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Profiles of functioning in 5.5-year-old very preterm born children in France: the EPIPAGE-2 study

Running title:

Outcome profiles after preterm birth

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Abstract

Objective: Very preterm born children are at risk for impairments in multiple neurodevelopmental domains, but outcomes vary between individuals. The present study aimed to distinguish subgroups with distinct profiles of functioning across motor, cognitive, behavioral, and psychosocial domains. These profiles were related to neonatal and social/environmental factors.

Methods: The sample included 1977 children born very preterm (<32 weeks' gestation) in 2011 from the French population-based EPIPAGE-2 cohort. Using latent profile analysis, subgroups of children were distinguished based on their functioning at 5.5 years. The relation between outcome profiles and neonatal and social/environmental factors was tested using multivariable multinomial logistic regression analysis.

Results: Four subgroups with distinct outcome profiles were distinguished: no deficit in any domain (45%), motor and cognitive deficits without behavioral/psychosocial deficits (31%), primarily behavioral and psychosocial deficits (16%), and deficits in multiple domains (8%). Male sex (OR=2.1-2.7), bronchopulmonary dysplasia (OR=2.1-2.8), low parental education level (OR=1.8-2.1), and parental non-European migrant status (OR=2.3-3.0) were independently associated with higher odds for all suboptimal outcome profiles compared to the favorable outcome profile.

Conclusion: Among 5.5-year-old very preterm born children, subgroups can be distinguished with distinct outcome profiles that vary in severity, type, and combinations of deficits. This information is important for the development of interventions that are tailored to the needs of large subgroups of children across multiple domains of functioning. General neonatal and social/environmental factors may be useful for early identification of very preterm born children at risk for general rather than domain-specific impairments.

Very preterm birth (<32 weeks' gestation) is associated with poorer intelligence,¹ academic outcomes,¹ and motor skills,² and an increased risk for behavioral and socio-emotional problems³ compared to full-term birth. These neurodevelopmental outcomes have not improved over the last decades^{1,4,5} and impairments do not ameliorate when children grow older.⁶⁻⁹ Moreover, there is currently little evidence in support of intervention programs that meaningfully improve long-term neurodevelopmental outcomes after very preterm birth.¹⁰⁻¹² However, most studies evaluated outcomes or intervention effects at group level, without addressing the large heterogeneity in the population. Consequently, there is lack of insight in the specific needs of subgroups of children and it remains poorly understood which children have an increased risk for impairment and why. This limits early identification of high-risk infants who may benefit from close monitoring and early support and development of tailored prevention and intervention strategies.

Recently, studies started examining the heterogeneity in outcomes after extremely/very preterm birth by identifying subgroups of children with different outcome profiles. Burnett and colleagues¹³ found four subgroups of extremely preterm born children with distinct profiles of behavioral and social-emotional problems. In a study on intelligence and executive function in extremely preterm born children, four subgroups were distinguished that mainly differed in terms of severity of deficits.¹⁴ However, the extent to which a child is able to successfully adapt to and function in daily life is not determined by functioning in one isolated domain but by functioning across multiple inter-related developmental domains. Therefore, identification of subgroups based on functioning in multiple domains would give a better reflection of the overall impact of very preterm birth and proportions of children with and without impairments. In a small sample of 85 very preterm and 40 full-term children, Lean et al.¹⁵ recently described four subgroups based on cognitive, language, and motor performance, and behavioral and socio-emotional difficulties at 5 years of age. Of the very preterm born children, 27% had no

impairments, 45% showed a profile with mild cognitive, language, and motor problems, 13% had moderate to severe parent-rated behavioral/psychosocial difficulties, while for 15% these difficulties were only reported by teachers. Although limited by the small sample size, these findings suggest that meaningful subgroups with distinct profiles of difficulties across multiple developmental domains may be identified in the very preterm population.

In addition to insight in distinct outcome profiles among very preterm born children, early identification of problems, support, and development of interventions will benefit from knowledge about which children are most likely to show which specific outcomes. Heeren et al.¹⁴ and Burnett et al.¹³ described differences in gestational age (GA), sex, social risk, and maternal mental health between profiles. Lean et al.¹⁵ found that family but not neonatal risk was associated with different outcome profiles. However, the lack of an association with neonatal factors could also be explained by the small number of very preterm born children included in that study. In moderately/late preterm born children, Johnson et al.¹⁶ found that GA, sex, pre-eclampsia, breastfeeding, and socio-economic risk were associated with different cognitive and behavioral profiles at 5 years of age. The present study extends previous research by (1) identifying subgroups of children with distinct profiles of functioning across cognitive, motor, behavioral, and psychosocial domains in a large population-based cohort of very preterm born children in France (EPIPAGE-2) at 5.5 years of age, and (2) by studying the association between profiles and neonatal and social/environmental factors.

Methods

Study population

EPIPAGE-2 is a prospective population-based cohort study designed to follow-up preterm infants born at 22-34 weeks GA in France in 2011 until age 12 years.¹⁷ The present study is focused on outcomes of children born very preterm (<32 weeks' gestation) at 5.5 years of age.

Participants were recruited at birth. From all live born infants at 22-31 weeks GA, 3254 children were alive and eligible for follow-up at age 5.5 years, of which 2313 children participated in assessments (71.1%). Participant flow from birth to follow-up at 5.5 years is presented in **Figure 1**. One infant born at 22-23 weeks' gestation survived, who was lost to follow-up at 5.5 years. Infants born at 22-26 weeks GA were recruited during an eight-month-period and infants born at 27-31 weeks GA during six months.

