






BMJ Open Retrospective evaluation of ophthalmological and neurological outcomes for infants born before 24 weeks gestational age in a Swedish cohort

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ABSTRACT

Objectives To retrospectively evaluate ophthalmological and neurological outcomes in a Swedish cohort of infants born before 24 weeks gestational age (GA) and explore risk factors for visual impairment.

Setting Eye and paediatric clinics in Sweden.

Participants Infants screened for retinopathy of prematurity (ROP) (n=399), born before 24 weeks GA, 2007–2018. Cases were excluded if ophthalmological follow-up records could not be traced.

Primary and secondary outcome measures Primary outcomes were ophthalmological, including visual acuity (VA), refractive error, strabismus, nystagmus and cerebral visual impairment (CVI). Secondary outcomes comprised neonatal and neurological morbidities. Data were retrospectively retrieved from medical records.

Results The 355 assessed children had a median GA of 23 weeks and 2 days and a median birth weight of 565 g. At the last available ophthalmological examination, the median age was 4.8 years (range 0.5–13.2 years). Nystagmus was recorded in 21.1%, strabismus in 34.8%, and 51.0% wore spectacles. Seventy-three of 333 (21.9%) were visually impaired, defined as being referred to a low vision clinic and/or having a VA less than 20/60 at 3.5 years of age or older. ROP treatment was a significant risk factor for visual impairment (OR 2.244, p=0.003). Visually impaired children, compared with children without visual impairment, more often had neurological deficits such as intellectual disability 63.8% versus 33.3% (p<0.001), epilepsy 21.1% versus 7.5% (p=0.001) and autism spectrum disorders 32.8% versus 20.9% (p=0.043). Nine of the 355 children had been diagnosed with CVI.

Conclusions Children born before 24 weeks GA frequently had visual impairment in association with neurological deficits. CVI was rarely diagnosed. A multidisciplinary approach for the evaluation and habilitation of these vulnerable infants is warranted. National follow-up guidelines need to be developed and implemented.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This study comprises data collected over a decade from a large number of infants born before 24 gestational weeks.
- ⇒ Medical records have accurately been identified and scrutinised through personal identification numbers.
- ⇒ The lack of data regarding variables that were not examined/recorded due to different regional policies in follow-up is a key issue.
- ⇒ The children's ages at the last ophthalmological examination ranged from 5 months to 13 years, making some comparisons difficult.

INTRODUCTION

Sweden has a tradition of an active approach when managing extremely preterm births, and survival of infants born before 24 weeks gestational age (GA) has increased notably during the last decade.^{1 2} Infants born extremely preterm have a high risk of somatic and neurological disorders with lifelong consequences.^{3–5} Retinopathy of prematurity (ROP) is a potentially sight-threatening disease affecting primarily the most extremely preterm infants.^{6 7} Ophthalmological problems and visual impairment are common after extremely preterm birth, even in the absence of previous ROP.^{8 9} The Extremely Preterm Infants in Sweden study, EXPRESS, reported that of the 42 surviving children born at GA 22–23 weeks in 2004–2007, 16.7% were visually impaired, 25.0% had strabismus and 46.3% had refractive errors at 6 years of age.¹⁰ The same study reported that having received treatment for ROP was the most significant risk factor for visual

impairment. ROP overall has been found to associate with retinal structural alterations, delayed maturation of cerebral white matter containing the primary visual pathways and altered diffusivity in the optic radiation.^{11–13} A common type of visual impairment in extremely preterm infants is cerebral visual impairment (CVI).⁸ In CVI, visual processing difficulties may substantially restrict the child's daily life performance, irrespective of visual acuity (VA).¹⁴ Preterm infants with hypoxic ischaemic injuries in the periventricular zone causing periventricular leukomalacia (PVL) are especially at risk for CVI.¹⁵ CVI is associated with other neurological morbidities such as cerebral palsy (CP), autism spectrum disorders and epilepsy (EP)¹⁶ as well as with ophthalmological morphological and functional deficits like optic nerve hypoplasia, nystagmus, strabismus, significant refractive error and suboptimal VA.¹⁷ Thus, it may be difficult to assess the relative contributions of eye and brain abnormalities in visually impaired preterm children. In Sweden, low vision clinics offer visual habilitation, support for parents and medical aids and visual habilitation strategies for the children. A child can be referred to a low vision clinic in Sweden if presenting a VA less than 20/60 or a deviant visual behaviour.

