Impact at Age 11 Years of Major Neonatal Morbidities in Children Born Extremely Preterm

AUTHORS: Aijaz Farooqi, MD, PhD,[a] Bruno Hägglöf, MD, PhD,[b] Gunnar Sedin, MD, PhD,[c] and Fredrik Serenius, MD, PhD[c]

Departments of [a]Pediatrics and [b]Child and Adolescent Psychiatry, Institute of Clinical Sciences, University Hospital Umeå, Umeå, Sweden; and [c]Department of Women's and Children's Health, Section for Pediatrics, Uppsala University, Uppsala, Sweden

KEY WORDS
extremely preterm, long-term outcome, major neonatal morbidities, functional limitations, school outcomes

ABBREVIATIONS
BPD—bronchopulmonary dysplasia
ROP—retinopathy of prematurity
IVH—intraventricular hemorrhage
PVL— periventricular leukomalacia
EPT—extremely preterm
NSI—neurosensory impairment
PMA—postmenstrual age
CP—cerebral palsy
SVI—severe visual impairment
QUICCC—Questionnaire for Identifying Children With Chronic Conditions
CI—confidence interval
aOR—adjusted odds ratio

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Address correspondence to Aijaz Farooqi, MD, PhD, Institute of Clinical Sciences, Department of Pediatrics, University Hospital, SE-901 85 Umeå, Sweden. E-mail: aijaz.farooqi@pediatri.umu.se

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WHAT'S KNOWN ON THIS SUBJECT: Children born extremely preterm are at risk for neurosensory, cognitive, behavioral, and academic impairments. Severe retinopathy of prematurity, brain injury, and bronchopulmonary dysplasia are associated with poorer outcomes at early ages.

WHAT THIS STUDY ADDS: Extremely preterm children, especially those with brain injury and severe retinopathy, have shown increased risk for poor outcome and increased needs for educational support services. This is the first study to examine the combined effect of the 3 most serious neonatal morbidities at 11 years in extremely preterm-born children.

abstract

BACKGROUND: Uncertainty continues regarding the extent to which neonatal morbidities predict poor long-term outcome and functional abilities in extremely preterm infants.

OBJECTIVE: The goal of this study was to determine the impact of bronchopulmonary dysplasia (BPD), ultrasonographic signs of brain injury, and severe retinopathy of prematurity (ROP) on 11-year outcomes in infants born at <26 weeks' gestation.

METHODS: A total of 247 infants were born alive before 26 completed weeks of gestation from 1990 through 1992 in all of Sweden, and 98 (40%) survived to a postmenstrual age of 36 weeks. Main outcome measures were (1) poor outcome, defined as combined end point of death after 36 weeks' postmenstrual age or survival with at least 1 major disability at 11 years, and (2) consequences of chronic conditions in the survivors according to a validated instrument administered to parents.

RESULTS: Brain injury and severe ROP but not BPD correlated independently with poor outcome at 11 years of age. Among children who were free from BPD, brain injury, and severe ROP, 10% had a poor outcome. Corresponding rates with any 1, any 2, and all 3 neonatal morbidities were 19%, 58%, and 80%, respectively. Multivariate analysis revealed that brain injury and severe ROP were associated with high rates of consequences of chronic conditions.

CONCLUSIONS: In infants born extremely preterm who survive to a postmenstrual age of 36 weeks, severe ROP and brain injury separately predict the risk of death or major disability at 11 years of age. Thus, continued research to determine how to prevent these complications of prematurity is critical. *Pediatrics* 2011;127:e1247–e1257

There are concerns about the occurrence of bronchopulmonary dysplasia (BPD), severe retinopathy of prematurity (ROP), intraventricular hemorrhage grade 3–4 (IVH), and periventricular leukomalacia (PVL) in extremely preterm (EPT) infants, as these morbidities are risk factors for neurosensory impairments (NSIs) in childhood.[1–7] However, the prevalence of NSIs in themselves does not provide an accurate measure of functional disabilities such as learning difficulties and behavioral problems in later childhood, and thus cannot adequately predict the quality of life.[8–10] It has been concluded that approximately half of the EPT children without major disabilities at later school age have subtle impairments such as learning disabilities, visual-perceptual impairments, language disorders, school problems, attention deficits, executive dysfunctions, and other behavioral difficulties affecting their functional outcome.[1,11–16] A better understanding of the relationship of major neonatal morbidities to neurosensory and functional outcomes is needed to define special health care requirements at middle school age and improve the ability to counsel parents and anticipate special needs. We studied the impact of BPD, severe ROP, and IVH/PVL on long-term outcomes in 11-year-old children who were born at a gestational age of <26 weeks and who survived to a postmenstrual age (PMA) of 36 weeks.

POPULATION AND METHODS

For this Swedish national study, data were collected prospectively for all extremely low birth weight infants (gestational age ≥23 weeks and birth weight <1000 g) who were born from March 1990 through April 1992 in the whole of Sweden (Fig 1). A total of 247 infants were born at <26 completed weeks (EPT); of these, 98 (40%) survived to a PMA of 36 weeks. Only infants who lived to this PMA were eligible for the study, since infants who die early during neonatal intensive care will not have survived long enough to have developed morbidities of significance. Of the 98 infants who survived to a PMA of 36 weeks, 9 (9%) died in the postneonatal period, with all deaths occurring in the first year of life.[17] The identification of EPT subjects at the present assessment, and other methodologic details, have been described elsewhere[18] and will be briefly repeated here. All neonatal outcomes were known in these 98 infants; 89 (36% of all 247 live births) of them survived to an age of 1 year, and all of these EPT children were identified and alive at 11 years of age.[18] Two children whose parents had refused their participation earlier[18,19] were included in the present study. One child did not participate. Thus, data for the poor outcome assessment were available for 88 of 89 survivors at 11 years (99%) and for all 9 infants who died. Data for the analyses of consequences of chronic conditions were available for 86 children (97% of all survivors) at 11 years of age. The study was approved by the regional ethical committee at Umeå University.