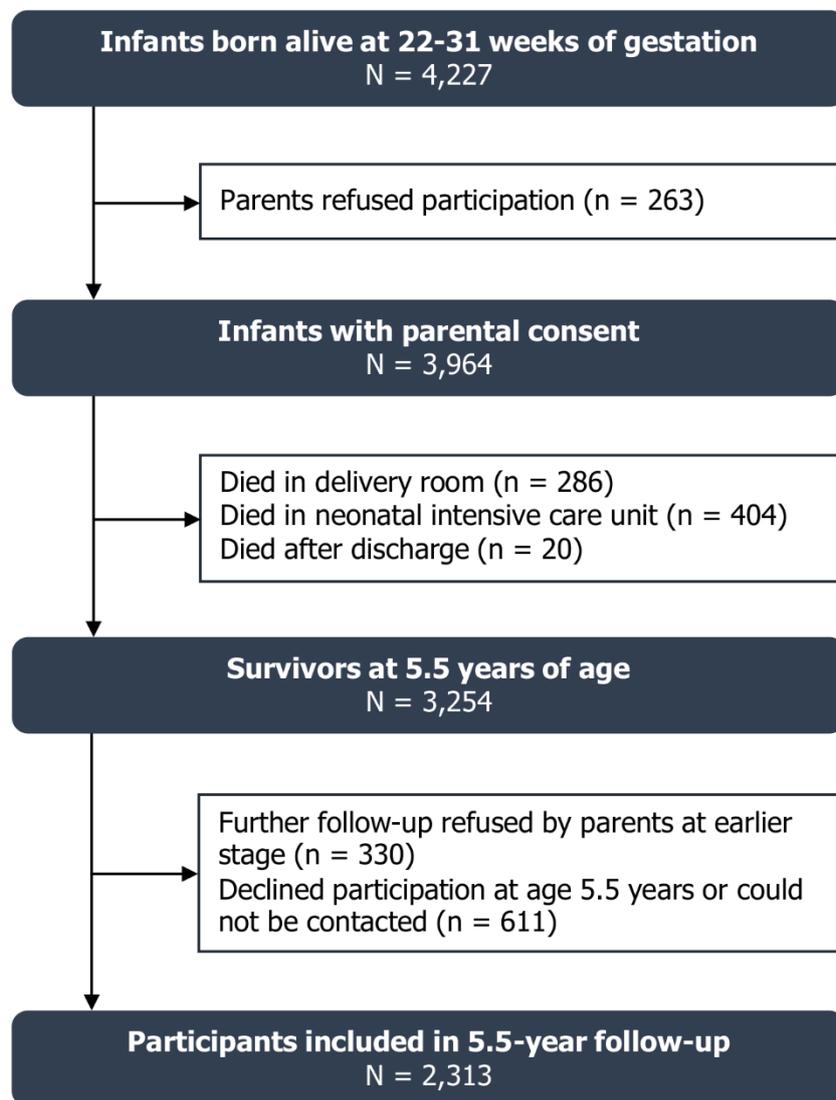


Figure 1: Participant Flow from Birth to Follow-Up at 5.5 Years of Age

A sample of 592 full-term peers (singletons, 37-40 weeks GA, born between September 27-December 5, 2011) was included as a reference sample. This sample was recruited from the population-based ELFE cohort ($N=18040$)¹⁸ to be assessed following the EPIPAGE-2 protocol. For financial and organisational reasons, 600 children could be assessed, which was sufficient to obtain estimates of main outcomes with good precision.¹⁹ From all eligible children ($N=3430$), 2846 parents agreed to participate, of whom 1405 parents were contacted. Recruitment was terminated after inclusion of the desired number of 600 children.¹⁹

Cognitive, motor, behavioral, and psychosocial functioning

The Wechsler Preschool and Primary Scale of Intelligence, fourth edition (WPPSI-IV) was used to assess cognitive abilities, using the indices verbal comprehension, visuospatial ability, fluid reasoning, working memory, and processing speed. Index scores were derived using age-specific norms. Indices have adequate to good internal consistency ($r=0.8-0.9$) and sufficient to good test-retest reliability ($r=0.6-0.8$).²⁰

The Movement Assessment Battery for Children, second edition (MABC-II)²¹ is a battery to test motor abilities in three domains: manual dexterity, aiming and catching, and balance. Subtests for the age band 3-6 years were administered. The test has age-standardized norms and test-retest reliability was sufficient to good for all domains ($r=0.7-0.8$).²¹

Parents rated their child's behavior on the 25 items of the Strengths and Difficulties Questionnaire (SDQ) to assess the degree of emotional symptoms, conduct problems, hyperactivity/inattention, and peer relationship problems. Subscale scores were only computed if the number of missing items per subscale was <3 (see <http://www.sdqinfo.org>). Internal consistency was low to moderate for peer and conduct problems ($\alpha=0.5-0.6$) and sufficient for emotional and hyperactivity/inattention problems ($\alpha=0.7-0.8$).²² Test-retest reliability was sufficient for all subscales ($r=0.7$).²²

The Social Communication Questionnaire (SCQ) was filled out by parents to rate symptoms of autism spectrum disorders on 40 items across three domains: social interaction, communication, and repetitive behavior. In line with Johnson et al.,²³ subscale scores were only computed for cases with <3 missing items on the repetitive behavior subscale and <4 missing items on the communication and social interaction subscales. In these cases, missing values were replaced by the most frequent value (0 or 1) within each subscale. Internal consistency of the SCQ was found to be good ($\alpha=0.8$).²⁴

Predictors of outcome profiles

Potential predictors of profiles of functioning were chosen based on previous studies,¹³⁻¹⁶ their known impact on brain function, and the incidence.¹ The following perinatal factors were included: sex, GA (weeks), small for gestational age (SGA; birth weight <10th percentile for GA and sex on French intrauterine growth curves²⁵), bronchopulmonary dysplasia (BPD; ≥ 28 days of >21% oxygen supply plus <30% oxygen (moderate) or $\geq 30\%$ oxygen and/or positive pressure (severe) at 36 weeks post-menstrual age²⁶), severe brain lesions (intraventricular hemorrhage grade 3/4, cystic periventricular leukomalacia), late onset sepsis (LOS; positive blood culture and ≥ 5 days antibiotics treatment), and receipt of breast milk at discharge (partly or exclusively). Socio-economic factors were measured at 5.5 years and included parental education level, as determined by the highest level of both parents or one parent in single-parent families (low: high school or lower; intermediate: post-secondary or short tertiary education; high: bachelor degree or higher), non-European country of birth of one or both parents (Maghreb, other African, other country), parent(s) without employment (one or both parents being unemployed or inactive), and single parenthood.

