

Child Neuropsychology

A Journal on Normal and Abnormal Development in Childhood and Adolescence

ISSN: (Print) (Online) Journal homepage: <https://www.tandfonline.com/loi/ncny20>

CE Are multidisciplinary neurodevelopmental profiles of children born very preterm at age 2 relevant to their long-term development? A preliminary study

Inge L. van Noort-van der Spek, Lottie W. Stipdonk, André Goedegebure, Jeroen Dudink, Sten Willemsen, Irwin K. M. Reiss & Marie-Christine J. P. Franken

To cite this article: Inge L. van Noort-van der Spek, Lottie W. Stipdonk, André Goedegebure, Jeroen Dudink, Sten Willemsen, Irwin K. M. Reiss & Marie-Christine J. P. Franken (2022)

CE Are multidisciplinary neurodevelopmental profiles of children born very preterm at age 2 relevant to their long-term development? A preliminary study, *Child Neuropsychology*, 28:4, 437-457, DOI: [10.1080/09297049.2021.1991296](https://doi.org/10.1080/09297049.2021.1991296)

To link to this article: <https://doi.org/10.1080/09297049.2021.1991296>



© 2021 The Author(s). Published by Informa UK Limited, trading as Taylor & Francis Group.



[View supplementary material](#)



Published online: 02 Nov 2021.



[Submit your article to this journal](#)



Article views: 681



[View related articles](#)




[View Crossmark data](#)



Citing articles: 1 [View citing articles](#)



CE Are multidisciplinary neurodevelopmental profiles of children born very preterm at age 2 relevant to their long-term development? A preliminary study

Inge L. van Noort-van der Spek ^{a*}, Lottie W. Stipdonk^{a*}, André Goedegebure^a, Jeroen Dudink^{b,c}, Sten Willemsen^d, Irwin K. M. Reiss^b and Marie-Christine J. P. Franken^a

^aDepartment of Otorhinolaryngology, Erasmus University Medical Center-Sophia Children's Hospital, Rotterdam, Netherlands; ^bDivision of Neonatology, Department of Pediatrics, Erasmus University Medical Center-Sophia Children's Hospital, Rotterdam, Netherlands; ^cDivision of Neonatology, Department of Pediatrics, UMCU-Wilhelmina Children's Hospital, Utrecht, Netherlands; ^dDepartment of Biostatistics, Erasmus Medical University Center, Rotterdam, Netherlands

ABSTRACT

To identify distinctive multidisciplinary neurodevelopmental profiles of relatively healthy children born very preterm (VPT) and describe the longitudinal course of these profiles up to age 10. At 2 years of corrected age, 84 children born VPT underwent standardized testing for cognitive, language, speech, motor, behavioral, and auditory nerve function. These data were submitted to factor and cluster analysis. Sixty-one of these children underwent cognitive, language, and behavioral assessment again at age 10. Descriptive statistics were used to analyze longitudinal trajectories for each profile. Four neurodevelopmental profiles were identified at age 2. Profile 1 children ($n = 22/26\%$) had excellent cognitive-language-motor function, normal behavioral and auditory nerve function, but showed an unexpected severe decline up to age 10. Profile 2 children ($n = 16/19\%$) had very low behavioral function, low cognitive-language-motor function, and accelerated auditory nerve function. Their scores remained low up until age 10. Profile 3 children ($n = 17/20\%$) had delayed auditory nerve function, low behavioral function, and slightly lower cognitive-language-motor function. They showed the most increasing trajectory. Profile 4 children ($n = 29/35\%$) had very low cognitive-language-motor function, normal behavioral and auditory nerve function, but showed wide variation in their trajectory. Our preliminary study showed that a multidisciplinary profile-oriented approach may be important in children born VPT to improve counseling and provide targeted treatment for at risk children. High performers at age 2 may not be expected to maintain their favorable development. Behavioral problems might negatively impact language development. Delayed auditory nerve function might represent a slow start and catch-up development.

ARTICLE HISTORY


Received 11 March 2021
Accepted 6 October 2021

KEYWORDS

Language; cognition;
behavior; prematurity;
longitudinal development

CONTACT Inge L. van Noort-van der Spek  i.vannoort-vanderspek@erasmusmc.nl; Lottie W. Stipdonk  l.stipdonk@erasmusmc.nl  Department of Otorhinolaryngology, Erasmus University Medical Center-Sophia Children's Hospital, Rotterdam, Netherlands

*Shared co-first authorship.

