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Neurodevelopment at age 5.5 years according to Ages & Stages questionnaire at 2 years' corrected age in children born preterm: The EPIPAGE-2 cohort study

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What is already known on this topic

Parental questionnaires, such as the Ages & Stages Questionnaires (ASQs) have some predictive ability for later cognitive or educational difficulties in term-born children.

What this study adds

In children born extremely, very, and moderately preterm, a positive screening for developmental delay with the ASQ at 2 years' corrected age was associated with neurodevelopment at age 5.5 years. Factors that were associated with outcomes differed according to whether the ASQ screening was positive or not, with social factors always playing a key role.

How this study might affect policy

The ASQ could be used as a first-line screening tool to enhance developmental surveillance of this high-risk population. Its interpretation needs to consider the number of domains below threshold and additional information, depending on whether the ASQ screening being positive or negative. This multidimensional assessment may help guide further assessments and follow-up.

ABSTRACT

Objective To report neurodevelopment at age 5.5 years according to developmental delay screening with the Ages & Stages Questionnaire (ASQ) in late infancy in preterm-born children

Design Population-based cohort study EPIPAGE-2

Setting France, 2011 to 2017

Participants 2504 children born at 24-26, 27-31 and 32-34 weeks, free of cerebral palsy, deafness or blindness at 2 years' corrected age.

Main outcome measures Moderate/severe, mild or no disability at age 5.5 years using gross and fine motor, sensory, cognitive, and behavioural evaluations. Results of the ASQ completed between 22- and 26-months' corrected age described as a positive screening or not.

Results Among 2504 participants, 38.3% had an ASQ positive screening. The probability of having moderate/severe or mild disability was higher for children with an ASQ positive versus negative screening: 14.2% versus 7.0%, adjusted odds ratio 2.5 (95% CI 1.8 to 3.4), and 37.6% versus 29.7%, adjusted odds ratio 1.5 (1.2 to 1.9). For children with an ASQ positive screening, the probability of having neurodevelopmental disabilities at age 5.5 years was associated with the number of domain scores below threshold, very low gestational age and severe neonatal morbidities. For children with an ASQ negative screening, this probability was increased for boys and children born small-for-gestational age. For both groups, maternal level of education was strongly associated with outcomes.

Conclusion In preterm-born children, ASQ screening at 2 years' corrected age was associated with neurodevelopmental disabilities at age 5.5 years. However, other factors should be considered when interpreting the ASQ data to draw further follow-up.

INTRODUCTION

Preterm birth is associated with increased risk of neurobehavioral developmental difficulties [1]. However, great variations are observed between individuals [2]. There is a large consensus that most immature children should be included in follow-up programs [3].

Accumulating evidence suggests that children born moderately preterm, which are much more numerous, could also benefit from those programs [4]. Improved identification associated with the provision of interventions is expected to lead to improved neurobehavioral developmental outcomes [5]. However, we lack resources. Therefore, adapted screening tools are of uttermost importance to ease developmental follow-up for children born preterm.

Parental questionnaires are increasingly used to identify children at risk of developmental delay [6]. The Ages & Stages Questionnaires (ASQs) are one of the most widely used [7]. Their concurrent validity has been studied in the general population as well as in children born preterm [8-10]. To what extent the ASQ could identify children at low or high risk of later multidimensional neurodevelopmental difficulties has not been studied.

The EPIPAGE-2 cohort study was designed to investigate outcomes of children born before 35 weeks' gestation. A developmental follow-up was performed at 2 years' corrected age (CA) using the ASQ [11]. Children were then followed at 5.5 years of age with a broad neurodevelopmental assessment [12]. In this study, we aimed to compare neurodevelopmental outcome at age 5.5 years for children included in the EPIPAGE-2 cohort with an ASQ positive or negative screening for developmental delay at 2 years' CA and, in each of these 2 groups, to investigate factors associated with neurodevelopmental difficulties at age 5.5 years. We hypothesize that the association of the ASQ screening alone and later neurodevelopmental disabilities would be moderate, but that it should be embedded in a multidimensional approach of children and their families.

METHODS

Study population

EPIPAGE-2 is a French prospective national population-based cohort which aimed to include children born at 22-34 weeks' gestation in all maternity units during 2011 in 24 of the 25 French regions [13]. All survivors were invited to participate in a follow-up study at 2 years' CA and at 5.5 years years. Only one child born at 23 weeks' gestation + 6 days survived and was included in the 24-26 weeks group. For the current study, we excluded children with severe congenital brain malformation identified in the neonatal period, cerebral palsy, and deafness or blindness recorded at 2 years' CA. Other exclusion criteria were an ASQ at 2 years' CA not completed or completed outside the 22- to 26-months' CA window [14]. All families had received information and provided written informed consent. This study was approved by the National Data Protection Authority (CNIL DR-2016-290) and by appropriate ethics committees (Consultative Committee on the Treatment of Data on Personal Health for Research Purposes, reference no. 16.263; Committee for the Protection of People Participating in Biomedical Research, reference 2016-A00333-48).

Data collection at 2 years' CA and age 5.5 years

At 2 years' CA, the French version of the 24-month ASQ, second edition, validated in France, was completed by parents [10]. The ASQ consists of 30 items covering 5 domains of development (gross motor skills, fine motor skills, communication abilities, problem-solving abilities and personal social skills) that are rated on a 3-point Likert scale: "yes", "sometimes" or "not yet". According to US norms, a positive screening was defined as a score less than 2 standard deviations (SDs) below the mean on any of the 5 domains [11].

At age 5.5 years, children were invited for a broad neurodevelopmental evaluation [12].

Motor and sensory functions were assessed through a clinical examination. Cerebral palsy was diagnosed using the criteria of the Surveillance of Cerebral Palsy in Europe network [15]

and classified using the Gross Motor Function Classification System [16]. Visual acuity was evaluated with the Sander-Zalonghi scale [17] and classified according to the World Health Organization [18]. Hearing disability was classified according to the severity of hearing loss and the need for hearing aids [3]. The Movement Assessment Battery for Children, second edition (MABC-2) was used to screen for developmental coordination disorders [19]. The French version of the Wechsler Preschool and Primary Scale of Intelligence, fourth edition (WPPSI-IV), was used to determine the Full-Scale Intelligence Quotient [20]. Finally, parents completed the Strengths and Difficulties Questionnaire (SDQ) [21] to rate emotional, conduct, hyperactivity/inattention, and peer relationship difficulties [22]. Results are reported with cut-offs for a contemporary sample born at term from the population-based ELFE cohort as a reference [12,23]. Children were finally classified as having moderate/severe, mild or no disability (Table 1).

Covariates

Several neonatal and maternal characteristics were used as potential confounders when studying the association between ASQ screening and later neurodevelopmental disabilities. Neonatal characteristics included gestational age in 3 groups (24-26, 27-31, and 32-34 weeks), small-for-gestational age (birth weight less than the 10th centile for gestational age and sex [24]), multiple pregnancy, sex, and severe neonatal morbidity (severe bronchopulmonary dysplasia, necrotizing enterocolitis (Bell stages 2-3), severe retinopathy of prematurity stage >3, intraventricular haemorrhage grade III or IV or cystic periventricular leukomalacia). Maternal characteristics included mother's age at child's birth, country of birth, language spoken at home, and level of education (high: bachelor's degree or higher; low: high school or less; intermediate: other situations).