Procedure

The study was approved by the National Data Protection Authority (CNIL DR-2016-290), the Consultative Committee on Treatment of Information on Personal Health Data for Research Purposes (no. 16.263) and the Committee for Protection of People Participating in Biomedical Research (no. 2016-A00333-48). Written informed consent of both parents was required for participation in the 5.5-year follow-up. Participants were invited at one of the regional centers for assessments. The MABC-II was administered during medical assessment by a pediatrician. The WPPSI-IV was part of a battery of neuropsychological tests administered by trained psychologists. The SDQ and SCQ were completed by parents.

Statistical analysis

Data weighting. Data of the very preterm sample were weighted to account for differences in the recruitment duration between children born at GA <27 weeks and 27-31 weeks. Data of the ELFE cohort,¹⁸ from which the full-term sample was selected, were weighted to increase the representativeness of the sample for the general population of term-born children in France in 2011. More details are provided elsewhere.^{18,19}

Latent profile analysis. Mplus version 8 (Muthen & Muthen, 1998-2017) was used for all analyses. Mixture modeling, more specifically latent profile analysis (LPA), was performed to distinguish subgroups of very preterm born children based on 15 indicator variables, i.e. subscale scores of the WPPSI-IV, MABC-II, SDQ, and SCQ. Data of the full-term sample were not included in the LPA, but weighted means and standard deviations were used to indicate the degree of impairments in the very preterm sample. The model was adjusted for clustering of children within families with multiples. Missing data on indicator variables were treated using full-information maximum likelihood estimation.²⁷ Models with an increasing number of profiles were tested. Bayesian Information Criterion (BIC), sample-size adjusted BIC (aBIC),

and Lo-Mendell-Rubin (LMR) likelihood-ratio test were used to guide model selection.²⁸ Discrimination between profiles is indicated by the entropy. Classification probabilities describe the probability that a case is assigned to a certain subgroup instead of the other subgroups. In addition, the decision on the number of profiles was informed by the meaningfulness and size of subgroups.²⁹ Subsequently, relations between latent profiles and potential risk factors were explored in a multivariable multinomial logistic regression model, adjusting for classification error introduced with profile assignment³⁰ by using the R3STEP command implemented in Mplus. For GA, both linear and non-linear relations with latent profiles were considered. Missing values in predictor variables were imputed using Bayesian estimation with 20 imputed datasets²⁷ based on available data on all indicators and predictors in the model.

Results

Sample characteristics and missing data

A total of 1977 of the 2313 very preterm born children who participated in the follow-up at 5.5 years (85.5%) completed at least three of the four tests. This sample was used for the LPA. Sample characteristics are shown in *Table 1*. The percentage of missing data for the 15 indicators was 12%, with 94.2% of the sample having ≤ 1 missing values. The percentage of missing values across the 11 predictors was 16.7%. The vast majority of cases (93.4%) had missing values for ≤ 1 predictor. The percentages per variable are presented in *Table S1* (end of document). Missing data for indicators were associated with observed values on other indicators. The same was true for missing data for predictors (data available from author).

The study sample ($N=1977$) was compared with very preterm born children who participated but had too many missing values on the indicator variables (i.e. more than one of the four tests was not completed) ($n=336$) and with children who were alive and eligible for

follow-up but did not participate in the 5.5-year follow-up ($n=941$) on neonatal and parental characteristics and presence of disabilities (**Table 1**). Percentage of parent(s) with a low education level, without employment, born outside Europe, or single parenthood was lower among very preterm born children included in the analysis than those not included. These groups did not differ on neonatal characteristics, except that a higher percentage of children in the study sample received breast milk at discharge. Percentage of children with cerebral palsy and moderate to severe cognitive impairment was significantly lower in the study sample compared to the group of children who did not complete more than one of the tests. The full-term reference sample was representative for the general population in terms of sex, single parenthood, maternal country of birth, and maternal education level (see **Table S2**).

Table 1: Characteristics of Very Preterm Born Children Included and Not Included in the Analysis

	Very preterm study sample (N=1977)	More than 1/4 tests not completed (n=336)	No participation in 5-year follow-up (n=941)	<i>p</i>
Neonatal characteristics				
Sex, % male	52.5	49.5	52.9	0.44
Gestational age, weeks, <i>M (SD)</i>	28.9 (1.9)	29.1 (1.8)	29.0 (1.9)	0.73
Birth weight, grams, <i>M (SD)</i>	1217.0 (345.0)	1256.4 (332.2)	1239.7 (342.7)	0.89
Small for gestational age, %	36.5	32.5	34.8	0.22
Multiple birth, %	33.0	36.2	29.8	0.03 ^a
Breast milk at discharge, %	52.8	47.8	35.7	<0.001
Moderate/severe bronchopulmonary dysplasia, %	12.1	11.1	9.9	0.15
Severe brain lesions, %	5.0	4.5	5.8	0.50
Late onset sepsis, %	21.7	19.5	18.5	0.07
Parental characteristics				
Parental education level at 5.5 years				
High school or lower	37.4	52.2	NA	<0.001
Post-secondary or short tertiary education	26.0	20.8	NA	
Bachelor degree or higher	36.6	27.0	NA	
Maternal education level at birth				
Less than upper secondary education	45.3	56.3	68.4	<0.001
Upper/post-secondary or short tertiary education	24.5	19.5	16.8	
Bachelor degree or higher	30.2	24.2	14.8	
Parent(s) without employment at birth, %	32.6	42.1	54.9	<0.001
Parent(s) without employment at 5.5 years, %	41.1	53.6	NA	<0.001
Parental place of birth				
Metropolitan France	70.1	65.4	56.3	<0.001 ^b

French overseas territories	5.3	5.8	5.8	
Other European country	2.7	4.9	4.3	
Maghreb country	9.5	13.5	12.9	
Other African country	7.5	6.5	12.1	
Other country	4.8	4.0	8.7	
Single parenthood at birth	7.1	8.4	13.4	<0.001 ^c
Single parenthood at 5.5 years	13.3	12.0	NA	0.50
Disability at age 5.5 years				
Cerebral palsy, ^d %	5.3	8.1	NA	0.02
Moderate/severe neurosensory impairment, ^e %	1.6	2.7	NA	0.48
Motor impairment, ^f %	12.8	15.1	NA	0.56
Cognitive impairment, ^g %	11.9	22.9	NA	0.02

Note: Percentages, means (M), standard deviations (SD) and corresponding chi-square and *t*-tests were weighted according to sampling weights.