 Supplemental data for this article can be accessed at <https://doi.org/10.1080/09297049.2021.1991296>.

© 2021 The Author(s). Published by Informa UK Limited, trading as Taylor & Francis Group.

This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License (<http://creativecommons.org/licenses/by-nc-nd/4.0/>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited, and is not altered, transformed, or built upon in any way.

Children born very preterm (VPT, <32 weeks' gestation) have repeatedly been shown to have neurodevelopmental problems that often persist throughout childhood and into adolescence (Aarnoudse-Moens et al., 2009; Barre et al., 2011; Lean et al., 2018; Nguyen et al., 2018; Pascal et al., 2018; Stipdonk et al., 2020; Van Noort-van der Spek et al., 2012; Wong et al., 2016; Zimmerman, 2018). A large number of studies have shown developmental problems on single neuro-cognitive domains in children born VPT, such as poor cognitive functions (Aarnoudse-Moens et al., 2009), language functions (Nguyen et al., 2018; Van Noort-van der Spek et al., 2012, 2010) and behavioral problems (Arpi & Ferrari, 2013). In the auditory domain, Auditory Brainstem Response (ABR) has been used to identify abnormal neural development, mainly reflected by delayed auditory conduction time toward and into the brainstem at term equivalent age (Stipdonk et al., 2016). As several studies have found a relation between abnormal ABR and long-term neurodevelopmental problems in preterm children (Mainemer & Rosenblatt, 1996; Wang et al., 2020), ABR measures may also be relevant to neurocognitive development of children born VPT. Moreover, two meta-analyses reported increasing neurodevelopmental difficulties in children born VPT throughout school age, suggesting a growing into deficits effect (Van Noort-van der Spek et al., 2012; Wong et al., 2016). The first meta-analyses evaluated language function between 2 and 12 years of age and the second evaluated early cognitive developmental between 1 and 3 years of age and cognitive outcomes at ≥ 5 years of age. These results are alarming, since neurodevelopmental problems significantly impact academic abilities and social functioning (Doyle & Anderson, 2010; Marlow, 2004). However, a substantial proportion of children born VPT did not have any problems, and a small group even showed a catch-up effect at adolescence (Luu et al., 2011). So far, the neurodevelopmental trajectory of individual children born VPT cannot be predicted. Studying the trajectories of distinctive, multi-variate profiles within children born VPT would gain more insight on which of these children will be at risk for long-term adverse neurodevelopmental outcomes as well as to which extent problems in different developmental domains might mutually affect each other. This knowledge might improve early detection of children at risk for long-term neurodevelopmental problems and will enable clinicians to provide early and targeted intervention for those who are truly at risk.

To the best of our knowledge, three studies have used statistical cluster analysis to identify profiles based on outcome measures within one domain in children born preterm (Lundequist et al., 2013; Ross et al., 2016; Stalnacke et al., 2015). In the study of Ross et al. (2016), children with very low birth weight were clustered into four groups based on three subscales of the Bayley Scales-III assessed at 18 months of age: consistently high, consistently average, average with delayed expressive language, and consistently low (Ross et al., 2016). Lundequist et al. (2013) identified five neuropsychological profiles based on five subscales of a neuropsychological assessment (NEPSY) in children born preterm and term assessed at age 5.5 years (Lundequist et al., 2013). Fifty-four percent of the children born preterm belonged to one of the three low-functioning profiles and also had more uneven profiles compared to 33% of children born at term age. Stalnacke et al. (2015) used four cognitive indices; two reflecting general cognitive ability and two reflecting executive functions in children born preterm (Stalnacke et al., 2015). In this study, in contrast to the studies of Ross et al. (2016) and Lundequist et al. (2013), a cluster-analysis was performed at two ages separately, and individual movements