This retrospective population-based national study comprising infants born before 24 weeks GA during 12 years, 2007–2018, aimed to explore ophthalmological and associated neurological outcomes and assess risk factors for visual impairment.

MATERIALS AND METHODS

Study population and study procedures

This retrospective cohort study included children with completed ROP screening (n=399) born before 24 weeks GA in Sweden 2007–2018. In Sweden, screening all infants born before 30 weeks GA for ROP is mandatory. Results are reported to the Swedish national register for ROP, SWEDROP, which has a coverage rate of 98%.¹⁸ Children were identified through SWEDROP, from which maximal ROP stage and ROP treatment were retrieved. Using personal identity numbers available in SWEDROP, infants' medical charts were identified at eye and paediatric clinics and local child healthcare centres.

Ophthalmologic outcomes were obtained from the child's last examination at the eye clinic, if available. Children who did not show up for ophthalmological follow-up or who had been dismissed from follow-up before VA testing at the eye clinic were traced, and if available VA measurements were obtained from child healthcare centres. According to Swedish national guidelines, a VA test should be performed at 4 years of age in all children at local child healthcare centres in Sweden. Linear VA had been assessed with the best habitual correction monocularly or binocularly, using HVOT and Lea Hyvärinen charts. Preferential-looking tests such as Cardiff and Teller Acuity Cards were used in some children. All VA results were converted to Snellen acuity for

statistical assessment. The better and the worse eye were identified if monocular VAs were unequal. If only a binocular VA was available, this was recorded.

In this study, visual impairment was defined as having been referred to a low vision clinic at any age and/or having a VA in the better eye <20/60 (with best habitual correction if appropriate) at 3.5 years or older (binocular, if monocular VA was not available). If a child <3.5 years of age had a VA <20/60, this child was not classified as visually impaired since immaturity of the visual system and/or inability to cooperate to VA testing may have affected the outcome.^{19,20} Blindness was defined according to the WHO as VA <3/60.²¹

Refraction was measured under cycloplegia. The spherical equivalent (SE) was calculated. Refractive errors were defined as hyperopia >3 diopters (D) SE, myopia >3 D SE, astigmatism >2 D or anisometropia >2 D. Strabismus was defined as all types of manifest and intermittent strabismus. Reports of nystagmus were recorded. The diagnosis of CVI was retrieved from medical records ICD-10 code H53.8 or H.47.7 or if the records clearly stated CVI after multidisciplinary evaluation. There are no generally accepted diagnostic criteria or evaluation procedures for CVI in Sweden.

Data on neonatal morbidities and diagnoses related to cerebral function were retrieved from the infants' paediatric records and/or from the National Board of Health and Welfare registry. The diagnosis CP was defined as ICD-10 code G80.0–G80.9, mild to severe intellectual disability defined as ICD-10 code F70.0–72.9, autism spectrum disorders defined as ICD-10 code F84, EP defined as ICD-10 code G40.1–40.9 and moderate to severe hearing impairment defined as depending on hearing aids or worse were recorded.

Patient and public involvement

Neither patients nor public were involved in the research design, conduct, reporting or dissemination plans.

Statistical analysis

Numbers and percentages are given for categorical variables, while ranges and median values, are applied for continuous variables. Univariate and multivariate logistic regression analyses were employed to evaluate the impact of different risk factors for visual impairment. ORs and 95% CIs were calculated for each risk factor. Pearson's χ^2 tests were used to evaluate the relationships between visual impairment and neurological disorders. A p value of <0.05 was considered statistically significant (two-sided tests). All analyses were carried out with IBM SPSS Statistics for Windows, V.25.0. Armonk, New York.

RESULTS

Of the 399 children screened for ROP 2007–2018, ophthalmological records were available for 355 (figure 1). One girl and one boy were born at 21 weeks of GA, 39 girls and 44 boys at 22 weeks and 128 girls and 138 boys at