^a Differences were not significant between the study sample and children who did not complete more than one of the four tests ($\chi^2(1)=1.70, p=0.19$) and between the study sample and children who were lost to follow-up ($\chi^2(1)=3.79, p=0.05$); ^b For the difference between the study sample and children who did not complete more than one of the four tests, test statistics were $\chi^2(5)=314.01, p=0.02$; ^c Differences were not significant between the study sample and children who did not complete more than one of the four tests ($\chi^2(1)=0.84, p=0.36$); ^d Any level of severity (Gross Motor Function Classification System level 1 or higher); ^e Binocular visual acuity <3.2/10 and/or uni- or bilateral hearing loss >40 dB not or partially corrected with hearing aids; ^f Total score Movement Assessment Battery for Children II <5th percentile of the full-term sample; ^g Full-scale IQ more than 2 SD below the mean of the full-term sample.

Model selection

Model fit statistics are presented in *Table S3*. LMR pointed to a model with four latent profiles. BIC and aBIC continued to decrease, although to a lesser extent, when fitting a five-profile model, but this resulted in one profile comprising a very small proportion of the sample (4%). In the four-profile model, one of the profiles also represents a relatively small percentage of children (8%). However, this profile is also distinguished in the three-profile model and describes an important subgroup of children, namely those children with the poorest outcomes. Considering both statistical information and qualitative differences between profiles, the four-profile model was selected.

Profiles of functioning

The four profiles are plotted in *Figure 2*. Two groups of profiles can be distinguished: one profile describing favorable outcomes across domains (45%) and three profiles describing suboptimal functioning (55%). The first is called the “favorable outcomes” profile, because functioning is highly similar to the full-term sample in all domains (within 0.5 SD), with significantly less symptoms of hyperactivity/inattention, conduct, and social problems. From the profiles describing suboptimal functioning, the “behavioral/psychosocial difficulties” profile was found in 16% of the children and mainly characterized by mild behavioral and psychosocial difficulties (~1 SD below full-term children). In contrast, 31% showed low-average to mildly impaired motor and cognitive functioning (~1 SD below full-term children) in absence of behavioral and psychosocial difficulties (“motor/cognitive deficits” profile). Lastly, a relatively small percentage of children (8%) showed a profile with mild to moderate difficulties in all domains (~1 to >2 SD below full-term children), except conduct and emotional problems. This profile is called “multidomain impairments”.

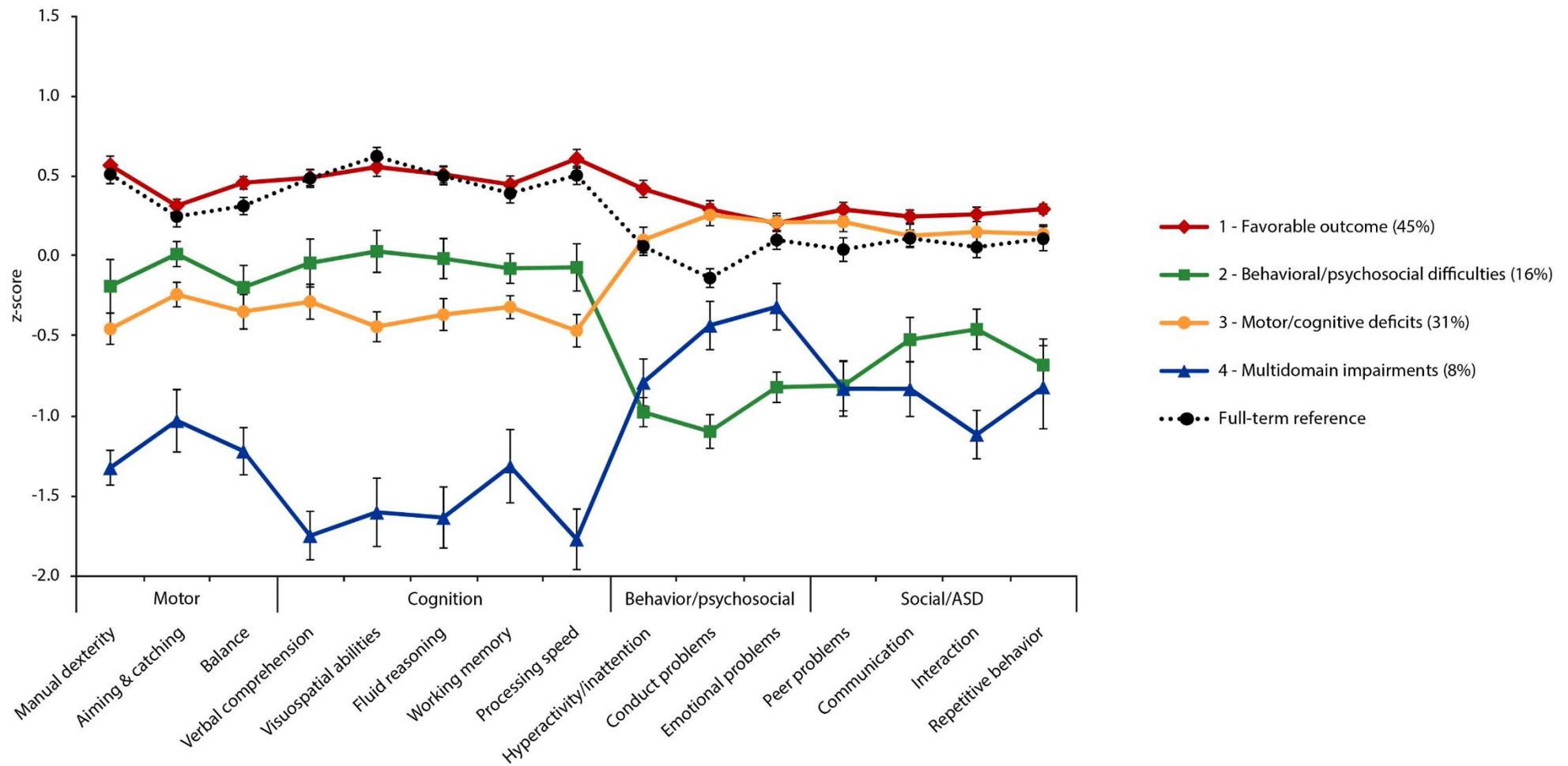


Figure 2: Estimates of Functioning Across Domains for the Four Latent Profiles

Note: Functioning of full-term children is plotted as a reference (dotted line). Scores for both the very preterm and full-term sample were standardized according to the very preterm sample (i.e. $z=0$ corresponds to the weighted mean of the very preterm sample) and scaled so that a lower z-score reflects poorer performance or an increase in difficulties for all indicators