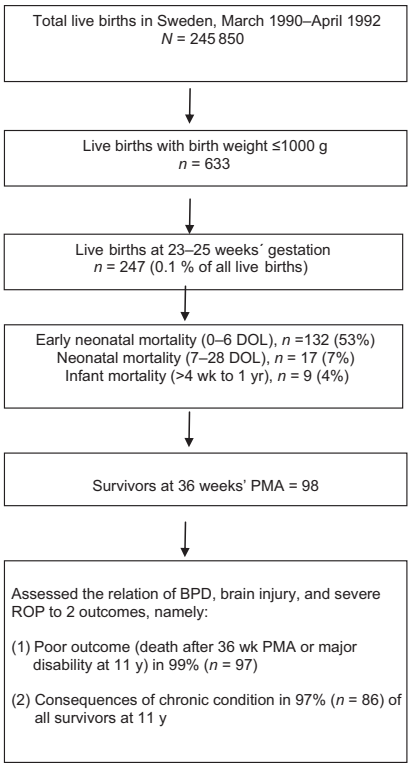

FIGURE 1
Flowchart showing selection of the study sample and numbers and proportions successfully followed up and assessed. This national sample was from all of Sweden. DOL indicates days of life.

Neonatal Morbidities

All obstetric and pediatric units in Sweden contributed to the study by prospectively completing predesigned forms at the time of birth of these infants. BPD, brain injury, and severe ROP were the prespecified outcomes in the 1000-g study.[20] BPD was defined as a need for supplemental oxygen at a PMA of 36 weeks.[21] Cranial ultrasonography was performed on all the study infants, usually on days 6 to 10 postnatally, and was repeated in all of the 97 infants between days 21 and 35 and before discharge from the hospital (ie, at 35–40 weeks of gestation). Cystic PVL was usually identified after 3 to 4 weeks of age. Uniform criteria were used for grading IVH[22] and staging of ROP.[23] Brain injury was defined as the presence of IVH grade 3 or 4 or of cystic PVL. Severe ROP was defined as ROP stage 3 or more. All infants with severe ROP received cryotherapy in at least 1 eye.

Outcome at 11 Years of Age

We studied the association of BPD, severe ROP, and brain injury with 2 types of outcomes: poor outcome (defined as death after a PMA of 36 weeks or at least 1 major disability in survivors) and the consequences of chronic conditions at 11 years of age.

Poor Outcome

The methods for identification and characterization of NSIs, major disability, and consequences of chronic conditions (ie, functional limitations, compensatory dependency needs and

services use of over and above routine) in the survivors at 11 years of age have been described previously.[18] NSI was defined as 1 or more of the following: moderate or disabling cerebral palsy (CP), severe visual impairment (SVI) including unilateral or bilateral blindness or visual acuity < 20/200 without glasses in at least 1 eye, and moderate, severe, or profound hearing loss in both ears requiring amplification.[18] CP was classified as hemiplegia, diplegia, or quadriplegia. CP was also categorized functionally as mild (no evidence of clinically important functional difficulty related to gait or use of hands), moderate (independent walking but with an abnormal gait), or disabling (not walking, severe motor disability). Formal psychometric tests were not conducted but had been performed in all EPT children ($n = 14$) who were attending special schools (special schools or special classes in regular schools or training schools for severely disabled children). All EPT children who attended special schools were diagnosed as having mental retardation (IQ <70). In Sweden, full-time special education in special schools or in special classes in mainstream schools are intended for children who are deemed unable to achieve the standard learning objectives of secondary school because of severe learning disability or children with severely impaired hearing or deafness/impaired vision who cannot attend compulsory comprehensive school. Three percent to 4% of children born at term receive education in special schools.

Major disability was defined as moderate or disabling CP; severe visual impairment including unilateral or bilateral blindness; moderate, severe, or profound hearing loss in both ears requiring amplification; or a need to attend special school as a measure of severe mental retardation.

Consequences of Chronic Conditions

Because neurosensory impairment may not be an accurate measure of functional disability in later childhood[8–10] such as behavioral and learning disabilities, we therefore investigated the relationship of BPD, severe ROP, and brain injury to the consequences of chronic conditions according to the Questionnaire for Identifying Children With Chronic Conditions (QUICCC).[24] The QUICCC incorporates the consequences of chronic health conditions that have a physical, psychological, or cognitive basis and have lasted or are expected to last for ≥12 months. It has 39 question sequences divided into 3 domains: functional limitations, with 16 items concerning physical, emotional, cognitive, and social development; dependence on compensatory aids, which has 12 items, including use of medications, special diet, assistive devices at home or at school, and personal assistance; and a need for services over and above those routinely needed by children, which has 11 items including medical, psychological, and educational services and special treatments and arrangements at school or at home. The QUICCC was administered as an interview to a parent or primary caregiver, usually the mother.[18] Socioeconomic information on the survivors ($n = 86$) was obtained by the Nordic Health and Family Questionnaire.[25] As has been described earlier, any social risk was defined as single-parent family, mother's educational level ≤9 years, or low family income.[18]

Statistical Analysis

Data were collected on the standardized form and encoded for analysis with use of SPSS 17.0 for Windows (SPSS Inc, Chicago, IL). The assessment data for each child in early intervention were examined before they were combined with the data sets from 2 previous studies.[17,20] Descriptive statistics such as frequency distribution, means, and SDs were used. The significance of the prognostic information associated with any term or group of terms was tested with the χ^2 test for trends as appropriate or Fisher's exact test. Exact 95% confidence intervals (CIs) were computed around the observed proportions of outcomes. Multivariate logistic regression analyses were used to estimate independent effects of BPD, severe ROP, and brain injury on 2 types of outcomes at 11 years of age (poor outcome and presence or absence of consequences of chronic conditions according to the QUICCC). *P* values were considered significant at <.05.