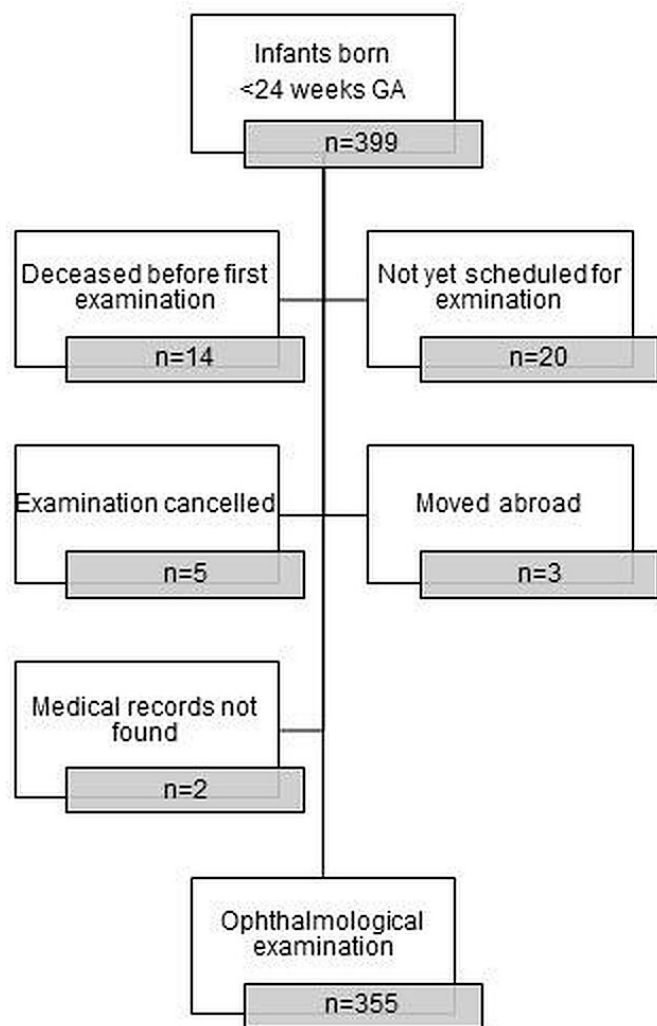


Figure 1 Flowchart of the study population. GA, gestational age.

23 weeks. The two infants born at 21 weeks were added to the 22-week group. Birth characteristics of the infants are presented in [table 1](#). Of the children with available ophthalmological records, 92.5% (329/355) had an ROP diagnosis, and 47.0% (167/355) had been treated for ROP. Details about ROP outcomes in the whole cohort have been published previously.²²

At the last available ophthalmological examination, the median age was 4.8 years (range 0.5–13.2 years) and 31.0% (110/355) of the children were younger than 3.5 years of age.

Visual acuity

VA was available for 84.8% (301/355) of the children, and monocular VA for 70.4% (250/355). For five children, VA was obtained from child healthcare centres. In children with spectacles, VA was recorded with the habitual correction. Altogether, 20.3% (72/301) of the children were younger than 3.5 years of age at their VA test. Nine children older than 3.5 years of age at the time of VA testing who had severe neurodevelopmental deficits were recorded as ‘being able to fixate and follow’ (n=4) or as

‘being unable to participate in VA testing’ (n=5). Thus, their VAs could not be determined. The monocular VA in the better eye (or binocular VA, if monocular VA was not recorded) was $\geq 20/25$ in 38.2% (115/301) of the children and less than 20/60 in 17.6% (53/301). [Table 2](#) presents details of the children’s VAs.

Overall ophthalmological outcome

Myopia >3 D was present in 10.5% (25/239) and hyperopia >3 D in 9.2% (22/239). There were no significant differences in age at the time of examination between the myopic and hyperopic children. Strabismus was detected in 34.8% (109/313) of the children. In children with strabismus, esotropia was the most common type and was found in 69.6% (71/109). Exotropia had been diagnosed in 28.4% (29/102), and two children had microtropia. Nystagmus was recorded in 21.0% (44/209). Spectacles were prescribed to 51% (154/302) of the children, often due to a combination of ophthalmological disorders.

Visual impairment and ocular problems

Fourteen children, 4.7% (14/299), were blind (VA $<3/60$) in one or both eyes. Of those, nine had bilateral blindness; in seven children due to retinal detachment (six had ROP stage 4B to 5 and one had retinal detachment diagnosed at 2.5 years most likely caused by ROP), one had a diagnosis of CVI and in one the exact origin was uncertain. Another five children were blind in their worse eye, two due to retinal detachment (stage 4B to 5 ROP), two due to retinal detachment and phthisis secondary to endophthalmitis after intravitreal injection with antivascular endothelial growth factor for ROP and one with high myopia. Of these five, four had VA $<20/60$ in their better eye.

Seventy-three children of 333 (21.9%) were visually impaired, defined as being referred to a low vision clinic or/and presenting with VA $<20/60$ at ≥ 3.5 years of age. Of the 64 children referred to a low vision clinic, 29 had a VA $<20/60$. Altogether, a majority, 67.3% (239/355) of the children, had significant eye and/or visual problems such as having been referred to a low vision clinic due to visual impairment, VA $<20/60$ (if 3.5 years and older at last ophthalmological examination) and treatment for ROP, manifest strabismus, nystagmus, myopia >3 D, hyperopia >3 D, astigmatism >2 D and/or anisometropia >2 D, [table 1](#).