Relation with risk factors

Figure 3 shows the results of the multivariable multinomial logistic regression model. For GA, a linear term was included in the model since bivariate regression analyses showed significant effects for the linear as opposed to quadratic ($p=0.57-0.76$) and cubic ($p=0.23-0.85$) terms. Male sex, BPD, low parental education level, parent(s) being born outside Europe, and having parent(s) without employment were independently associated with increased odds of all three suboptimal outcome profiles in comparison to the favorable outcome profile. For example, when all other risk factors in the model were taken into account, boys had 2.7 times higher odds than girls to show a profile of behavioral/psychosocial difficulties as opposed to a favorable outcome profile. When controlling for other factors, GA and SGA were only negatively associated with a profile of multidomain impairments and not with behavioral/psychosocial or motor/cognitive deficits. LOS, receipt of breast milk, and single parenthood were not independently associated with any profile. *Table S4* presents characteristics of the four subgroups according to outcome profile, classified based on the highest probability for one of the profiles.

Further specification of results according to parental place of birth is shown in *Table S5*. For children from parent(s) born in Maghreb or other African countries odds for all three suboptimal profiles were increased compared to children of whom both parents were born in Metropolitan France/Europe. For children from parent(s) born in other non-European countries or in French overseas territories odds were higher for behavioral/psychosocial and multidomain impairments but not motor/cognitive deficits. Results for the latter group may mainly be driven by the large proportion of these children who were born in the overseas territories themselves (70%), which was associated with increased odds for multidomain (OR=5.06, 95% CI 2.75, 9.31) and behavioral/psychosocial difficulties (OR=2.44, 95% CI 1.29, 4.62). It should be noted that confidence intervals for all these results are wide (see *Table S5*), requiring cautious interpretation.

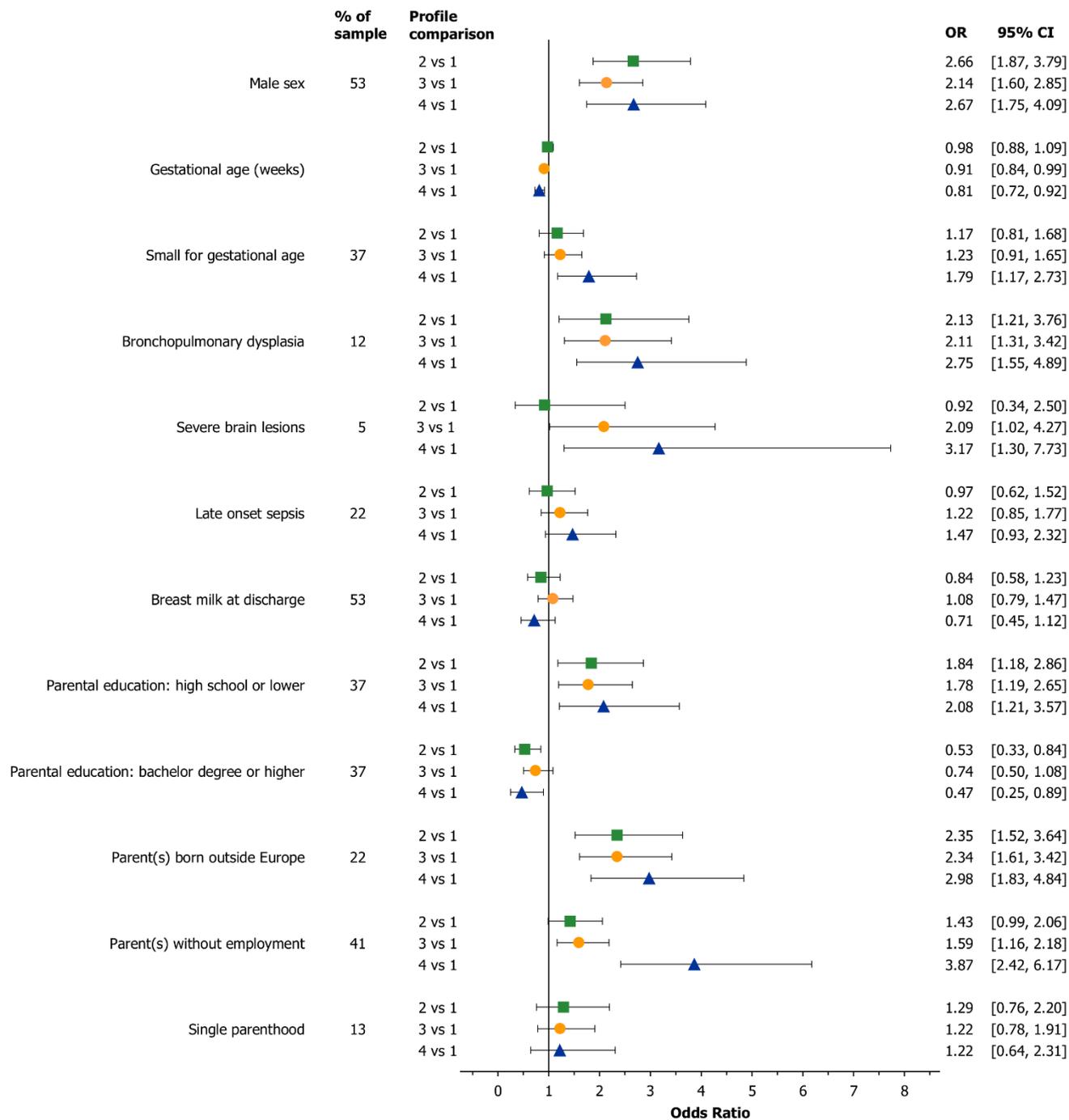


Figure 3: Odds Ratios for the Relation Between Predictors and Suboptimal Outcome Profiles Relative to the Favorable Outcome Profile

Note: 1 = “favorable outcome”, 2 = “behavioral/psychosocial difficulties”, 3 = “motor/cognitive deficits”, 4 = “multidomain impairments”.