RESULTS

The perinatal data and sociodemographic characteristics of the 97 EPT infants and their mothers are listed in Table 1. Of the 97 infants, 28 (29%) had a poor outcome: they died after a PMA of 36 weeks ($n = 9$) or had a major disability (NSI or being in special schools) at 11 years ($n = 19$). Of the 9 infants who died after a PMA of 36 weeks, 7 deaths were related to BPD, either as the primary cause ($n = 3$) or in association with severe brain injury ($n = 4$). In the remaining 2 infants, death was related to severe brain injury in association with sepsis. Of 88 survivors at 11 years, 6 (7%) had moderate or disabling CP, 11 (12.5%) had SVI, 5 (6%) had moderate, severe, or profound hearing loss in both ears requiring amplification, and 14 (16%) were in special schools. Of the 11 (12.5%) EPT children with SVI, 4 had unilateral blindness and all of these had visual acuity of 60/200 in the other eye. In the remaining 7 EPT children with SVI, 1 had visual acuity of <20/200 in both eyes (legally blind), and 6 had 60/200 in their best eye. All the EPT children with SVI were cared for by eye rehabilitation centers in the country.

TABLE 1 Perinatal Data and Sociodemographic Characteristics of the Study Population ($N = 97$)

Birth and neonatal data	
Gestational age, mean (SD), wk	24.6 (0.7)
23–24 wk, *n*	31
25 wk, *n*	66
Birth weight, mean (SD), g	765 (111)
SGA, *n* (%)[a]	9 (9)
z scores, birth weight, mean (SD)[a]	−0.68 (1)
Multiple births, *n* (%)	17 (18)
IVF, *n* (%)	9 (9)
Female gender, *n* (%)	52 (54)
Received antenatal steroids, *n* (%)	29 (30)
Surfactant, *n* (%)	24 (25)
Sociodemographic characteristics	
Maternal age, mean (SD), y[b]	29.8 (4.8)
Maternal education, *n* (%)	
9 y	10 (12)
10–12 y	51 (59)
>12 y	25 (29)
Monthly family income, mean (SD), US$	3729 (1544)
Single-parent family, *n* (%)	11 (13)
Low-income, *n* (%)	24 (28)
Social risk (any), *n* (%)[c]	30 (35)

SGA indicates small for gestational age (birth weight less than −2 SDs); IVF, in vitro fertilization.

[a] *z* scores were derived from a Swedish reference population.[46]

[b] Mother's age at birth of EPT child.

[c] Social risk was defined as single-parent family, mother's education level ≤ 9 years, or low family income.

TABLE 2 Univariate Relationships Between Individual Neonatal Morbidities or Combinations of Neonatal Morbidities With Poor Outcome at 11 Years in 97 EPT Children

	Poor 11-y Outcome[a] (Death After 36 wk PMA or Major Disability[b] at 11 y)		
	n/Total (%)	Odds Ratio (95% CI)[c]	*P*
Neonatal morbidity			
BPD			
Present	18/43 (43)	3.2 (1.3–7.9)	.014
Absent	10/54 (19)	—	—
Brain injury			
Present	15/19 (79)	18.8 (5.4–65.7)	<.001
Absent	13/78 (17)	—	—
Severe ROP			
Present	14/28 (50)	3.9 (1.5–10.1)	.004
Absent	14/69 (20)	—	—
Neonatal morbidities in different combinations			
BPD plus brain injury			
Present	13/16 (81)	19.1 (4.8–75.4)	<.001
Absent	15/81 (21)	—	—
BPD plus severe ROP			
Present	12/21 (57)	5.0 (1.8–13.9)	.002
Absent	16/76 (21)	—	—
Severe ROP plus brain injury			
Present	10/12 (83)	18.6 (3.7–92.6)	<.001
Absent	18/85 (21)	—	—
All 3 morbidities			
Present	8/10 (80)	13.4 (2.6–68.3)	.001
Absent	20/87 (23)	—	—

[a] The rate of poor outcome in the entire cohort was 28 of 97 (29%).

[b] Major disability included moderate or disabling CP, severe visual impairment, bilateral hearing loss or deafness including sensorineural disability requiring a hearing aid, or a need for special schools.[18]

[c] Derived from Mantel-Haenszel estimate.

Of the 5 children with bilateral hearing disability, 2 had profound hearing loss without any help of hearing aids (>90 dB), 1 had severe hearing loss (75–80 dB) with some correction of hearing, and the remaining 2 had moderate hearing loss (<70 dB) that was partially corrected by bilateral digital amplification. Of the 14 EPT children with ≥1 NSI, 3 had severe multiple disabilities with wheelchair dependence, severe mental retardation, and profound bilateral hearing loss. Nine of 14 (64%) EPT children with NSI were in special schools. Only 1 EPT child was legally blind (could see only light in the better eye).

No significant differences were found in rates of poor outcome between children born at 23 to 24 weeks ($n = 30$) and those born at 25 weeks ($n = 67$) (27% vs 35%; $P = .47$). These rates were 33% and 27% in children with birth weights of ≤750 and >750 g, respectively ($P = .5$).

