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Co-occurrence and severity of neurodevelopmental burden (cognitive impairment, cerebral palsy, autism spectrum disorder, and epilepsy) at age 10 years in children born extremely preterm

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Abstract

Objective—To determine the prevalence of isolated and multiple neurodevelopmental impairments at age 10 years among children born extremely preterm (<28 weeks gestational age) and to offer a framework for categorizing neurological limitations.

Design—A multicenter, prospective cohort follow-up study (Extremely Low Gestational Age Newborn Study) recruited 889 10 year-old children (92% of eligible children) born from 2002–

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2004. We assessed prevalence of cognitive impairment, measured by intelligent quotient (IQ) and tests of executive function, cerebral palsy (CP), autistic spectrum disorder (ASD), and epilepsy singly and in combination. The three-levels of impairment severity were: Category I: no major neurodevelopmental impairment. Category II: normal cognitive ability with CP, ASD, and/or epilepsy. Category III: children with cognitive impairment.

Results—214 of 873 children (25%) had cognitive impairment, 93 of 849 children (11%) had CP, 61 of 857 children (7%) had ASD, and 66 of 888 children (7%) had epilepsy. 19% of all children had 1 diagnosis, 10% had 2 diagnoses, 3% had 3 diagnoses, and none had 4 diagnoses. Decreasing gestational age was associated with increasing number of impairments ($p<0.001$). Half the children with cognitive impairment and a third of children with CP, ASD, or epilepsy had a single impairment. 601 (68% [95% CI, 64.5%–70.7%]) of children were in Category I, 74 (8% [95% CI, 6.6%–10.3%]) were in Category II, and 214 (24% [95% CI 21.7%–27.4%]) were in Category III.

Conclusions—Three quarters of children had normal intellect at age 10 years; nearly 70% were free of neurodevelopmental impairment. 40% of those with impairments had multiple diagnoses.

Keywords

Extremely preterm; neurological; follow-up; multiple disabilities

Introduction

Over the past two decades, studies of children born extremely preterm (EP) have found that the prevalence of major adverse neurodevelopmental disorders ranges from 15 to 40% for deficient IQ,[1–7] 5 to 18% for cerebral palsy (CP),[8–13] 7 to 8% for autism spectrum disorder (ASD),[14,15] and 2 to 10% for epilepsy.[16,17] Prevalence data such as these usually do not account for multiple disorders occurring in the same child. Yet, disorders of development occur together more often than expected by chance. For example, a third to half of children with CP have deficient IQ[18] but only 1 to 3% of children in the general population without CP have deficient IQ.[19]

Children born EP are at particularly increased risk of having multiple neurodevelopmental disorders, including deficient IQ, impaired executive functioning, CP, ASD, and epilepsy. In the Extremely Low Gestational Age Newborn (ELGAN) cohort, the prevalence of CP at age 2 years was 11%.[20] In the same cohort, at age 10 years, the prevalence of IQ less than 70 was 15%,[1] cognitive impairment as assessed by a summary categorization of IQ and executive function (EF) ability was 25%,[21] ASD was 7%,[22] and epilepsy was 7%.[22] Here we report the frequency with which these disorders occur in isolation and in combination.

Beyond whether children born EP have single or multiple impairments is the question of how to understand the severity of the neurological burden carried by the child. Most often, overall impairment is determined either by specific criteria for each neurological disorder or, less commonly, by assigning a composite descriptive designation based on a combination of findings.[3,6,7,23,24] Studies of EP cohorts born in the past 20 years largely using such combinations estimate rates for moderate to severe overall impairment ranging from 19 to

45%.[2,3,5–7,23,24] We propose a conceptual framework for categorizing neurodevelopmental impairment based on four of the most common neurological impairments in children born EP that we reason will impact the ability to live independent adult lives - cognitive impairment, cerebral palsy, autism, and epilepsy.[25]

Methods

Participants

The ELGAN Study is a multicenter observational study of the risk of structural and functional neurologic disorders in EP infants. One thousand two hundred forty-nine mothers delivering 1506 live-born infants before 28 weeks gestation were enrolled between 2002–2004 (Figure 1). From the 1198 ELGAN Study children who survived to 10 years of age, we actively recruited the 966 surviving members of the ELGAN cohort from whom we had collected blood spots during the first postnatal month for the measurement of inflammation-related proteins. The institutional review boards of all participating institutions approved the study. Because of a combination of severe motor, visual and cognitive disability, 40 children were assigned the lowest score on some or all tests. Eleven children did not accompany the caregiver during the follow-up visit, and 5 children could not complete the assessment,[1] leaving 873 children available for analyses.