Data management and statistics

Children who participated at age 5.5 years were first compared with children eligible but not included. Neurodevelopmental outcomes at age 5.5 years were compared for the 2 subgroups defined according to the ASQ screening at 2 years' CA, positive or negative. Percentages were weighted to account for differences in recruitment time between gestational age groups (See web appendix 1 for details). All tests were 2-sided; $p < 0.05$ was considered statistically significant. We calculated sensitivity and specificity of the ASQ screening for both moderate/severe and mild disabilities, as well as odds ratios (ORs) with their 95% confidence intervals (CIs) of moderate/severe or mild disability at age 5.5 years according to the ASQ screening before and after adjustment for all covariates listed previously. Outcomes at age 5.5 years were further described according to the number of ASQ domains with scores below threshold. All analyses were conducted for the whole population (24-34 weeks), with adjustment or weighting for gestational age group, as well as for each gestational age group. Finally, factors associated with neurodevelopmental outcomes at age 5.5 years were determined among the covariates previously described, separately for the groups of children with an ASQ positive or negative screening. Indeed, factors associated with later developmental outcomes may vary when considering children at different risk level. Multinomial generalized estimating equation logistic regression models with an independent working correlation structure were used to study disabilities at age 5.5 years to account for non-independence of multiple children born from the same mother. Multiple imputation was used for missing data on outcome, ie neurodevelopmental evaluation at age 5.5 years among children with available ASQ data at 2 years' CA. Specific multiple imputation detail are provided in Web Appendix 1. Percentages and means with standard deviations are presented for imputed data. Data are also presented for complete cases as supplementary data.

RESULTS

The EPIPAGE-2 cohort study included 5170 live-born premature infants; 4441 were alive at 2 years' CA with parents who accepted follow-up. Results of the ASQ performed between 22- and 26-months' CA were available for 2504 preterm children (59.0% of those eligible), and 2060 (82.3%) were assessed at least partially at age 5.5 years (eFigure 1). Baseline characteristics of these 2504 children are displayed in Table 2. Children eligible but not included differed in several ways from those included at age 5.5 years (eTable 2).

The ASQ was completed at a median CA of 23 months (interquartile range 23–24); 1022 (38.3%) children had a positive screening. At age 5.5 years, 48.2% had no disability, 37.6% had mild disabilities, and 14.2% had moderate/severe disabilities. Children with an ASQ positive screening more frequently had a diagnosis of cognitive impairment or developmental coordination disorders at age 5.5 years than those with an ASQ negative screening. They had significantly lower mean MABC-2 score, lower mean Full-Scale Intelligence Quotient or higher mean SDQ score (Table 3; see eTable 3 for complete cases). These findings were consistent for all gestational groups, except for developmental coordination disorders in children born at 24-34 weeks. After adjustment for covariates, an ASQ positive screening was independently associated with probability of moderate/severe disability (adjusted OR [aOR] 2.5, 95% CI 1.8 to 3.4) and mild disability (aOR 1.5, 95% CI 1.2 to 1.9) in the overall population and in each gestational age group, although significance was not always reached (Figure 1). Figure 1 also displays sensitivities and specificities for the ASQ screening. Among the 1022 children with an ASQ positive screening, for 580 (56.8%), the score for only one domain was below threshold, for 222 (21.7%) two domains, and for 220 (21.5%) three or more domains. There was an increase in disabilities at 5.5 years as the number of domain scores below threshold increased (eFigure 2).

For both groups of children with an ASQ positive or negative screening, low maternal level of education was strongly associated with the probability of neurodevelopmental disabilities at age 5.5 years (Table 4). Other maternal characteristics (language spoken at home, birth outside France) were statistically related to outcomes only for children with an ASQ negative screening. For these children, the probability was increased for boys and children small-for-gestational age. For children with an ASQ positive screening, the probability of disabilities was associated with the number of domains with a score below threshold, very low gestational age and severe neonatal morbidities.

DISCUSSION

In this population-based cohort of children born preterm, an ASQ positive screening at 2 years' CA was independently associated with moderate/severe and mild disabilities at age 5.5 years. Disabilities increased as the number of domains scores below threshold increased.

Although sensitivities and specificities could be considered as moderate, including additional information could help to interpret the results.

This study has several strengths. First, we had access to a broad neurodevelopmental evaluation, including cognition but also motor and behavioural dimensions. The cohort was large and population-based and included children born up to 34 weeks' gestation. However, several limitations must be considered. First, the number of children lost to follow-up was high. Multiple imputation was used to account for selection bias between age 2 and 5.5 years. However, there were many dropout patients before 2 years' CA that we could not include in the analysis. These children had a significantly lower socioeconomic background. Thus, the frequency of ASQ positive screening and neurodevelopmental disabilities at 5.5 years were probably underestimated. However, it is unlikely that our association measures were affected. Second, we were not able to consider interventions conducted to support neurodevelopment

that could have modified the associations, either during the first 2 years or between age 2 and 5.5 years. Third, we did not consider which ASQ domain scores were below threshold and to which extent the outcomes differed according to the specific domains with a score below threshold.

A meta-analysis about the ASQs evaluated its utility to identify developmental delay in children aged 12 to 60 months [25]. The probability of identifying children at low risk of developmental delay or high risk of severe motor or cognitive delay was reported as moderate, although better for children aged 24 months or older. However, most children included were born at term, and the concurrent validity of the ASQ seems better for preterm children [8]. Associations between infant developmental test performed by professionals, such as the Bayley-III, and later IQ scores are generally low, although better in children born preterm [26]. In one study, predictive measures were similar when using the ASQ or the Bayley-III [27]. Two systematic reviews studying the predictive value of the ASQ for later cognitive [28] or educational [29] difficulties were published in 2021. The limitations of these reviews are the large heterogeneity between studies, with most of them reporting results for term-born populations. Therefore, the current study adds important information about the usefulness of the ASQ in preterm-born infants.

We report specificities of 0.63 to 0.69 in the different gestational age groups, with sensitivities of 0.44 to 0.88 depending on gestational age and type of disabilities. Sensitivity and specificity levels of 0.70 to 0.80 have been deemed acceptable for developmental screening according to the American Academy of Pediatrics [30]. These values are lower than those generally considered acceptable for diagnosis tests because of the challenge inherent to child development. Many values we calculated were lower, thus underlying the fact that not only positive / negative screening has to be considered when using the ASQ to determine further follow-up or support.