Relationship Between Neonatal Morbidities and Poor Outcome at 11 Years

During the neonatal period, 43 (44%) of the 97 infants developed BPD, 28 (29%) had severe ROP, and 19 (20%) showed ultrasonographic evidence of brain injury. Table 2 shows the relationship between each of the neonatal morbidities, combinations of different pairs of neonatal morbidities, or the presence of all 3 morbidities, and a poor outcome at 11 years of age. Each of these neonatal morbidities was associated with a poor outcome at 11 years. Brain injury was the least prevalent morbidity but was strongly associated with the risk of developing a poor outcome ($P < .001$). BPD was the most prevalent neonatal morbidity but was less predictive of the long-term outcome than were severe ROP and brain injury. In EPT children with 2 morbidities, each pair of morbidities was significantly associated with an increased risk for poor outcome (Table 2). The observed risk of poor outcome was 10% (4 of 42 [95% CI: 1%–22%]) in children who were free of all 3 neonatal morbidities. This increased to 19% (5 of 26 [95% CI: 3%–35%] with any 1 morbidity, 58% (11 of 19 [95% CI: 33%–82%]) with any 2 morbidities, and 80% (8 of 10 [95% CI: 50%–100%]) with all 3. In the multivariate logistic regression analysis (Table 3), severe ROP and brain injury but not BPD were strongly and independently associated with the risk of a poor outcome at 11 years.

Relationship of Birth Weight, Gestational Age, and Gender to Poor Outcome

We investigated whether the observed independent association of morbidity

TABLE 3 Relationship of the Neonatal Morbidities to Poor Outcome in EPT Children at 11 Years ($N = 97$): Multivariate Logistic Regression Model

Variable	Regression Coefficient (SE)[a]	aOR (95% CI)[b]	*P*
Intercept	−2.36 (0.59)	—	—
BPD	0.25 (0.59)	1.3 (0.4–4.1)	.67
Brain injury	2.77 (0.71)	16 (4.4–64.6)	<.001
Severe ROP	1.28 (0.62)	3.6 (1.1–12.2)	.037
Gender (males vs female)	0.53 (0.56)	1.7 (0.57–5.1)	.34
Gestational age, wk	−0.25 (0.63)	0.78 (0.23–2.7)	.69

[a] Regression coefficient associated with each term is a log odds ratio.

[b] aOR was derived from the logistic regression adjusting for neonatal morbidities (BPD, brain injury, and severe ROP), gender, and gestational age.

count with a poor outcome was influenced by birth weight (≤750 vs >750 g), gestational age (23–24 weeks versus25 weeks), or gender (male versus female). For each of these possible risk factors we fitted a logistic model that contained terms for the direct effects of morbidity count, the respective covariate, and an interaction. The association of morbidly counts remained strong ($P < .001$) in all 3 models. None of the interactions was significant. This indicated that the morbidity count was independently associated with a poor outcome in each of the 2 strata of birth weight, gestational age, and gender (Fig 2). Birth weight, gestational age, and gender did not add to the prognostic information provided by the morbidity count.

Relationship Between Neonatal Morbidities and Consequences of Chronic Conditions at 11 Years According to the QUICCC

Relationship With Functional Limitations, Compensatory Dependency Needs, and Service Use Above Routine

In our earlier report on this cohort, we reported that significantly more EPT children than controls had consequences of chronic conditions, including functional limitations (64% vs 11%, respectively; $P < .001$); compensatory dependency needs (59% vs 25%; $P < .001$), and services above those routinely required by children (67% vs 22%; $P < .001$).[18] Severe functional limitations (such as difficulty with feeding, dressing, washing, being blind, or unable to walk) were restricted to only 4 of 86 (5%) EPT children with neurosensory impairment.[18] Table 4 shows the rates of consequences of chronic conditions identified in the 3 domains of the QUICCC in children with BPD, severe ROP, and brain injury on 97% of all survivors at 11 years. The rates of ≥1 functional limitation in the total group of EPT children and the NSI-free group were significantly higher in those with brain injury. A significantly higher percentage of EPT children with severe ROP had compensatory dependency needs or a need for use of services beyond routine (Table 4). This was also true for the EPT group without NSIs.

Multivariate logistic regression analysis revealed that severe ROP was associated with an increased risk for compensatory dependency needs and use of services above routine (Table 5). When the analysis was limited to the NSI-free children, severe ROP retained its significant association with these 2 domains. In the multivariate logistic regression analyses of the 3 individual domains of the QUICCC, boys in the total EPT group and in the group without NSIs showed an increased risk for 1 or more functional limitations. Severe ROP was significantly associated with presence of ≥1 consequences of chronic conditions identified in all 3 domains of the QUICCC in children who received early intervention (Table 6). These statistical associations did not alter when the analysis was repeated in the NSI-free group. Social risk was significantly related to presence of consequences of chronic conditions in all 3 domains of the QUICCC in the NSI-free EPT children.

Relationship With Some Individual Items of Functional Limitations and Service Use Above Routine According to the QUICCC at 11 Years

We also conducted analyses of individual items of the 3 domains of the QUICCC to evaluate their relationships with individual neonatal morbidities. Significantly higher rates were found in EPT children with brain injury than in those without brain injury regarding mental or emotional delay (83% vs 28%; $P < .001$), being restricted or prevented from doing any kind of activity (58% vs 10%; $P < .001$), and a need for attending special schools (58% vs 8%; $P < .001$). A significantly higher proportion of EPT children with severe ROP (61%) had reduced vision despite using prescription glasses, compared with those who were without ROP (16%) ($P < .001$). Eighty-three percent of EPT children (20 of 24) with severe ROP had school difficulties (defined as special arrangements in mainstream schools or attending special schools according to the QUICCC) compared with 50% of those (31 of 62) without severe ROP ($P = .007$). The corresponding rates in the NSI-free EPT children were 75% and 47%, respectively ($P = .043$). Twelve of 14 EPT children (86%) with severe ROP and reduced vision despite glasses had school difficulties. These figures were 80% (8 of 10) in the NSI-free group who had severe ROP but a favorable visual status at 11 years. Multivariate logistic regression analyses revealed that brain injury significantly increased the risk of the following items in the QUICCC