Procedures

Cognitive evaluations were administered by certified child psychologists and all examiners underwent in-person training and verification of competency for administration of the test battery. Further, all autism evaluators participated in research-level training in administration and scoring of the Autism Diagnostic Interview - Revised (ADI-R)[26] and Autism Diagnostic Observation Schedule-2 (ADOS).[27] In this paper we use the term deficient IQ when talking about an IQ less than 70, and restrict the use of the terms cognitive ability/cognitive impairment to children who have deficiencies in the latent profile analysis construct of IQ and executive function (see below).

Intellectual quotient (IQ)—IQ was assessed with the School-Age Differential Ability Scales–II (DAS-II)[28] Verbal and Nonverbal Reasoning scales.[29] The mean of these two measures was used as an estimate of overall IQ because the DAS-II Verbal and Nonverbal IQ scores were strongly correlated within the sample. An IQ score more than two standard deviations below the normative mean (i.e., < 70) is considered in the intellectually disabled or deficient range.

Executive function (EF)—Attention and EF were assessed with the DAS-II and the NEPSY-II[30] for measures of verbal working memory, auditory attention, set switching and inhibition, concept generation, and mental flexibility.

Latent profile analysis (LPA)—Using LPA, we classified children in our sample into subgroups based on similarities in their profiles of IQ and EF scores. We have found that this profile is a more sensitive predictor of academic achievement than IQ alone,[21] and is likely to have long-term implications for individual and societal burden.[31] LPA identified four

subgroups corresponding to the following levels of "cognitive functional class" (CFC): normal (CFC 1) in 34% of the cohort with mean IQ and EF scores within normal range on all measures, low-normal (CFC 2) in 41% of the cohort with mean IQ and EF scores ranging from 0.5 to 1 standard deviation (SD) below the norm, moderately impaired (CFC 3) in 17% of the cohort with mean IQ and EF measures between 1.5 and 2.5 SD below the norm, and severely impaired (CFC 4) in 8% of the cohort with mean IQ and EF measures 3 to 4 SD below the norm.[21]

Cerebral palsy (CP)—For the diagnosis of CP, neurologic examiners utilized a standardized manual and data collection form, and viewed an instructional CD designed to minimize examiner variability.[32]

Autism spectrum disorder (ASD)—All children determined to be at risk on the Social Communication Questionnaire (SCQ)[33] were assessed with the Autism Diagnostic Interview – Revised (ADI-R),[26] an in-depth parent interview. Children meeting ADI-R criteria for ASD were administered the Autism Diagnostic Observation Schedule-2 (ADOS-2).[27] Children meeting standardized research criteria for ASD on the ADOS-2 were classified as having ASD.

Seizure and epilepsy determination—Identification of seizures involved a two-stage process.[34,35] Parents of children were asked to complete part one of a validated seizure screen.[34] Parents of children with a positive part one screen completed a structured interview with a study coordinator followed by an open-ended interview with a pediatric epileptologist. Then, a second epileptologist independently reviewed interview responses and similarly rated event types as seizures or not. A third epileptologist served as a tie-breaker in the 3% for which the evaluators were discordant. For these analyses, we defined epilepsy as having 2 or more unprovoked seizures.[35]

Impairment severity

We devised a three-level categorization of impairment for neurodevelopmental burden among EP infants. The first level (Category I) constitutes children free of major neurodevelopmental impairment. The second level (Category II) includes children who have normal IQ (greater than or equal to 70) or normal range cognitive ability (CFC 1 or 2) but have one or more of the other three neurological impairments, CP, ASD, and epilepsy. The third level (Category III) includes children with cognitive impairment whether or not co-morbidities coexist. We do not include visual or hearing impairment in our categorization because only seven children were blind or hearing impaired.[1]

Statistical analyses

When determining the prevalence of isolated conditions and severity, we restrict analysis to the children for whom we had data on the condition: status of cognition for 873 children, CP for 849 children, ASD for 857 children, and epilepsy for 845 children (Figure 1). When analyzing comorbid conditions, we included all children and treated missing data as unimpaired.