Numerous factors intervene in a child's developmental trajectory [31], and children with an ASQ positive screening have more social and neonatal risk factors [14]. However, for both groups of our children, maternal level of education was still strongly linked with later disabilities, which highlights that social disadvantage has a prolonged effect. The number of domains with a score below threshold reflects the extent of difficulties a child experiences. We found a clear link between this number and the probability of later disability. ASQ screening could therefore be considered not only as binary, but more as a scale. Several factors describing the burden of immaturity, namely gestational age and neonatal morbidities, were also associated with disabilities at age 5.5 years in children with a positive screening. Most immature children may have less opportunity to compensate for their developmental difficulties over time. In contrast, for children with an ASQ negative screening, later risk of disabilities was associated with factors usually associated with neurodevelopment in the general population: sociodemographic factors, male sex and small-for-gestational age. The absence of a relation between outcome and gestational age was previously found in a selected low-risk population of immature children [32].

Finally, when trying to transpose our results in clinical practice, a negative ASQ screening at 2 years's corrected age cannot be used solely to fully rule out later specific neurodevelopment follow-up. Recommendations when the ASQ screening is positive may vary with the clinical context, from giving advice to the family and rescreening the child later to performing a developmental test or to share the results with others and start remediation [33]. Indeed, when using the ASQ in a clinical setting dedicated to children born preterm, the neonatal history, the child's environment, the clinical examination of the child, and parental concerns [12] are important additional information available.

CONCLUSIONS

In this population of children born preterm, a positive screening with the ASQ completed by parents at 2 years' CA was independently associated with neurodevelopmental disabilities at 5.5 years old. Considering the number of domains below threshold enriched the interpretation of a positive screening. The use of the ASQ should have a place in the follow-up of preterm-born children at the end of infancy. However, it cannot be used solely to guide further follow-up and assessment.

FIGURE LEGEND

Figure 1. Association between ASQ at age 2 years' corrected age positive screening and overall neurodevelopmental disability at age 5.5 years

Footnotes :

* Includes cerebral palsy, vision, hearing, full-scale intelligence quotient, developmental coordination disorders, and behavioural difficulties (Table 1).

† Generalised estimating equations (GEE) for multinomial outcome model to account for non-independence of outcomes related to multiple births, after multiple imputation of missing data.

‡ Adjusted for gestational age, small-for-gestational age, single or multiple birth, sex, severe neonatal morbidities, mother's age, mother's birth country, language at home, mother's level of education.

§ Observed data, weighted to consider the differences in survey design between gestational age groups and with a clustered data approach to account for nonindependence of outcomes related to multiple births.

¶ Included one survivor born at 23 weeks + 6 days.

Table 1: Definition of neurodevelopmental outcome measures at age 5.5 years and classification of neurodevelopmental disabilities

Neurodevelopmental outcome measure	Definition and Classification
Cerebral palsy Moderate and severe Mild None	Medical examination GMFCS level 2/3 to GMFCS level 4/5 GMFCS level 1 No cerebral palsy
Developmental coordination disorders	Movement Assessment Battery for Children, second edition (MABC-2) Total MABC-2 score $\leq 5^{\text{th}}$ percentile (cut-off point ≤ 5)*
Sensory disability (vision and hearing): Moderate and severe Mild None	Visual acuity measured with the Sander-Zanlonghi scale† and with glasses if needed and hearing disability assessed during clinical examination: Bilateral binocular visual acuity < 3.2 to $< 1/10$ or unilateral or bilateral hearing loss 40 to > 70 dB not corrected or partially corrected with hearing aid Binocular visual acuity $< 5/10$ but $\geq 3.2/10$ or hearing loss < 40 dB Binocular visual acuity $\geq 5/10$ and no hearing loss
Cognitive deficiency Moderate and severe Mild None	Full-Scale Intelligence Quotient (FSIQ) measured with the WPPSI-IV‡ FSIQ < 78 (< -2 SD) FSIQ 79-92 (-2 to < -1 SD) FSIQ 93-119 (-1 to $+1$ SD) or ≥ 120 (≥ 1 SD)
Behavioural difficulties	Strengths and Difficulties Questionnaire (SDQ) completed by parents Total SDQ score $\geq 90^{\text{th}}$ percentile (cut-off point ≥ 19)‡
Classification of overall neurodevelopmental disabilities Moderate and severe Mild None	At least one of moderate and severe cerebral palsy, sensory disability, or cognitive deficiency At least one of mild cerebral palsy, sensory disability, cognitive deficiency, developmental coordination disorders, or behavioural difficulties Not classified as severe, moderate, or mild using the above definitions

* Cut-off points were determined in relation to distributions from the reference group born at term (37-41 weeks) after excluding children with cerebral palsy, severe or moderate vision or hearing disabilities, and FSIQ < 2 SD below the mean

† Sander-Zanlonghi scale [17]

‡ Cut-off point determined in relation to distribution of the reference sample born at term (37-41 weeks).

GMFCS = Gross Motor Function Classification System [16]; MABC-2 = Movement Assessment Battery for Children, second edition [19]; FSIQ = Full-Scale Intelligence Quotient; WPPSI-IV=Wechsler Preschool and Primary Scale of Intelligence, fourth edition [20]; SDQ= Strengths and Difficulties Questionnaire [21]; SD = standard deviation

Table 2: Baseline Characteristics of the study participants, N=2504.

	Study participant children, N=2504	
	n/N	%
Neonatal characteristics		
Gestational age		
24-26 weeks	312/2504	4.6
27-31 weeks	1570/2504	31.2
32-34 weeks	622/2504	64.2
Small-for-gestational age*	883/2504	34.6
Multiple birth	911/2504	38.7
Male	1315/2504	52.8
Severe neonatal morbidities†	284/2387	6.2
Maternal characteristics		
Age (years)		
<25	315/2504	10.0
25-34	1591/2504	65.1
≥35	598/2504	24.9
Born in France	2028/2499	84.4
Language spoken at home, french only	1820/2475	76.9
Level of education‡		
Low	1160/2461	45.1
Intermediate	540/2461	22.5
High	761/2461	32.4
ASQ at 2 years corrected age		
ASQ positive screening	1022/2504	38.3
No of domains with score < - 2 SD below the mean		
0	1482/2504	61.7
1	580/2504	22.7
2	222/2504	8.5
3 and more	220/2504	7.1

Denominators vary according to the number of missing data for each variable. Percent are weighted to consider the differences in survey design between gestational age groups, proportions are not exactly number of events/numbers in groups due to the weighting.

* Small-for- gestational age was defined as birth weight less than the 10th percentile for gestational age and sex based on French intrauterine growth curves [24]

† Severe neonatal morbidity was defined as severe bronchopulmonary dysplasia or necrotizing enterocolitis stage 2-3 or severe retinopathy of prematurity stage >3 or any of the following severe cerebral abnormalities on cranial ultrasonography: intraventricular haemorrhage grade III or IV or cystic periventricular leukomalacia.

‡ Mother's education was divided into 3 classes: high level (Bachelor's degree or higher), low level (high school or less) and intermediate level

ASQ: Ages & Stages Questionnaire [11], SD: Standard deviation.

Table 3: Neurodevelopmental outcomes at age 5.5 years according to the Ages & Stages Questionnaires (ASQ) score at 2 years' corrected age by gestational age group. Results after multiple imputation, N=2504.