between clusters across time were investigated. At age 5.5 and 18 years, six distinct and similar cognitive patterns were identified in both ages. More than half of the children born preterm performed at low levels at 5.5 years and did not catch up but rather deteriorated in relative performance. Taken together, these studies have shown the variability of cognitive functioning within groups of children born VPT. A relatively high percentage of children born VPT had unfavorable profiles without catch-up to the age of 18. The conclusions of the three above mentioned studies, however, are based on a rather limited number of distinctive neuro-developmental outcomes. So far, no studies have clustered children born VPT based on a broad array of neurodevelopmental outcomes at 2 years of age and investigated the long-term trajectories of these outcomes within distinct multidisciplinary profiles. Longitudinal follow-up of neurodevelopmental profiles defined by statistical cluster analysis may provide more comprehensive and clinically meaningful developmental trajectories. Such profiles may clarify which children will catch up, which children will remain stable (either high or low) and which children will grow into deficit. This approach may improve predicting the developmental trajectories of very young children born VPT. We expected to find different trajectories for each neuro-developmental profile defined at 2 years of age. Accordingly, we expected that the neuro-developmental profiles of children born VPT at age 2 have additional predictive value for language, cognitive and behavior outcomes at 10 years of age compared to a prediction based on single outcomes.

Therefore, the first aim of this study was to identify distinctive profiles of children born VPT at age 2 based on a broad array of neurodevelopmental outcomes (obtained from domain-specific tests) by using factor and cluster analysis. The second aim was to describe the longitudinal course of each of the neurodevelopmental profiles defined at age 2. The third aim was to explore whether adding profile membership to the prediction model for, respectively, language, cognition, and behavioral outcome at age 10 will provide a significant better prediction than when only the single neurodevelopmental outcome at age 2 was included.

Method

Study group

This study was part of a longitudinal cohort study on speech and language function in children born VPT (<32 weeks' gestation) admitted between October 2005 and September 2008 to a level III neonatal intensive care unit (NICU) at the Erasmus MC-Sophia Children's Hospital Rotterdam. Data used in this study were obtained from assessments at 2 years of corrected age and 10 years of age. Corrected age, chronological age minus the number of weeks the child was born prematurely, was used for the first assessment because the brain and nervous system of children born VPT have not developed to the same degree as those of a full term born children at the age of 2. Parents gave written informed consent separately at age 2 and age 10, and the study was approved by the Medical Ethics Committee of Erasmus MC, Rotterdam (MEC-2012-149 and MEC-2015-591).

A total of 232 children born VPT met the inclusion criteria for the cohort study: (1) no severe disabilities (i.e., cerebral palsy with Gross Motor Function Classification System (GMFCS) level >1 or severe vision or hearing disabilities); (2) no congenital abnormalities involving speech organs; (3) no multiple birth; and (4) primary language spoken at home is Dutch. Regarding the inclusion criteria, *no severe disabilities*, in total 10 children were excluded from the initial sample due to cerebral palsy or severe sensory issues: Blindness ($n = 2$), deafness ($n = 2$), and CP ($n = 6$). One hundred and twenty-five of the 232 children were randomly selected for speech and language assessment at 2 years of corrected age, of which 84 children participated in this study. The study inclusion flowchart is presented in Figure 1. Of the originally 84 children born VPT, a total of 61 children born VPT participated at 10 years of age.