Forty-three of 273 children screened at-risk for seizures could not be contacted for interview by the epileptologist and so were missing data on seizures. We used inverse probability weighting to account for this missing data when analyzing seizures, with the probability of missingness based on gestational age (GA) and the result of the initial seizure screen.[36] Weighted counts and prevalence are given for analyses involving seizures.

We conducted two sets of analyses. In the first set, we defined cognitive impairment as levels of cognitive functional class (CFC 3 or 4), which, as noted above, includes measures of IQ and EF. In the second set, we considered only IQ less than 70, and these results are described in the Supplement.

Prevalence is described through percentages and 95% confidence intervals. The association between number of impairments and GA category was tested through the Mantel-Haenszel chi-square test for trend. The increased risk for another impairment, for children with one particular impairment, was described through relative risks and 95% confidence intervals. Statistical analyses were conducted using the Stata Release 14[37] and SAS Version 9.3[38] software packages.

Results

Sample description (eTable 1 in the Supplement)

Of children with any neurodevelopmental impairment, 52% (n=97) were born at 23–24 weeks GA, 32% (n=128) were born at 25–26 weeks GA, and 21% (n=63) were born at 27 weeks GA. Demographic characteristics associated with any neurodevelopmental impairment were mother's identification as black, mother's age less than 21 years, single marital status of mother, and mother's enrollment in public insurance. Newborn characteristics associated with neurodevelopmental impairment were lower GA, lower BW Z-score, and male sex.

Percentage of children with impairments

Twenty-five percent (n=214) of children had cognitive impairment (CFC 3 or 4), 11% (n=93) of children had CP, 7% (n=61) of children had ASD, and 7% (n=66) of children had epilepsy (Table 1). Sixty-eight percent of children did not meet criteria for any diagnosis at age 10 years when cognitive impairment included measures of IQ and EF (CFC 3 or 4) (Table 2) and 77% did not meet criteria for any diagnosis when considering only IQ less than 70 (eTable 2 in the Supplement).

When cognitive impairment included measures of IQ and EF (CFC 3 or 4), 19% of all children had 1 diagnosis, 10% of children had 2 diagnoses, 3% of children had 3 diagnoses, and no child had all 4 diagnoses; i.e., 60% of children with impairment had a single diagnosis (Table 2). There was a significant trend for decreasing number of impairments with increasing GA ($p<0.001$). These percentages did not change substantially if we assumed that missing values represented presence of a diagnosis.

Description of co-morbidities (Table 3)

Children with cognitive impairment measured by IQ and EF (CFC 3 or 4) had more than 5 times the risk for having CP and/or epilepsy and 7 times the risk for having ASD, compared to children without cognitive impairment. At age 10 years, those who had been diagnosed with CP at age 2 years had 3.3 times the risk for having cognitive impairment (CFC 3 or 4) and 4.0 times the risk for having epilepsy, compared with children without CP at age 10. Children with ASD had 3.6 times the risk of having cognitive impairment (CFC 3 or 4) and 2.6 times the risk for having epilepsy compared to children without ASD. Children with epilepsy had between 2.5 and 3.6 times the risk of having ASD, cognitive impairment (CFC 3 or 4), and/or CP compared to children without epilepsy.

Percent of children with single impairments or with co-morbidities

One-third of the cohort had at least one neurodevelopmental impairment, and of these children, 40% had more than one other impairment (Table 2). Of the children with only one finding, 61% had cognitive impairment measured by IQ and EF (CFC 3 or 4), 17.5% had CP, 10.5% had ASD, and 11% had epilepsy. Among the 117 children with multiple impairments, 94% were classified as CFC 3 or 4, 54% had CP, 37% had ASD, and 40% had epilepsy, leaving only 6% (n=7) of the children with multiple deficits and preserved cognitive abilities.