	Total: 24-34 weeks*			24-26 weeks*			27-31 weeks			32-34 weeks		
	ASQ positive screening		P-value	ASQ positive screening		P-value	ASQ positive screening		P-value	ASQ positive screening		P-value
	Yes, N=1022 %†	No, N=1482 %†		Yes, N=157 %	No, N=155 %		Yes, N=640 %	No, N=930 %		Yes, N=225 %	No, N=397 %	
Outcomes at 5 ½ years												
Motor evaluation												
Cerebral Palsy	2.4	1.2	0.097	5.1	3.4	0.49	3.8	1.6	0.015	1.4	0.9	0.56
Total MABC-2 Score, mean (SD)‡	9.8 (3.2)	10.4 (3.1)	<0.001	7.7 (3.4)	9.4 (3.3)	<0.001	9.3 (3.4)	10.2 (3.1)	<0.001	10.2 (3.0)	10.6 (3.1)	0.19
Total MABC-2 Score ≤ 5th percentile‡,§	7.6	4.7	0.046	23.9	12.2	0.025	12.5	5.1	<0.001	3.9	4.1	0.62
Sensory disability												
Moderate/severe disability¶	1.5	1.0	0.47	2.2	1.9	0.65	1.5	1.0	0.42	1.4	1.0	0.56
Cognitive evaluation												
FSIQ Score, mean (SD)	95.0 (15.4)	101.1 (14.3)	<0.001	89.7 (16.8)	95.6 (14.4)	0.004	92.1 (15.8)	98.6 (14.5)	<0.001	97.1 (14.6)	102.6 (13.9)	<0.001
FSIQ Score, by categories§												
<-2 SD	13.0	6.0	<0.001	25.6	9.8	0.009	18.5	8.0	<0.001	8.7	4.9	0.003
-2 to <-1 SD	28.5	20.1		27.1	28.8		29.3	22.7		28.2	18.4	
-1 to +1 SD or ≥1 SD	58.6	74.0		47.3	61.4		52.2	69.3		63.2	76.8	
Behavioral evaluation												
Total SDQ Score, mean (SD)	10.8 (5.7)	9.4 (5.7)	<0.001	11.9 (6.0)	10.1 (5.5)	0.015	11.6 (6.0)	9.8 (5.9)	<0.001	10.2 (5.4)	9.2 (5.6)	0.053
Total SDQ Score ≥ 90th percentile§	10.1	8.3	0.28	15.9	6.9	0.024	14.1	9.0	0.007	7.4	8.0	0.62
Neurodevelopmental disabilities**												
Moderate/severe disability	14.2	7.0	<0.001	27.1	11.3	0.002	19.7	8.9	<0.001	9.9	5.9	0.009
Mild disability	37.6	29.7		41.2	37.8		38.9	33.3		36.6	27.6	
None	48.2	63.3		31.7	50.9		41.4	57.8		53.5	66.5	

Results after multiple imputation of missing 5 years outcomes.

* Included one survivor born at 23 weeks + 6 days.

† Percent are weighted to consider the differences in survey design between gestational age groups.

‡ Cut-off point of the distribution related to the reference group born at term (37-41 weeks).

§ For children without cerebral palsy, severe or moderate vision or hearing disabilities, and full-scale intelligence quotient less than two standard deviations below the mean.

¶ Bilateral binocular visual acuity <3.2 to <1/10 or unilateral or bilateral hearing loss 40 to >70 dB not corrected or partially corrected with hearing aid.

** Includes cerebral palsy, vision, hearing, FSIQ, developmental coordination disorders, and behavioural difficulties (Table 1).

ASQ: Ages & Stages Questionnaire [11]; MABC-2: Movement Assessment Battery for Children, second edition [19]; FSIQ: Full-Scale Intelligence Quotient [20]; SDQ: Strengths and Difficulties Questionnaire [21]; SD: Standard deviation.

Table 4: Factors associated with neurodevelopmental disabilities at age 5.5 years among preterm children with and without ASQ positive screening at 2 years' corrected age. Multinomial regression models, after multiple imputation.

	Neurodevelopmental Disabilities at 5.5 years*											
	Children with a ASQ positive screening, N=1022						Children with a ASQ negative screening, N=1482					
	Moderate/ Severe, %†	Mild, %†	None, %†	aOR (95% CI)‡ Moderate/ Severe	aOR (95% CI)‡ Mild	Pvalue	Moderate/ Severe, %†	Mild, %†	None, %†	aOR (95% CI)‡ Moderate/ Severe	aOR (95% CI)‡ Mild	Pvalue
Neonatal characteristics												
Gestational age												
32-34 weeks	10.0	36.6	53.5	1	1	0.076	5.9	27.6	66.5	1	1	0.26
27-31 weeks	19.7	38.9	41.4	2.1 (1.1-3.9)	1.3 (0.9-1.9)		8.9	33.3	57.8	1.3 (0.7-2.5)	1.2 (0.9-1.7)	
24-26 weeks	27.1	41.2	31.7	3.1 (1.4-7.0)	1.6 (0.9-2.8)		11.3	37.8	50.9	1.8 (0.7-4.5)	1.7 (1.0-2.8)	
Small-for-gestational age§												
Birth weight ≥ 10 th percentile	13.2	37.4	49.4	1	1	0.35	5.7	28.9	65.4	1	1	0.011
Birth weight < 10 th percentile	15.8	37.9	46.3	1.4 (0.9-2.1)	1.1 (0.8-1.5)		9.7	31.5	58.8	1.9 (1.1-3.1)	1.4 (1.0-1.8)	
Multiple birth												
Singleton	15.5	38.3	46.2	1	1	0.59	7.9	30.5	61.6	1	1	0.73
Multiple	12.0	36.6	51.4	1.2 (0.8-1.9)	1.0 (0.7-1.4)		5.6	28.4	65.9	0.8 (0.5-1.4)	1.0 (0.7-1.3)	
Sex												
Female	12.0	36.5	51.5	1	1	0.53	6.3	28.0	65.7	1	1	0.028
Male	15.9	38.5	45.6	1.2 (0.8-1.9)	1.2 (0.9-1.6)		7.6	31.4	61.0	1.8 (1.1-2.8)	1.2 (1.0-1.6)	
Severe neonatal morbidities¶												
No	12.9	37.0	50.2	1	1	0.015	6.7	29.5	63.8	1	1	0.24
Yes	28.8	44.7	36.5	2.4 (1.3-4.3)	1.5 (0.9-2.5)		12.3	33.4	54.3	1.9 (0.9-4.0)	1.2 (0.7-1.8)	
Maternal characteristics												
Age (years)												
<25	26.4	37.8	35.8	1.7 (0.9-3.2)	1.1 (0.6-1.8)	0.41	12.6	35.8	51.6	1.4 (0.8-2.7)	1.4 (0.9-2.2)	0.12
25-34	13.4	38.0	48.6	1	1		6.7	28.3	65.0	1	1	
≥35	11.9	36.7	51.4	1.2 (0.7-2.2)	1.1 (0.8-1.6)		5.5	31.0	63.5	0.6 (0.3-1.1)	1.0 (0.7-1.3)	
Born outside France												
No	12.3	37.3	50.4	1	1	0.42	5.7	28.6	65.7	1	1	0.009
Yes	22.2	39.2	38.6	1.4 (0.8-2.7)	1.3 (0.8-2.1)		15.2	36.8	48.1	2.5 (1.3-4.8)	1.5 (1.0-2.3)	
Language spoken at home												
French only	11.6	36.8	51.6	1	1	0.31	5.6	27.4	67.1	1	1	0.024
French plus another language	21.6	40.0	38.5	1.5 (0.9-2.7)	1.0 (0.7-1.6)		12.3	38.4	49.3	2.2 (1.2-4.0)	1.3 (0.9-1.9)	

Table 4: Continued.