Severe ROP requiring treatment was the major risk factor for visual impairment in this study (OR 2.244 95% CI 1.311 to 3.842, $p=0.003$), [table 3](#). ROP treatment persisted as an independent risk factor for visual impairment in the multivariate logistic analysis, including GA week at birth, sex, bronchopulmonary dysplasia (BPD) and ROP treatment (OR 2.011 95% CI 1.159 to 3.492, $p=0.013$). Of the visually impaired children, 64.4% had received ROP treatment compared with 44.6% of those without visual impairment ($p=0.003$). There was a tendency for visual impairment to be more common in children born at 22 weeks of gestation than at 23 weeks,

Table 1 Birth characteristics and ophthalmological examination outcomes

Birth characteristics	Children with no ophthalmological examination (n=44)	Ophthalmological examination (n=355)	
Gestational age, (weeks+days)	23+2 (22+1–23+6)	23+2 (21+6–23+6)	
Birth weight, (g)	575 (400–707)	565 (340–874)	
Sex, boys	54.5% (24/44)	52.4% (186/355)	
Ophthalmological outcome		Available data (%) n	Missing data, n
Strabismus		34.8% (109/313)	42/355
Nystagmus		21.1% (44/209)	146/355
Refraction (the better eye refraction error)		Available data	Missing data, n
Hyperopia (>3 D)		9.2% (22/239)	116/355
Myopia (>3 D)		10.5% (25/239)	116/355
Astigmatism (>2 D)		14.2% (34/239)	116/355
Anisometropia (>2 D)		17.7% (41/232)	123/355
Spectacles prescribed		51.0% (154/302)	53/355
Visual impairment variables		Available data	Missing data, n
VA <20/60 (better eye or binocular if monocular VA missing)		17.6% (53/301)	54/355
Referred to a low vision clinic		25.8% (64/248)	107/355
Visual impairment*		21.9% (73/333)	22/355
Significant eye or/and visual problems†		67.3% (239/355)	–

Values are presented as the median (min–max.) or % (n).

The number of children with the available outcome is presented as the denominator.

*Defined as referred to low vision clinic at any age and/or visual acuity <20/60 if 3.5 years and older at the last ophthalmological examination.

†Significant eye or/and visual problems defined as VA <20/60 if 3.5 years and older at the latest ophthalmological examination, referred to a low vision clinic, treated for ROP, manifest strabismus, nystagmus, or refractive error (ie, myopia >3 D, hyperopia >3 D, astigmatism >2 D in the better eye or anisometropia >2 D).

D, diopters; ROP, retinopathy of prematurity; VA, visual acuity.

29.4% versus 19.4%; however, not statistically significant ($p=0.053$). Boys tended to have increased frequency of visual impairment compared with girls, 61.6% versus 38.4%, but this difference was not statistically significant ($p=0.089$). There was no significant difference in age at examination between children with and without visual impairment ($p=0.486$).

Cerebral visual impairment

Nine of the 355 children were diagnosed with CVI, of whom five were referred to a low vision clinic. A team had established the CVI diagnosis in most cases, including a paediatric neurologist, a paediatric ophthalmologist and a clinical low vision specialist. Most commonly, a questionnaire and tests of visual perceptual skills were used in

Table 2 VA, in the better (n=250) and the worse eye (n=248) at the last ophthalmological examination and binocular if monocular VA was missing (n=51)

	Better eye (n=250)*	Worse eye (n=248)†	Binocular (n=51)‡
VA \geq 20/25	43.4% (109/250)	30.6% (76/248)	11.8% (6/51)
VA 20/40 to <20/25	30.8% (77/250)	29.8% (74/248)	43.1% (22/51)
VA 20/60 to <20/40	9.6% (24/250)	11.7% (29/248)	19.6% (10/51)
VA 20/200 to <20/60	12.8% (32/250)	21.0% (52/248)	23.5% (12/51)
VA 20/400 to <20/200	–	1.6% (4/248)	–
VA <20/400	3.2% (8/250)	5.2% (13/248)	2.0% (1/51)

The number of children with the available outcome is presented as the denominator.

*20.8% (52/250) under 3.5 years of age at VA exam.

†20.5% (51/248) under 3.5 years of age at VA exam.