Cognition based only on IQ

When deficient IQ was analyzed without consideration of EF, 14% of children had 1 diagnosis, 6% of children had 2 diagnoses, 2% of children had 3 diagnoses, and no child had all 4 diagnoses; 64% of children with impairment had a single diagnosis (eTable 2 in Supplement). Of those children with only one diagnosis, 14% had IQ less than 70, 37% had CP, 25% had ASD, and 24% had epilepsy. Among the 75 children with multiple impairments, 84% involved deficient IQ, 61% had CP, 39% had ASD, and 48% had epilepsy, leaving 15% children with multiple deficits and preserved IQ (eTable 3 in the Supplement). Children with IQ less than 70 had 6.9, 9.8, and 6.6 times the risk for having CP, ASD, and/or epilepsy, compared to children with IQ greater than or equal to 70 (eTable 4 in the Supplement). Children with CP had 8.0 times the risk for having IQ less than 70 and 4.0 times the risk for having epilepsy, compared to children without CP. Children with ASD had 10.5 times the risk for having IQ less than 70 and 2.6 times the risk for having epilepsy, compared to children without ASD. Finally, children with epilepsy had 6.0, 3.6, and 2.6 times the risk for having IQ less than 70, CP, and/or ASD compared to children without epilepsy.

Impairment severity

When cognitive impairment was defined by both IQ and EF using latent profile analysis (CFC 3 or 4), 601 (68% [95% CI, 64.5%–70.7%]) of children were free of major impairment (Category I). Seventy-four (8% [95% CI, 6.6%–10.3%]) of the 873 children had normal or low-normal cognitive abilities (CFC 1 or 2), but had one or more other impairments (Category II): CP (5%), ASD (3%), and/or epilepsy (4%). Two hundred fourteen (24% [95%

CI 21.7%–27.4%]) of the 873 children had moderate to severe cognitive impairment (CFC 3 or 4) (Category III).

When we considered deficient IQ (less than 70) without regard to EF, 687 (77% [95% CI, 74.5%–80.0%]) of children were free of major impairment (Category I). One hundred twenty-one children of the 873 children (14% [95% CI, 11.6%–16.2%]) did not have deficient IQ, but had one or more other impairments (Category II): CP (7%), ASD (5%), and/or epilepsy (5%). Eighty-one of the 873 children (9% [95% CI, 7.4%–11.2%]) had deficient IQ (Category III).

Discussion

In this sample of 889 children born from 2002 to 2004 before 28 weeks gestation, 68% percent were free of major impairment. Among the 32% with cognitive impairment as assessed by IQ and EF (CFC 3 or 4), CP, ASD, and/or epilepsy, 19% had 1 diagnosis, 10% had 2 diagnoses, 3% had 3 diagnoses, and no child had all 4 diagnoses considered here. Half the children with cognitive impairment (CFC 3 or 4) and one-third of children with CP, ASD, or epilepsy had a single impairment. The remainder had multiple impairments.

IQ and EF as a measure of cognitive function

According to the American Association on Intellectual and Developmental Disabilities (AAIDD), intellectual disability is defined and characterized by significant limitations both in intellectual functioning and in adaptive behavior as expressed in conceptual, social, and practical adaptive skill.[25] Adaptive function impairment appears to be closely aligned with disturbances in EF.[39–42]

Category III is based on the premise that impaired cognition involves both IQ and EF, approximating the AAIDD definition of intellectual disability, and predicts a child's ability to function later as an independent adult.[25] We posit that children in Category II will have less impact on family[43,44] and a greater capacity to live independent lives[45,46] than children in Category III.

Supplementing IQ measures with EF assessments appears to add to the precision in predicting academic and other outcomes[21,47] and clarifies the individual and societal burden of extreme prematurity when compared to IQ alone,[21] a point that Chung et al highlight: "When executive function deficits and intellectual deficits are considered together, as they are in the LPA groupings, the life-long individual and societal burden of extreme prematurity becomes clear. Outside of complex chronic disease, the single most individually and societally costly childhood condition might be school failure. School failure is a threshold event, creating sudden and marked discontinuities in long-term economic and civic potential and productivity, thus predisposing individuals, and even subsequent generations, to early morbidity and mortality.[31]" In our sample, the prevalence of cognitive impairment as assessed by IQ and EF (24%) and the prevalence of major neurodevelopmental disorders (32% in Categories II + III) is substantially higher than rates of deficient IQ (9%) or major neurodevelopmental disorders (23% in Categories II + III) when using IQ alone (IQ less than 70).