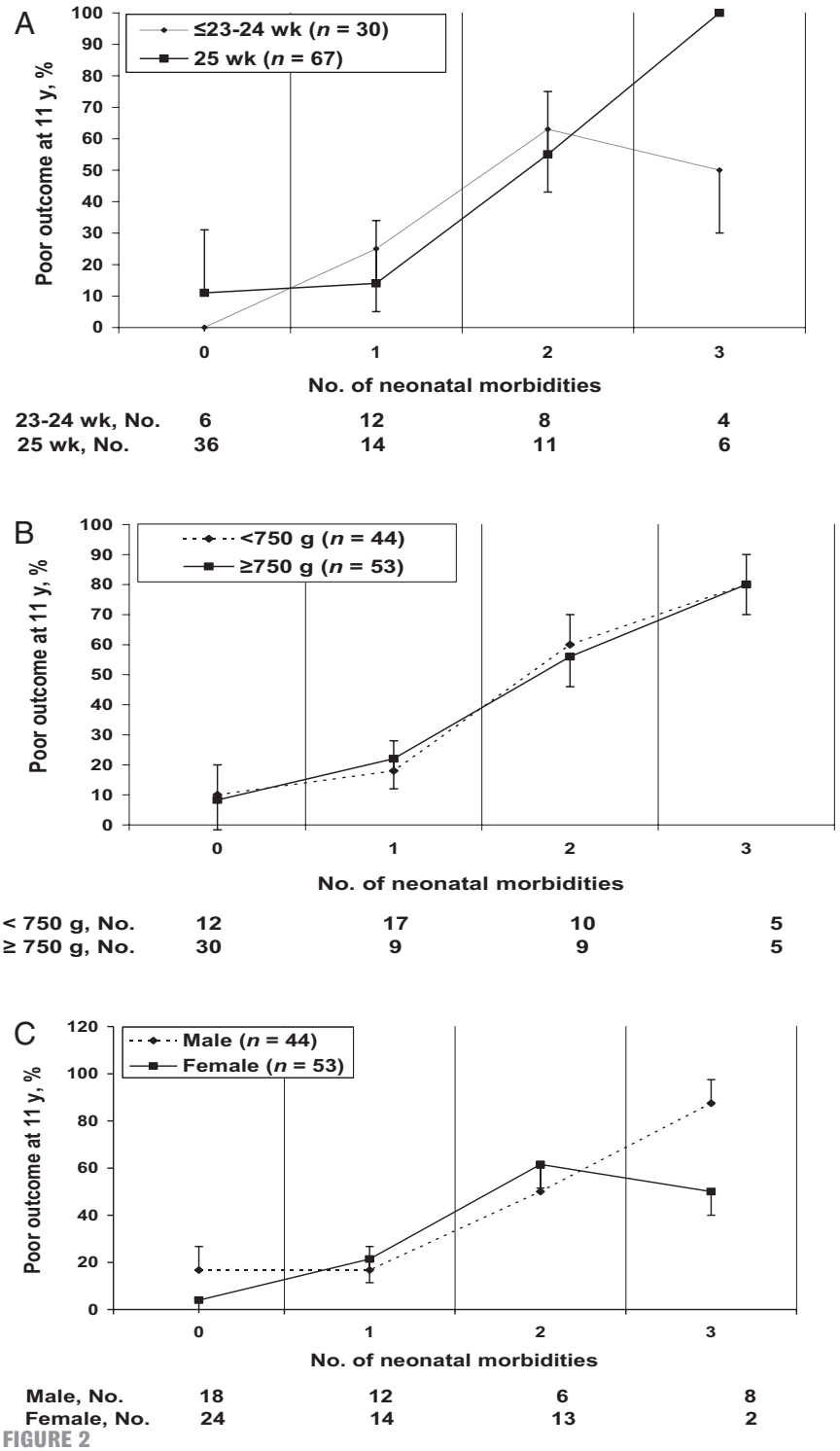

FIGURE 2

Observed rates of poor 11-year outcome according to morbidity count, which comprises the number of morbidities of BPD, brain injury, or severe ROP, stratified according to gestational age, birth weight, and gender: A, gestational age; B, birth weight; C, gender.

(Table 7): emotional and mental delay (adjusted odds ratio [aOR]: 14; $P = .005$), being restricted in kind of activity (aOR: 8.6; $P = .008$), and having a need for attending special schools (aOR: 19.7; $P = .002$). In the EPT children without NSIs, brain injury retained its significant risk for full-time special education in special schools (aOR: 70; $P = .017$) (Table 7). Multivariate analysis also revealed that severe ROP was associated with significantly increased risk for reduced vision despite glasses and for school difficulties both in the whole group and in the NSI-free group.

DISCUSSION

Our study assessed the relationship between major neonatal morbidities and traditional measures of the neurologic, developmental outcome, functional health status, and special health care needs. We chose BPD, severe ROP, and brain injury as indicators of a poor outcome, as they are known risk factors for a poor long-term outcome and functional disability.[1–7] To our knowledge, this is the first study that has examined the combined effect of the 3 most serious neonatal morbidities at 11 years in children born at <26 weeks' gestation. The strength of the study are the national composition of the cohort, the prospective follow-up, a very low attrition rate, narrow gestational age span, and gestational age–based data. Possible weaknesses include a relatively small sample size and a large battery of statistical tests conducted on a small study cohort that might have increased the risk for type II errors. On the other hand, random statistical significance (type I error) as a result of multiple testing might also have occurred. However, the main results are consistent throughout the test battery used, and we therefore believe that our findings are valid and robust.