	Neurodevelopmental Disabilities at 5.5 years*											
	Children with a ASQ positive screening, N=1022						Children with a ASQ negative screening, N=1482					
	Moderate/ Severe, %†	Mild , %†	None, %†	aOR (95% CI)‡	aOR (95% CI)‡	Pvalue	Moderate/ Severe, %†	Mild , %†	None, %†	aOR (95% CI)‡	aOR (95% CI)‡	Pvalue
Level of education**												
High	4.9	35.8	59.3	1	1	<0.001	3.4	23.4	73.2	1	1	<0.001
Intermediate	8.6	38.2	53.2	1.8 (0.8-3.8)	1.2 (0.8-1.8)		4.9	31.5	63.5	1.4 (0.5-3.5)	1.3 (0.9-1.8)	
Low	21.4	38.3	40.3	3.5 (1.9-6.4)	1.3 (0.9-2.0)		11.3	34.2	54.6	4.5 (2.3-8.7)	1.7 (1.2-2.3)	
ASQ score, No of domains with score < - 2 SD below the mean												
1	9.1	36.1	54.8	1	1	<0.001						
2	15.6	40.8	43.6	1.8 (1.0-3.0)	1.3 (0.9-2.0)							
3 and more	28.9	38.7	32.4	4.0 (2.3-6.8)	1.8 (1.2-2.8)							

Results after multiple imputation of missing data.

Generalised estimating equations (GEE) for multinomial outcome model to account for non-independence of outcomes related to multiple births.

* Includes cerebral palsy, vision, hearing, full-scale intelligence quotient, developmental coordination disorders, and behavioural difficulties (Table 1)

† Percent are weighted to consider the differences in survey design between gestational age groups.

‡ Adjusted for gestational age, small-for-gestational age, single or multiple birth, sex, severe neonatal morbidities, mother's age, mother's birth country, language at home, mother's level of education and number of ASQ domains with score below threshold.

§ Small-for- gestational age was defined as birth weight less than the 10th percentile for gestational age and sex based on French intrauterine growth curves [24]

¶ Severe neonatal morbidity was defined as severe bronchopulmonary dysplasia or necrotizing enterocolitis stage 2-3 or severe retinopathy of prematurity stage >3 or any of the following severe cerebral abnormalities on cranial ultrasonography: intraventricular haemorrhage grade III or IV or cystic periventricular leukomalacia.

** Mother's education was divided into 3 classes: high level (Bachelor's degree or higher), low level (high school or less) and intermediate level

ASQ: Ages & Stages Questionnaire [11], SD: Standard deviation.

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Contributions: MLC, GK and VP had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. MLC, VP, ST, ASM, HT and SM conceptualized the study and wrote the manuscript. GK performed the statistical analysis. VB coordinated data collection and had responsibility for technical support. PYA obtained funding and supervised the study. All authors contributed to the analysis plan and interpretation of the results and reviewed and approved the final manuscript. All members of the writing group were involved in the regional organisation for data collection, reviewed and/or approved the final manuscript.

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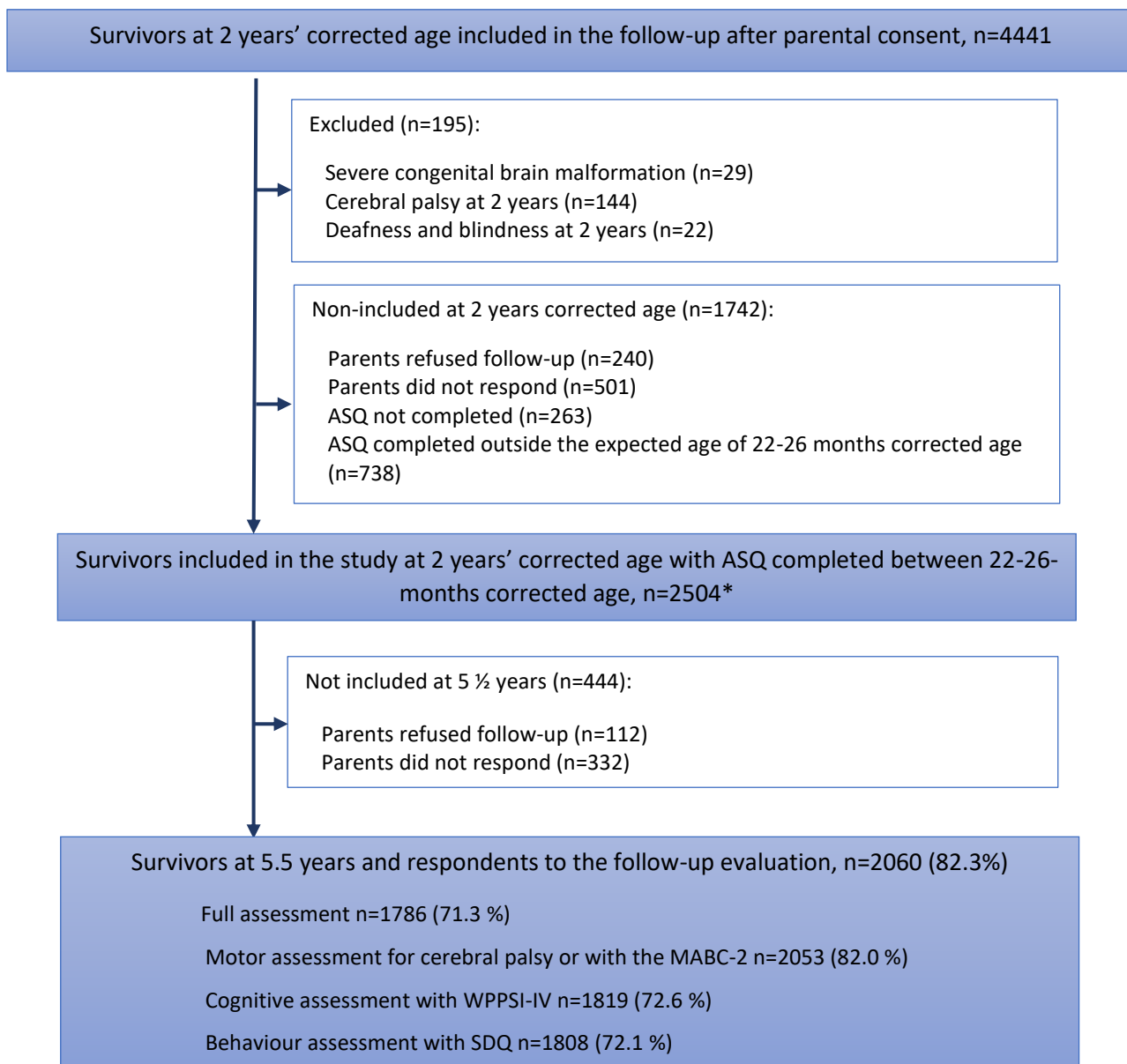
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eFigure1: Flow-chart of the studied population.