Comparison with prior studies

The majority of follow-up studies of children born EP over the past 20 years, which are listed in Table 4, use IQ scores without consideration of EF as a key measure of cognition when categorizing impairment severity. Applying similar IQ-only criteria for cognitive outcome to our cohort, 23% of children are categorized as having moderate to severe impairment (Categories II + III), which falls on the low end of the range (18 – 45%) of impairment reported in other studies.[2,3,5–7,23,24]

The relatively low prevalence of subnormal IQ may be due to several factors. First, it may reflect advances in care and interventions.[48–53] Second, some studies listed in Table 4 use lower GA criteria, often associated with increased severity of neurodevelopmental impairment, compared to our cutoff of 28 weeks.[2,3,7,24] Third, our study used published IQ test norms as measures of comparison rather than data from a control population. Published norms may underestimate contemporary measures of IQ (Flynn effect),[54] leading to an underestimate of the prevalence of deficient IQ.[2,3,6,7,55–57]

Given these caveats, about one-third of EP children have moderate to severe impairment when EF is taken into account (CFC 3 or 4). A recent Swedish study showed that 15% of children born EP with no neurosensory impairment and a normal IQ had an EF score more than 2 standard deviations below the mean compared to 3% among control children.[58] That study further showed that these executive dysfunctions were strongly associated with academic, behavioral, and learning skill deficits.

To our knowledge, no other studies have evaluated the co-occurrence of the 4 neurodevelopmental disabilities included here - cognitive and motor disorders, ASD, and epilepsy. The EPICURE Study investigated cognitive, motor, vision, and hearing impairments and found 75% of children with major impairment in 1 domain, 17% in 2 domains, 8% in 3 domains, and none in all domains.[2] Other studies that defined disabilities more broadly to include behavioral, attentional and/or mild impairments found multiple impairments in 30%[59] and 44% of children.[5,60] The biological basis of multiple impairments in EP children remains to be defined and is likely multifactorial, involving both pre- and post-natal influences on brain development.[1]

Strengths/Limitations

Strengths of our study include a large number of infants with minimal attrition. We selected infants based on GA, not birth weight, in order to minimize confounding related to fetal growth restriction.[61] Well-validated tools are used for assessment of neurodevelopmental functions, and examiners were unaware of the children's medical histories. We also characterized severity at school age, when assessment of cognitive and neurodevelopmental deficits is more reliable than at earlier ages.[6,7,55,62]

Limitations include possible underestimation of the prevalence of impairment in our cohort because some children who were missing data were considered to not have an impairment. However, if we assumed presence of impairment, our findings did not change substantially. Another limitation is that we used standardized population-based normative means and standard deviations rather than control term peers. We did not conduct analyses of

antecedent risk factors using the disability construct proposed in this paper, although previously we have reported antecedent risks for each of the individual outcomes considered.[1,14,22,35] While psychiatric and behavioral outcomes might contribute to school failure and independence, we did not consider them at age 10 because they will manifest most clearly in adolescence. We also did not consider bilateral visual or hearing impairments because there were very few children with these disorders in our cohort.