In the univariate models, BPD, severe ROP, and brain injury were related to increased risk for poor outcome at 11 years. In the multivariate models, brain injury and severe ROP but not BPD were significantly associated with poor outcome at 11 years. Contrary to some reports[26,27] but in agreement

TABLE 4 Univariate Relationship Between Individual Morbidities and Consequences of a Chronic Condition Identified in the 3 Domains of the QUICCC at 11 Years

Neonatal Morbidity	Functional Limitation				Compensatory Dependency Needs				Services Needed Above Routine			
	Total Population ($N = 86$)		NSI-Free ($N = 73$)		Total Population ($N = 86$)		NSI-Free ($N = 73$)		Total Population ($N = 86$)		NSI-Free ($N = 73$)	
	n/N (%)	P	n/N (%)	P	n/N (%)	P	n/N (%)	P	n/N (%)	P	n/N (%)	P
	55/86 (64)		42/73 (58)		30/86 (35)		20/73 (27)		58/86 (67)		46/73 (63)	
BPD												
Present	25/33 (76)	.10	20/28 (71)	.08	14/33 (42)	.25	9/28 (32)	.59	21/33 (64)	.63	16/28 (57)	.46
Absent	30/53 (57)		22/45 (49)		16/53 (30)		11/45 (24)		37/53 (70)		30/45 (67)	
ROP												
Present	19/24 (79)	.08	11/16 (69)	.39	16/24 (67)	$<.001$	9/16 (56)	.009	22/24 (92)	.002	14/16 (88)	.038
Absent	36/62 (58)		31/57 (54)		14/62 (23)	$<.001$	11/57 (19)		36/62 (58)		32/57 (56)	
Brain injury												
Present	12/12 (100)	.003	6/6 (100)	.003	7/12 (8)	.10	2/6 (33)	1.0	11/12 (91)	.09	5/6 (83)	.40
Absent	43/74 (58)		36/67 (54)		23/74 (31)		18/67 (27)		47/74 (64)		41/67 (61)	

TABLE 5 Relationship of the Neonatal Morbidities to the Consequences of Chronic Conditions in the 3 Domains of the QUICCC at 11 Years: Multivariate Logistic Regression Models

Variable	Functional Limitation		Compensatory Dependency Needs		Services Needed Above Routine	
	Total Population ($N = 86$), aOR (95% CI)[a]	NSI Free ($N = 73$), aOR (95% CI)[a]	Total Population ($N = 86$), aOR (95% CI)[a]	NSI Free ($N = 73$), aOR (95% CI)[a]	Total Population ($N = 86$), aOR (95% CI)[a]	NSI Free ($N = 73$), aOR (95% CI)[a]
BPD	1.5 (0.44–4.9)	1.4 (0.4–5.3)	1.1 (0.38–3.5)	0.68 (0.18–2.6)	1.2 (0.57–4.2)	1.7 (0.53–3.1)
Brain injury	NA	NA	1.5 (0.35–6.9)	0.83 (0.1–6.6)	5.9 (0.58–64.7)	4 (0.31–52.8)
Severe ROP	2.1 (0.52–8.5)	1.3 (0.29–6.3)	7.2 (2.2–28.9)[b]	10.6 (2.2–52.0)[c]	10.6 (1.9–58.4)[b]	8.6 (1.5–49.7)[c]
Gender (male vs female)	5.3 (1.7–16.8)[b]	7.6 (2.2–27.2)[b]	2.5 (0.88–7.2)	3.5 (1.1–12.5)[c]	2.4 (0.83–7.2)	2.5 (0.82–7.4)
Gestational age, wk	0.29 (0.11–1.1)	0.24 (0.07–1.1)	1.1 (0.32–3.25)	1.7 (0.41–7.5)	0.43 (0.12–1.6)	0.56 (0.15–2.2)
Social risk (any vs none)[d]	1.7 (0.9–3.2)	1.9 (0.99–3.8)	1.2 (0.67–2.0)	1.4 (0.75–2.7)	1.1 (0.65–1.9)	1.1 (0.63–2.0)

NA indicates not appropriate for calculation (ie, wide CIs for exponents).

[a] aOR was derived from the logistic regression adjusting for neonatal morbidities (BPD, brain injury, and severe ROP), gender, gestational age, and social risk.

[b] $P \leq .005$.

[c] $P < .05$.

[d] Social risk was defined as single-parent family, mother's education level ≤ 9 years, or low family income.

TABLE 6 Relationship Between the Neonatal Morbidities and ≥1 Consequence of Chronic Conditions in All 3 Domains of the QUICCC: Multivariate Logistic Regression Model

Variable	Total Population ($N = 86$), n (%)		NSI Free ($N = 73$), n (%)	
Consequences of chronic conditions in all 3 domains of QUICCC	26 (33)		16 (22)	
	Regression Coefficient (SE)[a]	aOR (95% CI)[b]	Regression Coefficient (SE)[a]	aOR (95% CI)[b]
BPD	0.44 (0.56)	1.60 (0.50–4.70)	−0.06 (0.74)	0.99 (0.24–4.10)
Brain injury	0.70 (0.76)	2.00 (0.45–8.90)	0.03 (1.10)	1.20 (0.12–9.10)
Severe ROP	1.70 (0.61)	5.30 (1.60–17.40)[c]	1.70 (0.83)	6.10 (1.20–29.70)[c]
Gender (male vs female)	0.76 (0.57)	2.10 (0.71–6.50)	1.20 (0.70)	3.40 (0.85–13.40)
Gestational age, wk	−0.44 (0.59)	0.64 (0.20–2.00)	−0.14 (0.73)	0.87 (0.21–3.60)
Social risk (any vs none)[d]	0.37 (0.29)	1.40 (0.82–2.60)	1.30 (0.71)	4.40 (1.20–15.80)[c]

[a] Regression coefficient associated with each term is a log odds ratio.