‡39.2% (20/51) under 3.5 years of age at VA exam.

VA, visual acuity.

Table 3 Risk factors for visual impairment* (n=73) in univariate logistic regression

Birth characteristics	OR	95% CI	P value
Gestational age, weeks	0.576	0.337 to 0.987	0.045
Birth weight, g	1.000	0.997 to 1.003	0.927
Birth weight SDS, SD	1.175	0.902 to 1.531	0.231
Sex, boys	1.583	0.931 to 2.691	0.090
Co-morbidities			
Bronchopulmonary dysplasia	1.904	0.768 to 4.718	0.164
Necrotising enterocolitis	1.106	0.596 to 2.052	0.750
Any ROP	1.944	0.561 to 6.735	0.224
ROP treatment	2.244	1.311 to 3.842	0.003

*Referred to low vision clinic at any age and/or visual acuity <20/60 if 3.5 years and older at the latest ophthalmological examination. ROP, retinopathy of prematurity; SDS, SD score.

the evaluation. In most children's medical records, there was no information regarding the presence, absence or attempts to identify visual perceptual problems. We found that 74.6% (265/355) of all participating children had signs that may indicate abnormal brain function such as intellectual disability, autism spectrum disorders, CP, hydrocephalus, EP, intraventricular haemorrhage grade 3–4 and hearing impairment, nystagmus, strabismus, optic nerve hypoplasia, refractive errors and suboptimal VA (VA <20/40 if 3.5 years and older at examination).

Visual impairment and associated neurological deficits

Details about neurological outcomes in the whole cohort have been published previously.⁵ Neurological diagnosis and deficits were more prevalent in children with, than without visual impairment; intellectual disability, 63.8% versus 33.3%, ($p<0.001$), EP, 21.1% versus 7.5% ($p=0.001$), CP, 27.1% versus 14.7% ($p=0.016$) and autism spectrum disorders, 32.8% versus 20.9%, ($p=0.043$), table 4. A total of 36 children had been diagnosed with PVL, 30.3% (10/33) of them were visually impaired and one of them had been diagnosed with CVI.

DISCUSSION

In this retrospective population-based national review of medical records of follow-up diagnoses in children born before 24 gestational weeks 2007–2018, we found that a majority had ophthalmological and neurological disorders. Visual impairment was found in 21.9% and most of the children had ocular and/or visual problems requiring ophthalmological follow-up. Comparisons with other populations are difficult due to variability in definitions in ophthalmological outcomes and the large age span in the present study.²³ However, the conclusion that infants born extremely immature are especially vulnerable to ophthalmological and neurological injury is in line with previous studies.^{1 5 8 10} In EXPRESS, including infants born before 27 weeks GA and full-term infants in Sweden, Hellgren *et al* reported strabismus at 6 years of age in 17.4% versus none, and spectacles wear in 36.4% versus 5.7%, respectively, as compared with in our study of children born before 24 weeks GA where we found strabismus were found in 34.8%, and 51.0% had been prescribed spectacles.¹⁰ In the present cohort of children born before 24 weeks GA, 21.9% were visually impaired,

Table 4 Neurological diagnosis and disorders in children with (n=73)* or without visual impairment (n=260)

	Visually impaired	Not visually impaired	P value
Intellectual disability	63.8% (44/69)	33.3% (77/231)	<0.001
Autism spectrum disorders	32.8% (22/67)	20.9% (47/225)	0.043
Epilepsy	21.1% (15/71)	7.5% (19/253)	0.001
Cerebral palsy	27.1% (19/70)	14.7% (35/238)	0.016
IVH at all	44.3% (44/73)	52.3% (136/260)	0.228
IVH grade 3–4	20.5% (15/73)	16.9% (44/260)	0.474
Hydrocephalus	13.7% (10/73)	6.9% (18/260)	0.065
PVL	13.7% (13/73)	8.8% (23/260)	0.220
Hearing impairment	5.6% (4/71)	4.4% (11/252)	0.654

Values are presented as % (n).

The number of children with the available outcome is presented as the denominator.

*Referred to low vision clinic at any age and/or visual acuity <20/60 if 3.5 years and older at the last ophthalmological examination.

