
<td>21% (p= &lt;0.01)</td>
<td>6% (p= 0.02)</td>
<td>n.s.</td>
</tr>
<tr>
<td>VCI</td>
<td>13% (p= 0.01)</td>
<td>27% (p=0.01)</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td>POI</td>
<td>9% (p= &lt;0.01)</td>
<td>18% (p= &lt;0.01)</td>
<td>17% (p=&lt;0.01)</td>
<td>n.s.</td>
</tr>
<tr>
<td>PSI</td>
<td>9% (p= 0.01)</td>
<td>n.s.</td>
<td>20% (p=&lt;0.01)</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

n.s., not significant
### Table 4

Adult neuropsychiatric and neurological diagnoses, education, wayfinding and physical activity

<table>
<thead>
<tr>
<th></th>
<th>Severe, treated ROP n=19</th>
<th>No or mild ROP n=20</th>
<th>Term controls n=23</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intellectual disability (FSI&lt;70)</td>
<td>5</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Attention deficit hyperactivity disorder</td>
<td>3</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Autism spectrum disorder</td>
<td>3</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Gender dysphoria</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Severe hearing problems</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Epilepsy</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Cerebral palsy</td>
<td>3</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td><strong>Maximum education</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than 12 years at school or special school</td>
<td>7</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Graduated after 12 years at school</td>
<td>0</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Vocational education</td>
<td>3</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>University</td>
<td>9</td>
<td>7</td>
<td>14</td>
</tr>
<tr>
<td><strong>Wayfinding</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No problems</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Some problems: helped by reading a map</td>
<td>2</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Gets lost often: not helped by reading a map</td>
<td>10</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Need a guide</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Physical activity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>self-reported hours/week</td>
<td>1,5 (0-5.5)</td>
<td>4 (1-12)</td>
<td>3 (0-12)</td>
</tr>
</tbody>
</table>

* missing data from one participant, ** missing data from three participants