[b] aOR was derived from the logistic regression adjusting for neonatal morbidities (BPD, brain injury, and severe ROP), gender, gestational age, and social risk.

[c] $P < .05$.

[d] Social risk was defined as single-parent family, mother's education level ≤9 years, or low family income.

with findings from a recent study,[2] we found no association between BPD and poor outcome, which may reflect low power for detecting a difference or may have been a result of the problems inherent in the definition of BPD. Our individual estimates of risk associated with either severe ROP or ultrasonographic evidence of brain injury are comparable with some reports on long-term follow-up at an earlier age and in children born more mature than in this study.[1,2,6,7,28] However, the clinical usefulness of risk estimates for major disability in survivors was limited by their low predictive accuracy. For example, 50% of the children who had severe ROP had a poor outcome, and conversely 20% who did not develop ROP died or survived with major disability. Furthermore, the variable with the strongest association with a poor outcome was the presence of brain injury. Nevertheless, 21% of EPT children with brain injury did not develop a poor outcome, and in EPT

TABLE 7 Relationship of Some of the Individual Items of the QUICCC That Were Significantly Associated With Severe ROP or Brain Injury at 11 Years: Multivariate Logistic Regression Models

	Emotional/Mental Delay		Restricted in Kind of Activity[a]		Reduced Vision		Special Schools[b]		School Difficulties[c]	
	Total Population ($N = 86$)	NSI-Free ($n = 73$)	Total Population ($N = 86$)	NSI-Free ($N = 73$)	Total Population ($N = 86$)	NSI-Free ($N = 73$)	Total Population ($N = 86$)	NSI-Free ($N = 73$)	Total Population ($N = 86$)	NSI-Free ($N = 73$)
n/*N* (%)	31/86 (36)	22/73 (30)	14/86 (16)	6/73 (8)	23/86 (27)	11/73 (15)	13/86 (15)	5/73 (7)	51/86 (59)	39/73 (53)
Variable, aOR (95% CI)[d]										
BPD, aOR (95% CI)[d]	0.70 (0.20–2.10)	0.70 (0.20–2.60)	1.20 (0.30–5.10)	0.60 (0.10–5.20)	0.60 (0.20–2.10)	0.70 (0.10–3.70)	0.80 (0.20–4.30)	0.40 (0.20–8.60)	0.40 (0.10–1.30)	0.40 (0.10–1.20)
Severe ROP, aOR (95% CI)[d]	0.80 (0.20–3.10)	0.40 (0.10–2.20)	3 (0.70–13.10)	7.10 (0.60–83.00)	7.80 (2.10–28.80)[e]	5.00 (0.90–26.90)	3.30 (0.50–20.60)	9.60 (0.10–654.00)	5.10 (1.30–19.50)[f]	3.90 (1.10–16.10)[f]
Brain injury, aOR (95% CI)[d]	14.00 (2.30–84.20)[e]	7.60 (1.01–58.30)[f]	8.60 (1.90–39.00)[f]	9.10 (0.80–99.00)	10.30 (1.80–57.80)[f]	5.20 (0.60–43.50)	19.70 (3.00–126.00)[e]	70.00 (2.60–2345.00)[f]	8.20 (0.80–79.30)	5.50 (0.50–61.00)
Gender (male vs female), aOR (95% CI)[d]	3.90 (1.30–11.50)[f]	3.90 (1.20–13.00)[f]	2.90 (0.70–12.50)	2.90 (0.40–21.80)	1.50 (0.50–5.20)	2.40 (0.50–11.20)	3.10 (0.60–15.00)	46.00 (0.70–3050.00)	1.40 (0.50–3.70)	1.40 (0.50–3.90)
Gestational age, aOR (95% CI), wk[d]	0.50 (0.16–1.80)	0.40 (0.10–1.70)	0.60 (0.14–2.90)	1.80 (0.10–22.80)	0.60 (0.20–2.00)	0.40 (0.10–2.00)	2.60 (0.40–18.20)	10.50 (0.30–322.00)	0.40 (0.13–1.30)	0.60 (0.20–1.50)
Social risk (any vs none), aOR (95% CI)[d,g]	1.70 (0.99–2.80)	1.60 (0.90–2.90)	0.80 (0.40–1.80)	0.70 (0.20–2.40)	1.30 (0.70–2.40)	1.20 (0.50–2.60)	2.50 (1.20–5.10)[f]	5.20 (1.10–24.60)[f]	1.10 (0.60–1.80)	1.00 (0.60–1.80)

[a] Child is prevented or restricted from doing any kind of activity that other children or youth of his or her age usually do.

[b] Attending special school or training school for the physically disabled and mentally retarded or receiving full-time special education attached to the mainstream schools.

[c] School difficulties were defined as special arrangements in mainstream schools or attending special schools or receiving full-time special education attached to the main stream school.[24]

[d] aOR is derived from the logistic regression adjusting for neonatal morbidities (BPD, severe ROP, and brain injury), gender, gestational age, social risk.

[e] $P \leq .005$.

[f] $P < .05$.

[g] Social risk was defined as single-parent family, mother's education level ≤9 years, or low family income.

children with all 3 morbidities 20% did not have a poor outcome.

Schmidt et al[6] analyzed the individual and combined prognostic effects of BPD, ultrasonographic signs of brain injury (grade 3–4 IVH, PVL, and ventriculomegaly), and severe ROP on the 18-month outcomes of children with birth weights of 500 to 999 g who had survived to a PMA of 36 weeks. They found that compared with children who had no morbidity, having only 1 of the 3 morbidities approximately doubled the risk of a poor 18-month outcome, whereas having 2 morbidities approximately tripled it. In a recent study, Luu et al[2] reported on the 12-year outcome in preterm children (600–1250 g). They found that severe brain injury had the strongest association with adverse cognitive sequelae. However, a sizable number of children in their preterm cohort (24%) with severe brain injury were developing normally without any support from school services at 12 years of age. These data indicate our imperfect ability to estimate the prognosis of individual EPT infants.