*No survivors were born at 22 weeks and only one survivor was born at 23 weeks, who was lost to follow-up at 5.5 years.

ASQ=Ages & Stages questionnaire (Squires, 2009); WPPSI-IV=Wechsler Preschool and Primary Scale of Intelligence, fourth edition (Wechsler, 2014); MABC-2 = Movement Assessment Battery for Children, second Edition (Henderson, 2007); SDQ= Strengths and Difficulties Questionnaire (Goodman, 1997);

eTable 1: Type of variables, models used to predict missing data, and percentages of missing values for each variable included in the imputation model, N=2504 survivors at 2 years corrected age eligible for the study.

Variables	Type of variable	Model used to predict missing data	Percentages of missing values
Maternal and neonatal characteristics			
Maternal age at birth	Categorical (3 categories)	No missing data	0%
Birth region	Categorical	No missing data	0%
Primiparity	Binary	Logistic regression	<1%
Maternal birth outside France	Binary	Logistic regression	<1%
Mother level of education*	Categorical (3 categories)	Multinomial regression	2%
Socio-economic status†	Categorical (3 categories)	Multinomial regression	3%
Language spoken at home	Categorical (3 categories)	Multinomial regression	1%
Multiple birth	Binary	No missing data	0%
Sex	Binary	No missing data	0%
Small-for-gestational age‡	Binary	No missing data	0%
Gestational age	Continuous	No missing data	0%
Antenatal steroids	Binary	Logistic regression	1%
Late onset sepsis	Binary	Logistic regression	<1%
Severe neonatal morbidity§	Binary	Logistic regression	4%
Breastmilk at discharge	Categorical (3 categories)	Multinomial regression	6%
At 2 years' corrected age			
ASQ score	Continuous	No missing data	0%
Corrected age at ASQ evaluation	Continuous	No missing data	0%
Language delay¶	Binary	Logistic regression	3%
At 5 ½ years			
Parents' concerns about child development	Binary	Logistic regression	11%
Cerebral palsy	Categorical (5 categories)	Multinomial regression	18%
Support at school, special schooling	Categorical (3 categories)	Multinomial regression	19%
Hearing disabilities	Categorical (4 categories)	Multinomial regression	19%
Complex developmental intervention**	Binary	Logistic regression	20%
Visual disabilities	Categorical (4 categories)	Multinomial regression	27%
MABC-2 Manual Dexterity score	Continuous	Predictive mean matching	27%
M-ABC-2 Aiming & Catching score	Continuous	Predictive mean matching	27%
M-ABC-2 Balance score	Continuous	Predictive mean matching	28%
M-ABC-2 Total score	Continuous	Predictive mean matching	28%
WPPSI Verbal Comprehension Index score	Continuous	Predictive mean matching	27%
WPPSI Visio-spatial Index score	Continuous	Predictive mean matching	27%
WPPSI Fluid Reasoning Index score	Continuous	Predictive mean matching	27%
WPPSI Working memory index score	Continuous	Predictive mean matching	27%
WPPSI Processing speed index score	Continuous	Predictive mean matching	27%
WPPSI FSIQ score	Continuous	Predictive mean matching	27%
SDQ Emotional difficulties	Continuous	Predictive mean matching	27%
SDQ Peer relations	Continuous	Predictive mean matching	27%
SDQ Hyperactivity	Continuous	Predictive mean matching	27%
SDQ Conduct problems	Continuous	Predictive mean matching	27%

* Divided in 3 levels: high level (Bachelor's degree or higher), low level (high school or less) and intermediate level.

† Highest occupational status between occupations of the mother and the father, or mother only if living alone.

‡ Birth weight less than the 10th percentile for gestational age and sex based on French intrauterine growth curves (Ego, 2016)

§ Severe bronchopulmonary dysplasia or necrotizing enterocolitis stage 2-3 or severe retinopathy of prematurity stage >3 or any of the following severe cerebral abnormalities on cranial ultrasonography: intraventricular hemorrhage grade III or IV or cystic periventricular leukomalacia (12)

¶ Lexicon size of < 28 words on the French version of the McArthur-Bates Inventories (Kern, 2010)

** At least two consultations with psychologist, psychiatrist, orthoptist, speech therapist, occupational therapist, physiotherapist, during the twelve last months or care in a rehabilitation centre (Pierrat, 2021)

ASQ=Ages & Stages questionnaire (Squires, 2009); WPPSI-IV=Wechsler Preschool and Primary Scale of Intelligence, fourth edition (Wechsler, 2014); MABC-2 = Movement Assessment Battery for Children, second Edition (Henderson, 2007); SDQ= Strengths and Difficulties Questionnaire (Goodman, 1997);

eTable 2: Comparison of children respondents at age 5.5 years with children not included at age 5.5 years and children not included at 2 years' corrected age.

	Respondents at 5 ½ years, N=2060		Not included at 5 ½ years, N=444		P-value*	Not included at 2 years' corrected age, N=1742		P-value†
	n/N	%	n/N	%		n/N	%	
Neonatal factors								
Gestational age								
23-26 weeks	252/2060	4.5	60/444	4.9	0.75	193/1742	3.6	<0.001
27-31 weeks	1299/2060	31.4	271/444	30.0		1004/1742	25.2	
32-34 weeks	509/2060	64.0	113/444	65.1		545/1742	71.2	
Male sex	1084/2060	54.2	231/444	46.2	0.030	914/1742	53.5	0.75
Small-for-gestational age‡	738/2060	35.0	145/444	32.5	0.47	572/1741	31.4	0.079
Severe neonatal morbidities§	236/1965	6.5	48/422	4.9	0.11	182/1637	5.5	0.19
Multiple birth	761/2060	39.7	150/444	33.8	0.17	533/1742	32.4	0.006
Maternal characteristics								
Age at birth (years)								
<25	235/2060	9.0	80/444	14.6	0.040	433/1741	23.4	<0.001
25-34	1328/2060	65.4	263/444	63.9		961/1741	57.1	
>35	497/2060	25.6	101/444	21.5		347/1741	19.6	
Birth outside France	363/2058	14.6	108/441	19.8	0.065	466/1703	26.2	<0.001
Level of education¶								
Low	903/2036	42.8	257/425	55.8	0.005	277/1467	65.3	<0.001
Intermediate	459/2036	22.9	81/425	20.7		214/1467	14.9	
High	674/2036	34.3	87/425	23.5		976/1467	19.8	
ASQ at 2 years corrected age								
ASQ positive screening	823/2060	38.0	199/444	39.3	0.73			

Denominators vary according to the number of missing data for each variable. Percent are weighted to consider the differences in survey design between gestational age groups, proportions are not exactly number of events/numbers in groups due to the weighting.