IVH, intraventricular haemorrhage; PVL, periventricular leukomalacia.



compared with 4.8% of infants born before 27 weeks GA, and 0.7% of full-term infants in the EXPRESS study with a similar definition of visual impairment.¹⁰ Nine children were blind in both eyes and five in one eye, with the predominant cause being retinal detachment as a sequel to severe ROP. Nine children had been diagnosed with CVI. Information regarding the presence, absence or attempts to identify visual perceptual problems was missing in most children's medical records. Neurological comorbidities such as intellectual disabilities, EP, CP and autism spectrum disorders were more common in children with than without visual impairment. Visual impairment itself may increase cognitive and psychomotor developmental delay and may lead to behavioural problems.²⁴

Not surprisingly, ROP treatment was found to be a risk factor for visual impairment. It is commonly assumed that reduced vision in a child treated for ROP has a retinal origin, although severe ROP is also commonly associated with cerebral dysfunction.^{11 25–27} Several studies have shown that ROP is associated with reduced brain volume and an impaired neurodevelopmental outcome, indicating common pathways of impaired neural and neurovascular development in the brain and retina.^{28 29} However, reduced VA, visual fields, contrast sensitivity, accommodation and colour vision have been reported in preterm children with a prior ROP history as well as in preterms without ROP.³⁰

In this study, a majority of visually impaired children had neurological deficits. However, we found that the possible contribution of cerebral abnormalities to visual impairment had rarely been taken into account. In contrast to visual impairment due to ocular causes, brain injury may cause visual perceptual problems that are not captured by eye examinations and visual assessment. In this national study, CVI was rarely considered or investigated. Dutton described five categories of impairment in CVI affecting recognition, orientation, depth perception, motion perception and simultaneous perception, resulting in a wide range of characteristic behaviours.¹⁴ Children with brain abnormalities may have difficulties recognising faces of family and friends, finding the way to school, judging the height of the pavement, seeing fast-moving objects and/or finding an object against a patterned background. CVI is more common in extremely preterm children than visual impairment due to ROP.¹⁴ Both retinal and cerebral causes of visual impairment may occur in the same individual.

In a recent study of 6.5-year-old children born extremely preterm, visual perceptual problems were well captured with a straightforward questionnaire.³¹ We suggest that screening for visual perceptual deficits with a structured questionnaire free of charge should be implemented in the follow-up of all extremely preterm infants. Information about a child's perceptual skills may help parents and teachers understand the child's behaviour and implement salient compensatory strategies to enhance and facilitate everyday life. In this study, the lack of diagnostic criteria and knowledge of CVI among ophthalmologists may contribute to failing to consider and investigate the visual consequences of brain dysfunction.

Strengths and limitations

The current study is, to our knowledge, the first to report a national cohort of children born before 24 weeks GA where ophthalmological and paediatric medical follow-up records were available. A strength in this study is that infants screened for ROP were identified in the national register, SWEDROP and access to personal identification numbers in SWEDROP, and Sweden facilitated the retrieval of medical records at eye and paediatric clinics and child healthcare centres.

A limitation in this retrospective file review is the extent of missing data for some of the included variables. The denominator variation in the tables illustrates that data have often neither been sought nor recorded as regional policies regarding follow-up times and ophthalmological clinical assessment and examination routines vary. Another drawback is the inclusion of patients born over the span of more than a decade, resulting in an age range at examination from 5 months to 13 years, making comparisons difficult.

CONCLUSIONS

Children born before 24 weeks GA often carry a heavy burden of visual dysfunction frequently associated with neurological deficits. Neurological and ophthalmological disorders known to be frequently associated with CVI were commonly identified in the cohort studied. However, CVI had been only rarely diagnosed, indicating that it had likely gone undiagnosed in many cases. National follow-up guidelines need to be implemented to more accurately identify these vulnerable children in need of multidisciplinary evaluation and treatment for their optimal overall development and quality of life.

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Contributors AH, PL and EM had full access to the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: AH, PL, EM, A-LH and LJ. Acquisition of data: AH, PL and GH. Analysis or interpretation of data: AH, PL, EM, LJ, A-LH and LS. Drafting of the manuscript: AH, PL, EM, A-LH and LJ. Statistical analyses: PL. Obtained funding: AH and LS. Administrative, technical or material support: AH, PL, EM, LJ, A-LH, AA-H, LH-W, AR, MJ, KS, GH, EL, LG, MS and BS. AH is acting as a guarantor. All authors contributed to the article with critical revision of the manuscript and approved the submitted version.

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Patient consent for publication Not applicable.

Ethics approval This study was performed according to the Declaration of Helsinki. It was approved by the ethics committee at the University of Gothenburg, diary number 2019-05265. Retrospective medical chart review. No consent is needed according to Swedish Ethical Review Authority.

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