The observed rate of poor outcome in children who remained free of morbidity was similar in the 2 subgroups with a lower and higher gestational age and in the 2 weight groups of ≤750 and >750 g.

This was also true for the 2 genders. Furthermore, birth weight and gestational age did not influence the prognostic ability of the neonatal morbidities in this narrow range of gestational age. Similar findings have been reported by others.[2,6,29,30] From our results and as reported by others,[6,29] it seems that neonatal morbidity has a more direct effect on causal pathways, leading to a poor long-term outcome than does birth weight or gestational age per se. We believe, like others,[6,29] that even the most immature infants have a good probability of surviving

without a poor outcome if their immediate neonatal period is not complicated by a major neonatal morbidity.

The presence of neurosensory impairment does not provide accurate information about ultimate functional disability and it is therefore difficult to make an accurate evaluation regarding future quality of life on this basis.[8–10] We used a noncategorical approach (independent of diagnosis) when studying the outcomes in survivors of neonatal intensive care by using the QUICCC instrument.[24] This allowed us to assess the impact of major neonatal morbidities on day-to-day functioning at 11 years and on special health care needs in EPT children with and without NSIs. The QUICCC also comprises most of the elements of the World Health Organization's international classification of functioning and disability, which includes limitations in body/structure, personal activity, participation in society, and environmental facilitation.[31–33] In the multivariate models, brain injury was associated with an increased risk of attending special schools, and of mental or emotional delay in the total EPT group. Even in the NSI-free EPT children with brain injury there was an increased risk of needing to attend special schools and of mental or emotional delay. Our findings are in conformity with a recent report by Luu et al,[2] who in their cohort of 12-year-old extremely low birth weight children found severe brain injury to be the strongest predictor of school failure and adverse cognitive sequelae, as mentioned above. However, there are other biological and environmental factors that contribute to the long-term outcome.

In the other multivariate models, severe ROP was associated with an increased risk of having special health care needs, such as compensatory dependency needs and use of services over and above the routine in EPT children. These statistical conclusions did not change when the analysis was limited to NSI-free children. In the QUICCC domain of use of services above the routine, severe ROP was associated with school difficulties. This was almost equally seen in EPT children with reduced vision despite glasses and in those who had a favorable visual status. In fact, we found that our cohort of NSI-free EPT children with severe ROP and a favorable visual status (who did not have reduced vision despite glasses) had a rate of 80% for school difficulties. Furthermore, the risk of having $\geq$1 consequence of chronic conditions in all 3 domains of the QUICCC was significantly higher among EPT children with severe ROP, both in the whole group and in the group without NSI. Our results are in conformity with findings in a prospective study of very low birth weight children (birth weight $<$ 1251 g),[10] in which high rates of developmental, educational, and social challenges were found at 8 years of age in children who had threshold ROP with or without a favorable visual outcome. It was shown that these rates were especially high when there was an unfavorable visual outcome, but substantially high rates of academic underachievement were also found in the group with threshold ROP and a favorable visual status. These data indicate that severe ROP is a marker of a high risk for long-term developmental and educational problems and it should indicate a need for early interventional services.

Sweden has a universal health care policy that renders professional support to the EPT children and their families in school-based and other services. In Sweden, children born at $<$26 weeks' gestation constitute $<$0.2% of all births and represent a very small fraction of all children with functional limitations and special health care needs. Although such special needs were significantly higher than those of the controls, very few children in our study had impairments so severe as to prevent them from performing their major daily activities such as eating, bathing, and dressing, or from attending school.[18] Although a significant number of preterm children needed additional support in reading, writing, and mathematics, the majority of EPT children (85%) were attending regular classes in mainstream schools.

The applicability and generalizability of our data may be questioned. Our outcome data reflect perinatal practices of almost 2 decades ago, and the results may not be relevant at present. These management practices have changed considerably. The majority of these infants were cared for before surfactant therapy and antenatal corticosteroid administration had become prevalent. The use of surfactant and antenatal corticosteroids to the mother has increased survival in extremely preterm infants.[34–36] Although studies have suggested that administration of antenatal corticosteroids to the mother have improved some early-childhood neurosensory and developmental outcomes over the last decade for some group of preterm infants,[1,37,38] evidence is lacking whether this trend applies to the most extremely preterm infants born at $<$25 weeks' gestation.[39–41] Furthermore, the temporal trends have shown a relatively constant gap in neuropsychological skills between preterm and term children.[26,27,42,43] Our outcome data can be compared with recent reports in showing similar estimates of risks associated with either ultrasonographic evidence of brain injury or severe ROP in children born extremely preterm or with extremely low birth weight.[1,2,6,28] Thus, we believe that our study provides valid analyses of the relation of the major neonatal morbidities such as severe ROP and brain injury to a poor outcome or functional limitation and special health care needs at 11 years, unless superseded

by more recent data. In 2 very recent reports, from a Swedish national study[44] and from a population-based English study (EPICure 2),[45] the rates of BPD, severe ROP, and brain injury in infants born at <26 weeks remain considerably high or have even significantly increased, especially the prevalence of ROP. Our data and the results from the other studies show a strong and lasting effect of 3 major neonatal morbidities on outcomes.[1,2,4–6] Continued research to prevent these complications of prematurity is thus critical.

CONCLUSIONS

For infants born extremely preterm who survive to a postmenstrual age of 36 weeks, severe ROP and brain injury separately predict the risk of death or major disability at 11 years of age. Thus, continued research to determine how to prevent these complications of prematurity is critical.

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