A few predictors were associated with differences in odds between the multidomain impairments profile and the other two suboptimal outcome profiles. Parental non-European immigrant status (OR=1.72, 95% CI 1.11, 2.66) and unemployment/inactivity (OR=2.35, 95% CI 1.46, 3.78) were associated with increased odds for multidomain impairments as opposed to mild motor/cognitive deficits. Lower GA (weeks; OR=1.20, 95% CI 1.05, 1.37), severe brain lesions (OR=3.40, 95% CI 1.12, 10.34), and unemployed/inactive parents (OR=2.63, 95% CI 1.57, 4.43) were associated with higher odds for multidomain impairments than a profile with mainly behavioral/psychosocial difficulties. None of the predictors were associated with differences in odds between the behavioral/psychosocial and motor/cognitive difficulties profiles.

Discussion

The present study is the first large-scale study to identify subgroups of very preterm born children according to their motor, cognitive, behavioral, and psychosocial functioning at 5.5 years of age in a population-based cohort of 1977 children. Four subgroups were distinguished, each showing a different profile of outcomes. A large minority of children (45%) showed no difficulties in any of the developmental domains. The majority (55%) of 5.5-year old very preterm born children showed one of three suboptimal outcome profiles that differed in severity, type, and combination of difficulties: 31% of the children showed low-average to mildly impaired motor and cognitive functioning in absence of behavioral and psychosocial difficulties, 16% had mild behavioral and psychosocial symptoms with low-average motor and cognitive functioning, and 8% showed moderate motor and cognitive deficits, in combination with mild hyperactivity/inattention and social/ASD symptoms. Male sex, BPD, low parental education level, and parental non-European migrant status were the most important predictors

of suboptimal outcome, increasing the odds for all three suboptimal outcome profiles. In contrast, few factors could distinguish between these suboptimal profiles.

The findings indicate clearly distinct profiles of functioning in subgroups of very preterm born children, in which children differ with respect to both the severity and the type of deficits that are predominant. Motor and cognitive performance differed between the profiles mainly in terms of severity of deficits. Within subgroups, motor and cognitive difficulties co-occurred with similar levels of severity. In a review, Diamond³¹ pointed at the close interrelationship between motor and cognitive development, given the co-occurrence of motor and cognitive difficulties in a variety of developmental disorders, similar time scales of development, and overlap in brain regions activated during cognitive and motor tasks. Executive processes that rely on large-scale brain networks have been identified as an important underlying mechanism of the relation between motor and cognitive development.³² Deficits in these processes and underlying brain networks have been widely reported in very preterm born children and in a range of developmental psychopathologies,^{33,34} which may explain the co-occurrence of motor and cognitive deficits across clinical populations.

The two profiles with behavioral and psychosocial difficulties, the “behavioral/psychosocial difficulties” and “multidomain impairments” profiles, described similar levels of hyperactivity/impulsivity and peer problems. However, the “multidomain impairments” profile showed generally increased ASD symptomatology, while in the “behavioral/psychosocial difficulties” profile hyperactivity/impulsivity and peer problems co-occurred particularly with conduct and emotional problems. This suggests that the similar levels of peer relationship problems in both profiles may have different underlying mechanisms. The co-occurrence of peer, conduct, and emotional problems has been described by Van Lier et al.,³⁵ who found some evidence that externalizing problems in early childhood hamper peer relationships, resulting in internalizing problems. Moreover, peer problems, more specifically

victimization by peers, worsened externalizing problems. Meta-analytic findings indeed showed that peer victimization can both precede and result from externalizing problems.³⁶ Extremely and very preterm born children are vulnerable for peer victimization which predicted later emotional problems.³⁷ Although conduct problems have not frequently been reported after very preterm birth at the group level, the present study and findings from Burnett et al.¹³ show there is a significant proportion of children with conduct problems that may affect peer relationships and emotional development.^{35,37} However, Burnett et al.¹³ showed that these problems do not necessarily co-occur. Further research on the co-occurrence of these symptoms is of interest to understand their potential interaction. The SDQ does not distinguish between hyperactivity and inattention, but these symptoms may also differ between profiles, with primarily hyperactivity in the “behavioral/psychosocial difficulties” profile and inattention in the “multidomain impairments” profile.³⁸ In sum, similar symptoms of behavioral and psychosocial problems in very preterm born children may have different underlying mechanisms and co-occurring problems in different subgroups of children and may thus require different approaches for treatment.

To facilitate early detection of problems in high-risk infants and to provide targeted prevention and intervention, it is important to understand which children are most at risk for which problems. We found a number of factors that were independently associated with suboptimal outcomes after very preterm birth, albeit with small non-significant differences in the strengths of the associations between the suboptimal outcome profiles. The odds for any of the three suboptimal profiles compared to an optimal outcome was on average 2.5 times higher for boys, 2.4 times higher for children with BPD, 1.9 times higher when parents had a low education level, and 2.5 times higher when parent(s) were non-European migrants. In a Swedish population-based study,³⁹ extremely preterm born girls outperformed boys at 2.5 years of age, while there were no sex differences for neonatal and socio-economic factors. These factors had

generally similar effects on outcomes in both sexes, with only a few sex-specific effects.³⁹ The present study also showed increased impairments in boys independent from neonatal morbidities and socio-economic factors. These findings thus suggest a specific vulnerability in boys for difficulties across developmental domains. In the general population, males have an increased risk for early-onset disorders, while females are overrepresented in adolescent-onset disorders.⁴⁰ Most research after very preterm birth has been conducted in (early) childhood. More research in adolescence and adulthood is needed to understand whether impairments after very preterm birth are characterized by an overall male preponderance or whether this is age-dependent.