Conclusions and Implications

Approximately one-third of children who were born extremely preterm had major impairment at 10 years of age, and cognitive deficits were the most prevalent. Nearly 70% of children had no major neurodevelopmental impairment. Our findings have implications for predicting prognosis of neurodevelopmental outcomes among school-age children born extremely preterm.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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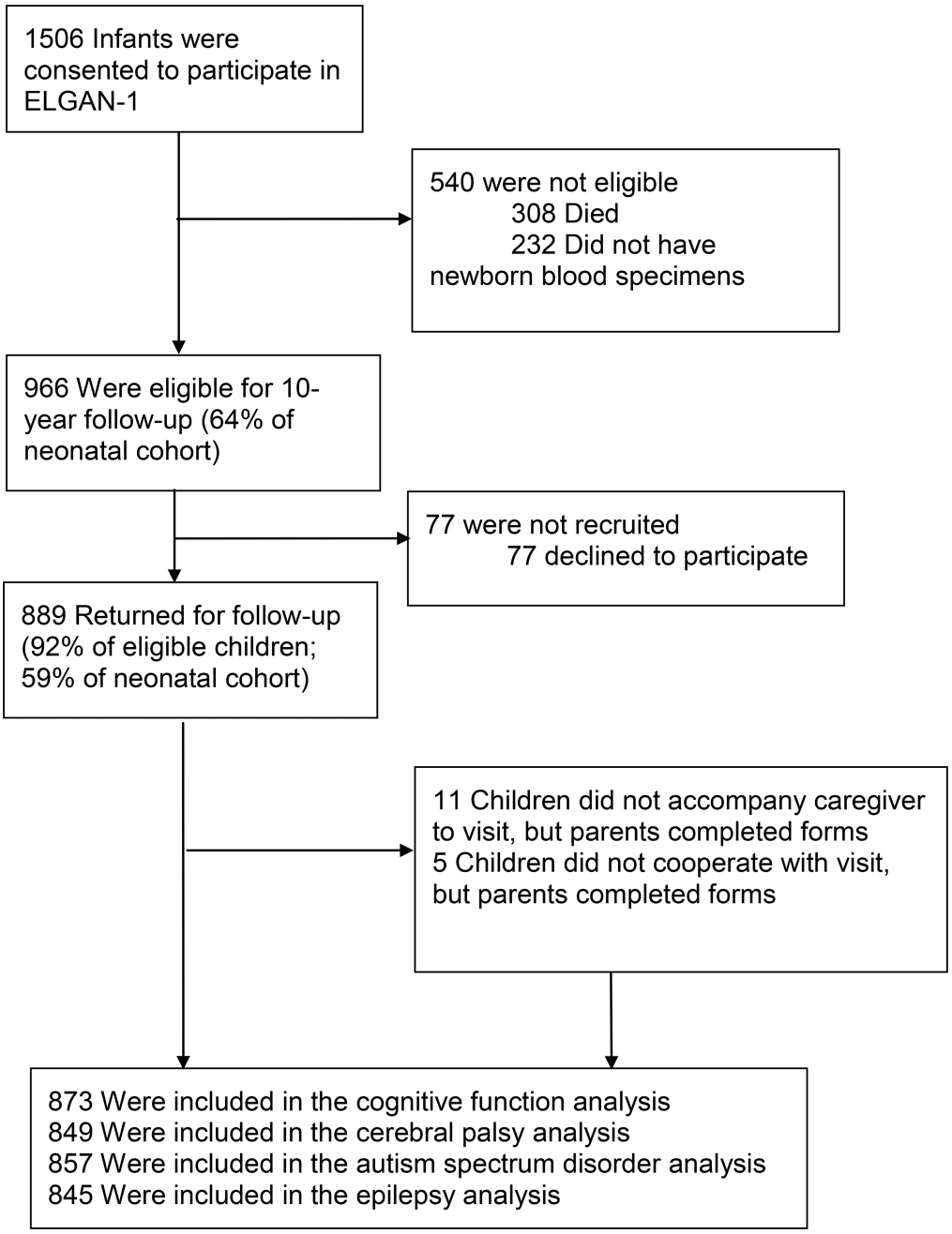

Figure 1.
Enrollment

Table 1

Distribution of each outcome among those with isolated impairments or with multiple impairments (row percents).

Adverse impairment (n)	% with isolated impairment (n=288)	% with multiple impairments (n=117)	Among those with multiple impairments, % of each adverse impairment associated with other impairments (maximum n=117)			
			CFC 3 or 4	CP	ASD	Epilepsy
CFC 3 or 4 (214)	49% (104/214)	51% (110/214)		55% (58/106)	48% (40/84)	38% (41/109)
CP at age 2 (93)	32% (30/93)	68% (63/93)	94% (58/62)		20% (8/40)	34% (21/62)
ASD (61)	30% (18/61)	70% (43/61)	93% (40/43)	20% (8/41)		21% (9/43)
Epilepsy (66)	29% (19/66)	71% (47/66)	89% (41/46)	47% (21/45)	26% (9/35)	

Table 2

Number of impairments (CFC 3 or 4, CP, ASD, and/or epilepsy) according to gestational age (column percents).