* Chi-squared test for difference between those respondents at 5 ½ years and those not included at 5 ½ years.

† Chi-squared test for difference between those respondents at 5 ½ years and those not included at 2 years' corrected age.

‡ Small-for-gestational age was defined as birth weight less than the 10th percentile for gestational age and sex based on French intrauterine growth curves²⁴

§ Severe neonatal morbidity was defined as severe bronchopulmonary dysplasia or necrotizing enterocolitis stage 2-3 or severe retinopathy of prematurity stage >3 or any of the following severe cerebral abnormalities on cranial ultrasonography: intraventricular haemorrhage grade III or IV or cystic periventricular leukomalacia.

¶ Mother's education was divided into 3 classes: high level (Bachelor's degree or higher), low level (high school or less) and intermediate level.

ASQ = Ages & Stages Questionnaire (Squires, 2009).

eTable3: Neurodevelopmental outcomes at age 5.5 years according to the Ages & Stages Questionnaires at 2 years' corrected age by gestational age groups, complete cases.

	Total: 24-34 weeks*			24-26 weeks*			27-31 weeks			32-34 weeks		
	ASQ positive screening Yes n/N (%)†	ASQ positive screening No n/N (%)†	Pvalue	ASQ positive screening Yes n/N (%)	ASQ positive screening No n/N (%)	Pvalue	ASQ positive screening Yes n/N (%)	ASQ positive screening No n/N (%)	Pvalue	ASQ positive screening Yes n/N (%)	ASQ positive screening No n/N (%)	Pvalue
Outcomes at 5 ½ years												
Motor evaluation												
Cerebral palsy	27/819 (2.2)	16/1228 (0.9)	0.041	6/128 (4.7)	4/123 (3.3)	0.56	19/505 (3.8)	10/784 (1.3)	0.003	2/186 (1.1)	2/321 (0.6)	0.58
Total MABC-2 score, N§	568	963		77	92		343	608		148	263	
mean (SD)	10.0 (3.1)	10.6 (3.0)	0.002	7.6 (3.3)	9.4 (3.2)	<0.001	9.5 (3.3)	10.5 (3.0)	<0.001	10.8 (2.9)	10.4 (2.8)	0.21
≤ 5th percentile‡	68/568 (6.8)	46/963 (3.9)	0.032	20/77 (26.0)	13/92 (14.1)	0.053	44/343 (12.8)	24/608 (3.9)	<0.001	4/148 (2.7)	9/263 (3.4)	0.69
Sensory disability												
Moderate or severe disability¶	9/703 (1.2)	9/1069 (0.8)	0.46	2/106 (1.9)	2/103 (1.9)	0.98	5/429 (1.2)	5/685 (0.7)	0.45	2/168 (1.2)	2/281 (0.7)	0.60
Cognitive evaluation												
FSIQ score, N	718	1088		111	107		439	694		168	287	
mean (SD)	96.3 (14.6)	102.2 (13.7)	<0.001	91.0 (17.1)	98.7 (12.7)	<0.001	93.6 (15.2)	99.8 (13.8)	<0.001	98.1 (13.7)	103.6 (13.4)	<0.001
By categories‡												
<-3 to <-2 SD	107/728 (10.4)	54/1091 (4.4)	<0.001	27/114 (23.7)	3/107 (2.8)	<0.001	69/445 (15.5)	40/697 (5.7)	<0.001	11/169 (6.5)	11/287 (3.8)	0.007
-2 to <-1 SD	203/728 (27.9)	224/1091 (18.6)		29/114 (25.4)	29/107 (27.1)		127/445 (28.5)	146/697 (20.9)		47/169 (27.8)	49/287 (17.1)	
-1 to +1 SD or ≥1 SD	418/728 (61.7)	813/1091 (77.0)		58/114 (50.9)	75/107 (70.1)		249/445 (56.0)	511/697 (73.3)		111/169 (65.7)	227/287 (79.1)	
Behavioral evaluation												
Total SDQ score, N	719	1089		112	106		445	700		162	283	
mean (SD)	10.7 (5.5)	9.2 (5.7)	<0.001	11.6 (5.8)	9.5 (5.0)	0.004	11.6 (5.9)	9.5 (5.8)	<0.001	10.1 (5.2)	9.0 (5.6)	0.031
≥ 90th percentile‡	87/719 (9.1)	85/1089 (8.0)	0.52	16/112 (14.3)	4/106 (3.8)	0.007	61/445 (13.7)	58/700 (8.3)	0.003	10/162 (6.2)	23/283 (8.1)	0.4
Neurodevelopmental disabilities**												
Moderate/severe disability	113/713 (11.7)	61/1073 (4.9)	<0.001	28/113 (24.8)	4/105 (3.8)	<0.001	72/437 (16.5)	45/685 (6.6)	<0.001	13/163 (8.0)	12/283 (4.2)	0.008
Mild disability	282/713 (38.4)	337/1073 (28.9)		48/113 (42.5)	39/105 (37.1)		173/437 (39.6)	222/685 (32.4)		61/163 (37.4)	76/283 (26.9)	
None	318/713 (49.9)	675/1073 (66.1)		37/113 (32.7)	62/105 (59.0)		192/437 (43.9)	418/685 (61.0)		89/163 (54.6)	195/283 (68.9)	

Denominators vary according to the number of missing data for each variable.

* Included one survivor born at 23 weeks + 6 days.

† Percent are weighted to consider the differences in survey design between gestational age groups.

‡ Cut-off point of the distribution related to the reference group born at term (37-41 weeks).