When looking at birth characteristics and neonatal morbidities, BPD was the most important risk factor, being associated with all suboptimal outcome profiles. This is in line with findings from a multivariable meta-regression analysis of cognitive outcomes¹ and bivariate analysis of motor, academic, and behavioral/psychosocial outcomes.^{41,42} Given the relatively high incidence in current populations of extremely preterm born infants,⁴³ the present findings indicate that BPD is an important factor for the identification of children with an increased risk for long-term impairments and may be a key target for prevention and interventions to improve outcomes, although the exact mechanisms underlying this association remains to be elucidated. GA, SGA, and severe brain lesions increased the odds for “multidomain impairments” but not for milder domain-specific problem profiles. Receipt of breast milk at discharge did not decrease the odds for any suboptimal profile compared to a favorable outcome profile. Generally, evidence supports the beneficial effects of breast milk on neurodevelopmental outcomes after very preterm birth.^{16,44-46} However, studies in preterm and full-term children showed diminished or non-significant effects of breast milk after controlling for socioeconomic factors and parental IQ.^{44,47} This was also seen in the present study. When socioeconomic and sociodemographic factors were taken into account, receipt of breast milk could not distinguish

very preterm born children with favorable and suboptimal outcome profiles. Another explanation for this finding may be that 47% of very preterm born infants in France received breast milk at discharge⁴⁸ of whom only 36% received breast milk at six months,⁴⁹ while associations with long-term neurodevelopmental outcomes are most pronounced with prolonged breastfeeding.^{50,51}

Low parental education level was independently associated with increased odds for any suboptimal outcome profile compared to a favorable outcome. Parental education level may affect preterm birth outcomes in multiple ways through parenting, health-related behavior before, during, and after pregnancy, access to high-quality healthcare and education, and better socio-economic position of the family and neighborhood.⁵² Independent of education level of parents, their country of birth (i.e. non-European country) was one of the most important predictors of suboptimal outcomes. Possible mechanisms include the worse position of non-European minorities on the French labor market irrespective of education,^{53,54} increased maternal mental health problems among first-generation immigrant mothers in France⁵⁵ that may be further increased in mothers of preterm children⁵⁶ and impact children's development,⁵⁷ and increased rates of unmet health care needs among minorities in France,⁵⁸ which have all been associated with perceived discrimination.⁵⁸⁻⁶⁰ Other potential mechanisms include lower attendance in preschool education programs⁶¹ and multilingualism, which has been associated with poorer cognitive outcomes after very preterm birth.⁶² Our findings remain largely inconclusive regarding more specific differences based on parental place of birth due to unprecise estimates, although outcomes were poorer in all specified minority groups. Moreover, place of birth is a proxy of ethnicity/race that may not capture diversity as covered by this broader concept. The findings nevertheless call for insight in factors contributing to the poorer outcomes of children from non-European migrants and disadvantaged socio-economic backgrounds, the needs of these families, and how to improve their access to services.

The findings should be interpreted in light of the study's limitations. The study sample, derived from a large representative population-based cohort, was representative for the very preterm population in terms of neonatal characteristics, but seemed selective in terms of social characteristics and disabilities. Given the importance of social factors for long-term outcomes, the proportions of children with suboptimal outcome profiles likely underestimate proportions and severity of impairments at the population level. However, severity was implicated by performance of a full-term reference sample, in which we also found evidence for similar forms of selection bias. This could imply that performance in both the very preterm and full-term reference sample was better than in the population. In contrast, behavioral/psychosocial symptoms were increased in our full-term reference sample compared to the total ELFE cohort,¹⁹ to a French SDQ validation study,⁶³ and to the very preterm subgroup with a favorable outcome profile. This may impact the interpretation of the severity of behavioral/psychosocial symptoms specifically, but does not affect our conclusions on which symptoms are predominant in which subgroups of very preterm born children. Another limitation is the use of a single- instead of multi-informant approach to assess behavioral/psychosocial functioning. Moreover, diagnostic instruments are preferable over screening tools, although less feasible in large-scale national studies. Lastly, outcome profiles were associated with important perinatal and social/environmental characteristics, but did not include parental mental health problems, which are increased in the preterm population⁵⁶ and known to be associated with suboptimal child development.⁵⁷

The present findings make an important contribution to our understanding of the core deficits and co-occurrence of problems in subgroups of very preterm born children. More than half of the 5.5-year-old children (55%) had motor and cognitive problems that co-occurred with similar levels of severity. A quarter of the very preterm born children showed additional behavioral/psychosocial problems: those with mild motor and cognitive deficits experienced

mainly hyperactivity/inattention, conduct, emotional, and peer problems, while more severe motor and cognitive deficits mainly co-occurred with symptoms of hyperactivity/inattention and ASD. These findings imply that similar problems may have a different etiology in different subgroups of children and may require a different approach of intervention and support. Although the findings need replication, the information is useful for the development of targeted interventions and support that is tailored to the needs of large subgroups of children across multiple domains of functioning. Moreover, the findings suggest that general demographic, neonatal, and social/environmental factors that are available at the time of discharge may be useful for the identification of very preterm born children with an increased risk for impairments. However, these factors were associated with a general rather than domain-specific vulnerability. Further research is necessary to determine how accurately such factors can predict the risk for impairments in individual infants.