Number of impairments	n (% of all children)	n (%) according to GA (weeks)		
	(n=889)	23–24 W (n=187)	25–26 W (n=400)	27 W (n=302)
0	601 (68%)	90 (48%)	271 (68%)	240 (79%)
1	171 (19%)	49 (26%)	82 (21%)	40 (13%)
2	90 (10%)	39 (21%)	38 (10%)	13 (4%)
3	25 (3%)	9 (5%)	8 (2%)	8 (3%)
4	2 (0%)	0 (0%)	1 (0.25%)	1 (0.3%)

$p<0.001$ from Mantel-Haenszel test for trend

Table 3

Relative risks of having other impairments, given presence of one impairment

Relative risk (95% CI):	Given Condition			
	CFC 3 or 4	CP at age 2	ASD	Epilepsy
CFC 3 or 4		3.29 (2.66, 4.08)	3.58 (2.84, 4.52)	2.96 (2.36, 3.72)
CP at age 2	5.51 (3.70, 8.19)		1.69 (0.85, 3.35)	3.62 (2.39, 5.49)
ASD	7.09 (4.25, 11.82)	1.71 (0.84, 3.46)		2.57 (1.34, 4.94)
Epilepsy	5.29 (3.28, 8.55)	4.01 (2.50, 6.45)	2.61 (1.24, 5.08)	

Conditions are not mutually exclusive

Table 4

Comparison with prior studies

Study	Mod/Sev	Mild	None
Johnson et al,[1] 2009[a]	45% IQ≤70, CP with GMFCS>2, mod/sev impaired vision and/or hearing loss	39% IQ 71–85, CP with GMFCS 1–2, mild visual impairment and/or hearing loss	16%
Roberts et al,[2] 2010[b]	19% IQ<70, CP with mod/sev limitations, blindness, deafness	40% IQ 70–85, CP with mild limitations	41%
Herber-Jonat et al,[3] 2014[c]	24% IQ<70, abnormal neurodevelopmental exam with mod/sev impaired mobility (GMFCS≥2), severe visual and/or hearing impairment	35% IQ 70–84, abnormal neurodevelopmental examination with normal/mildly impaired mobility (GMFCS≤1)	41%
Holsti et al,[4] 2014[d]	34% IQ≤72, mod/sev CP, severe visual impairment, hearing impairment with bilateral hearing aids	31% IQ 73–88, mild CP, unilateral blindness	35%
Serenius et al,[5] 2016[e]	33% IQ<77, CP with GMFCS≥2, mod/sev visual impairment, hearing impairment	30% IQ 77–89 or mild cognitive disability by a clinical examination or record review, CP with GMFCS=1, mild visual impairment	36%
Stahlmann et al,[6] 2009[f]	31% IQ<70, CP with GMFCS≥1, abnormal neurodevelopmental signs with severe difficulties of muscle tone regulation, coordination and balance, blindness, deafness	39% IQ 70–85, weak muscle tone, difficulties in coordination, balance, or clumsiness	30%
Neubauer et al,[7] 2008[g]	28% IQ<70, CP, blindness, deafness, intractable epilepsy	42% IQ 70–84, gross and fine motor deficits, language disorders, visual and audit defects, ADHD, abnormal socio-emotional development	28%
ELGAN[h] (Proposed)	Category III: 24% CFC 3 or 4 (with or without CP, ASD, epilepsy)	Category II: 8% CFC 1 or 2 with CP, ASD, and/or epilepsy *	Category I: 68% CFC 1 or 2 without CP, ASD, or epilepsy

Abbreviations: ASD, autism spectrum disorder; CFC, cognitive functional class; CP, cerebral palsy; GMFCS, Gross Motor Function Classification System; IQ, General cognitive ability; Mod/sev, moderate to severe

Inclusion criteria (weeks GA):

[a] ≤25

[b] 22–27

[c] <25

[d] 23–25

[e] 22–27

[f] <27 weeks

[g] <26 (n=50)

[h] <28

[*] 63–67% of all children with CP, ASD, and/or epilepsy had comorbid cognitive impairment (CFC 3 or 4)