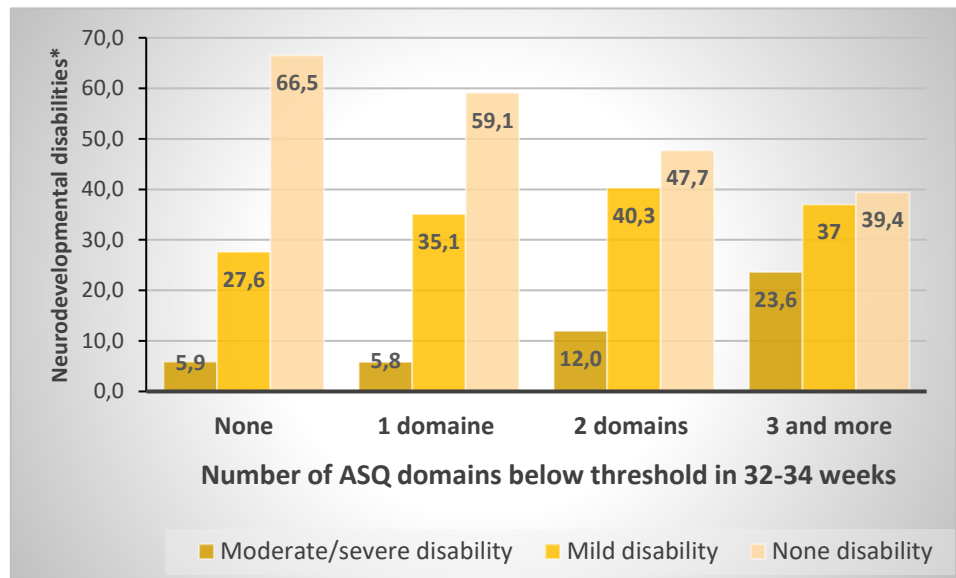
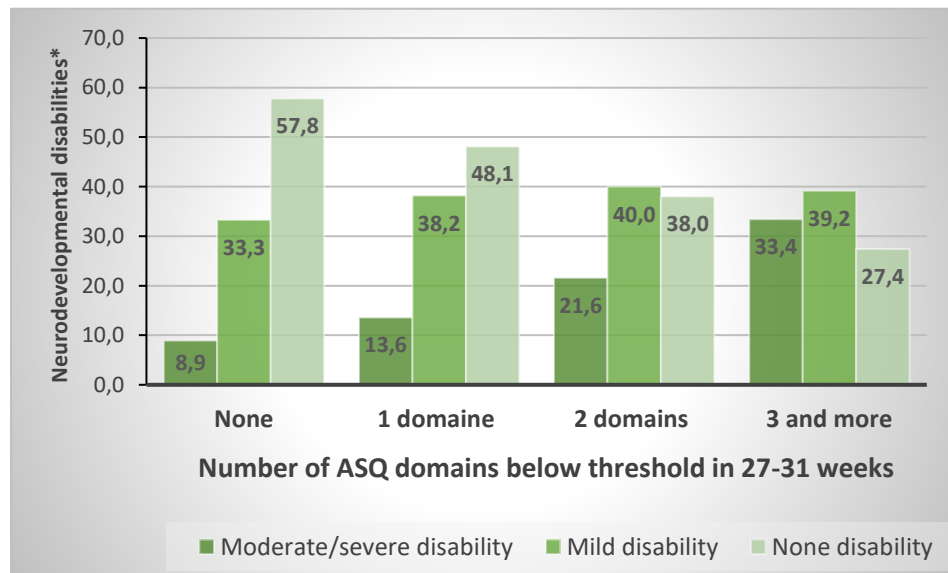
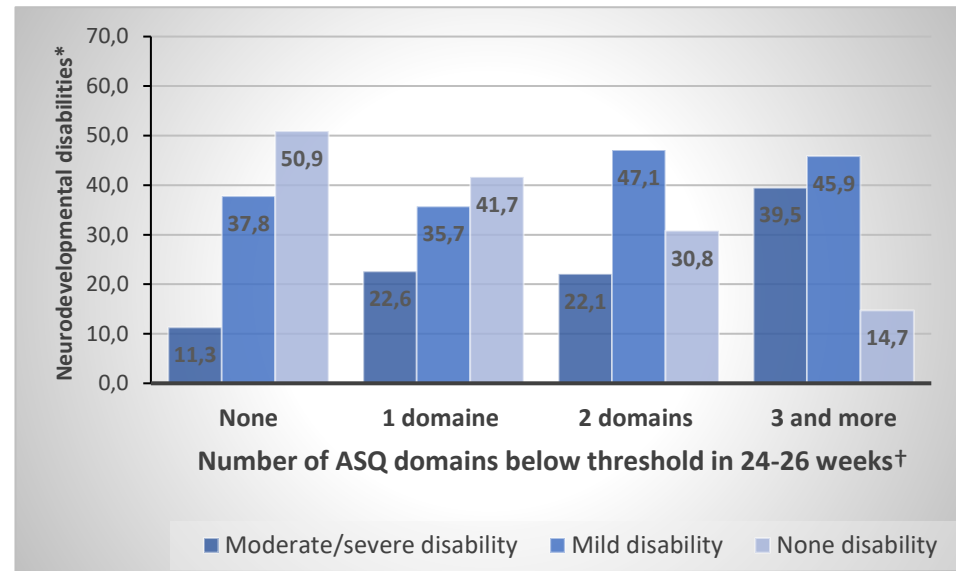
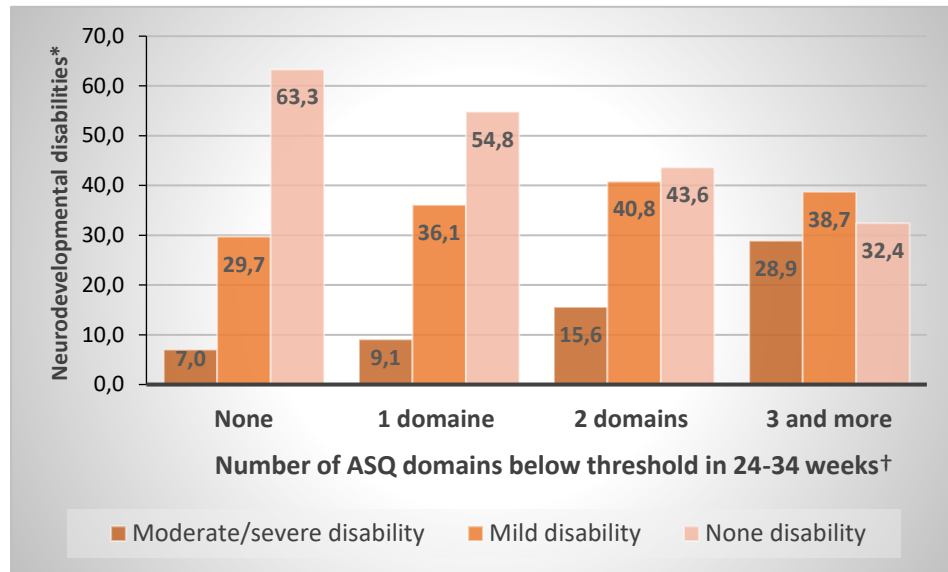
§ For children without cerebral palsy, severe or moderate vision or hearing disabilities, and full-scale intelligence quotient less than two standard deviations below the mean.

¶ Bilateral binocular visual acuity <3.2 to <1/10 or unilateral or bilateral hearing loss 40 to >70 dB not corrected or partially corrected with hearing aid.

** Includes cerebral palsy, vision, hearing, FSIQ, developmental coordination disorders, and behavioural difficulties (Table 1).

ASQ=Ages & Stages questionnaire (Squires, 2009); WPPSI-IV=Wechsler Preschool and Primary Scale of Intelligence, fourth edition (Wechsler, 2014); MABC-2 = Movement Assessment Battery for Children, second Edition (Henderson, 2007); SDQ= Strengths and Difficulties Questionnaire (Goodman, 1997); SD: Standard deviation.

eFigure 2: Neurodevelopmental disabilities* at age 5.5 years according to numbers of ASQ domain scores below threshold at 2 years' corrected age, N=2504.



Results after multiple imputation of missing 5 years outcomes. * Includes cerebral palsy, vision, hearing, full-scale intelligence quotient, developmental coordination disorders, and behavioural difficulties (Table 1). † Included one survivor born at 23 weeks + 6 days. ASQ=Ages & Stages questionnaire (Squires, 2009).