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Supplemental material

Table S1: Percentage of Cases in Study Sample (N=1977) with Missing Values for Each Variable Included as Indicator in the Latent Profile Analysis or as Predictor in the Multiple Multinomial Logistic Regression Model

	% of missing data
Indicators	
<i>MABC-II</i>	
Manual dexterity	3.2
Aiming and catching	3.2
Balance	4.8
<i>WPPSI-IV</i>	
Verbal comprehension	1.8
Visuospatial abilities	1.6
Fluid reasoning	1.8
Working memory	2.0
Processing speed	2.2
<i>SDQ</i>	
Hyperactivity/inattention	0.5
Conduct problems	0.4
Emotional problems	0.6
Peer problems	0.6
<i>SCQ</i>	
Communication	3.2
Interaction	1.6
Repetitive behavior	1.4
Predictors	
Sex	0.0
Gestational age	0.0
Small for gestational age	0.0
Bronchopulmonary dysplasia	1.7
Brain lesions	1.4
Late onset sepsis	1.3
Breast milk at discharge	5.9
Parental education level	6.4
Parent(s) born outside Europe	0.4
Parent(s) without employment	5.6
Single parenthood	5.9

Table S2: Characteristics of Full-Term Reference Sample and General Population Sample

	Full-term reference sample present study (N=592)	General population sample (N=14903) ^a
Male sex	53.6	52.3
Single parenthood at time of birth	6.1	7.3
Mothers born outside Europe	15.8	14.3
Maternal education level at time of birth, <i>high school or lower</i>	43.3	48.2

Note: Data are presented as percentages. For the full-term reference sample, these percentages were weighted to increase the representativeness of the sample (see Charles et al.¹⁸).

a. Data were derived from the French National Perinatal Survey 2010, which comprised all births in metropolitan France at a gestational age of ≥ 22 weeks and with a birth weight ≥ 500 grams between March 15-28, 2010 (see Blondel et al.⁶⁰).

Table S3: Model Fit Statistics

Number of profiles	Log-likelihood	Entropy	BIC	aBIC	LMR, <i>p</i> -value	Classification probabilities	Class proportions				
							1	2	3	4	5
2	-39528	0.8	79405	79259	<0.001	0.92-0.97	72%	28%			
3	-39009	0.8	78489	78292	0.02	0.90-0.92	8%	51%	41%		
4	-38625	0.8	77841	77593	0.02	0.85-0.91	8%	31%	45%	16%	
5	-38420	0.8	77553	77255	0.11	0.79-0.92	7%	15%	31%	42%	4%

Note: BIC, Bayesian Information Criterion; aBIC, sample-size adjusted Bayesian Information Criterion; LMR, Lu-Mendell-Rubin likelihood-ratio test. Lower BIC and aBIC indicate improved model fit and an LMR *p*-value <0.05 indicates improved model fit compared to the model with one profile less.

Table S4: Characteristics of the Subgroups According to Outcome Profile

	Favorable outcome	Behavioral/ psychosocial problems	Motor/ cognitive problems	Multidomain impairments
Demographic characteristics				
Male sex	44.9	61.8	57.4	60.2
Age at assessment, <i>years, M (SD)</i>	5.6 (0.2)	5.6 (0.2)	5.6 (0.2)	5.6 (0.2)
Neonatal characteristics				
Gestational age, <i>weeks, M (SD)</i>	29.1 (1.8)	29.0 (1.8)	28.7 (1.9)	28.2 (2.0)
Birth weight, <i>grams, M (SD)</i>	1259.0 (330.0)	1233.7 (347.8)	1186.2 (356.1)	1068.4 (329.1)
Small for gestational age	34.1	37.6	37.3	44.5
Multiple birth	35.4	26.2	35.2	23.5
Breast milk at discharge	55.9	48.0	54.1	38.6
Moderate/severe bronchopulmonary dysplasia	8.0	13.0	14.8	23.3
Severe brain lesions	3.7	3.4	6.4	9.9
Late onset sepsis	17.9	19.8	24.9	34.5
Parental characteristics at 5.5 years				
Parental education level				
High school or lower	27.1	47.1	42.6	57.3
Post-secondary or short tertiary education	26.6	27.1	25.0	24.8
Bachelor degree or higher	46.2	25.8	32.4	17.9
Parent(s) without employment	32.3	44.8	45.5	67.2
Parental place of birth				
Metropolitan France	77.5	63.7	66.2	55.2
French overseas territories	3.9	7.6	4.9	10.8
Other European country	2.9	2.7	2.7	1.9
Maghreb country	6.8	12.0	12.0	10.5
Other African country	5.2	8.0	9.5	12.2
Other country	3.7	6.0	4.7	9.4
Single parenthood	11.0	15.3	14.6	17.7
Disability at 5.5 years				
Cerebral palsy ^a	1.4	4.1	7.8	19.6
Moderate/severe neurosensory impairment ^b	0.5	1.5	2.2	7.5
Motor impairment ^c	0.6	12.2	21.7	66.6
Cognitive impairment ^d	0.1	4.7	15.5	88.4

Note: Values are percentages unless otherwise indicated. Percentages, means (M), and standard deviations (SD) were weighted according to sampling weights. ^a Any level of severity (Gross Motor Function Classification System level 1 or higher). ^b Binocular visual acuity <3.2/10 and/or uni- or bilateral hearing loss >40 dB not or partially corrected with hearing aids. ^c Total score Movement Assessment Battery for

Children II <5th percentile of the full-term sample. ^d Full-scale IQ >2 SD below the mean of the full-term sample.

Table S5: Odds Ratios (95% Confidence Interval) for the Three Suboptimal Outcome Profiles as Opposed to a Favorable Outcome Profile According to Parental Place of Birth

	Behavioral/psychosocial difficulties	Motor/cognitive deficits	Multidomain impairments
Parental place of birth			
Metropolitan France or other European country	reference	reference	reference
French overseas territory	2.78 (1.36, 5.68)	1.51 (0.76, 3.00)	4.94 (2.33, 10.47)
Maghreb country	2.64 (1.48, 4.71)	2.46 (1.48, 4.11)	2.36 (1.14, 4.88)
Other African country	2.56 (1.16, 5.63)	2.92 (1.50, 5.65)	4.32 (1.94, 9.64)
Other country	2.42 (1.05, 5.58)	1.75 (0.85, 3.63)	5.24 (2.33, 11.80)

Note: Odds ratios were derived from a multivariable multinomial logistic regression model (imputed) including the same variables as shown in Figure 3: male sex, gestational age, small for gestational age, bronchopulmonary dysplasia, severe brain lesions, late onset sepsis, breastmilk at discharge, parental education level, parent(s) without employment, single parenthood.