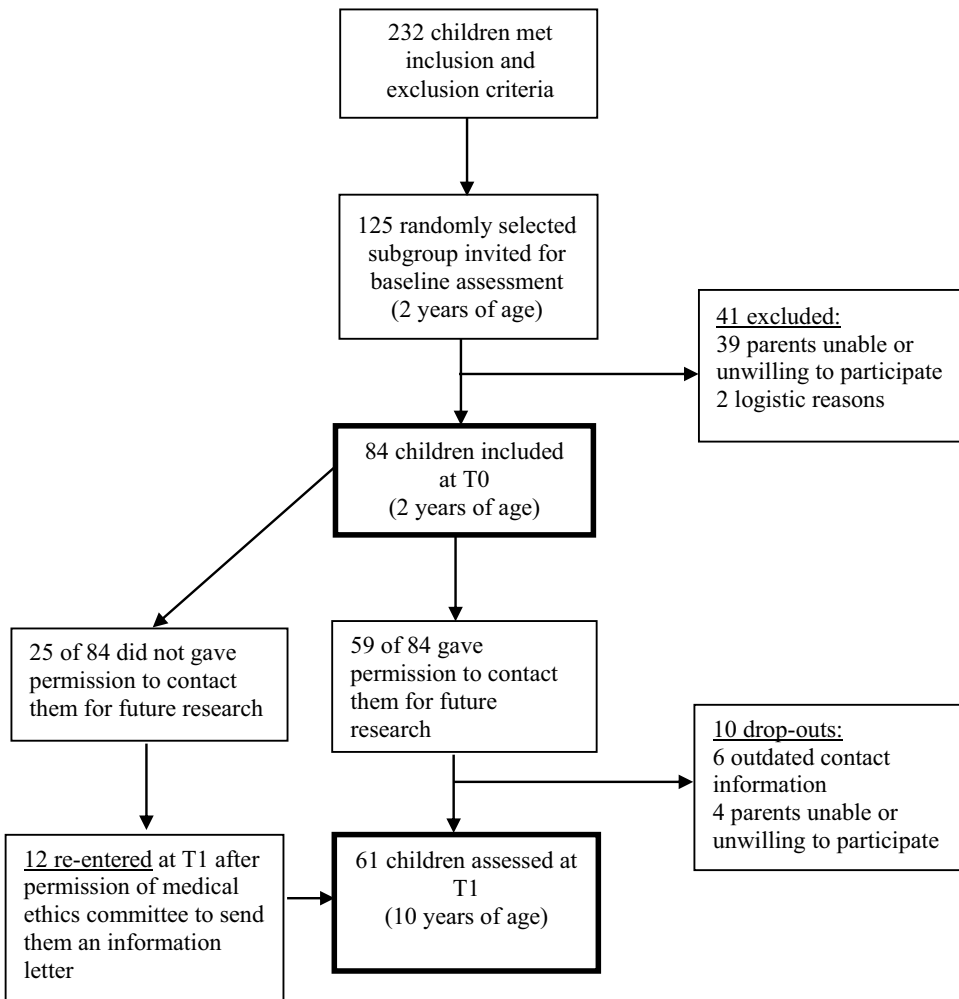


Figure 1. Flowchart of inclusion process of cohort for each measuring point of the longitudinal study.

A comprehensive multidisciplinary assessment as described below was performed at 2 and 10 years of age at the Erasmus MC-Sophia Children's Hospital Rotterdam. Data regarding perinatal and demographic factors were retrieved from the children's hospital medical records. In addition, data regarding mother's educational level and vocabulary level of one of the parents was collected during the assessments at 10 years of age.

Neurodevelopmental outcomes

Cognitive and motor function

At age 2, cognitive and motor function were assessed using the Dutch version of the Bayley Scales of Infant Development (BSID, version II or III (Steenis & Van Baar, 2012; Van der Meulen et al., 1993). The BSID-II scores were converted into BSID-III scores, using generally accepted algorithms (Jary et al., 2013; Lowe et al., 2012).

At age 10, the total intelligence quotient (TIQ) of the Wechsler Intelligence Scale for Children (WISC-III) (Wechsler, 2005) was used to measure cognitive function.

Language function

At age 2, receptive language function was assessed using the Dutch version of the Reynell Developmental Language Scales (Van Eldik et al., 2004). Expressive language function was assessed using the Word Development Scale of the Schlichting Test for Language Production (Schlichting et al., 1999) and the Dutch Lexi list (Schlichting & Spelberg, 2002) which is an expressive language checklist completed by the parents.

At age 10, receptive language function was assessed using the Receptive Language Index of the Clinical Evaluation of Language Fundamentals, Fourth Edition (CELF-4) (Semel et al., 2010). Expressive language function was assessed using the Expressive Language Index of CELF-4. Of 54 of the included children, receptive vocabulary knowledge of either the mother ($n = 45$; 83%) or the father ($n = 9$; 17%) was assessed with the Peabody Picture Vocabulary Task-III (PPVT-III) (Schlichting, 2005). These scores provide a language-specific familial risk factor. The native language of all parents was Dutch.

Spontaneous speech production

At age 2, speech production was defined by the number of acquired, syllable initial consonants measured by the "Fonologische Analyse van het Nederlands," the Dutch standard assessment of phonological development in children (Beers, 1995). The number of acquired consonants was derived from a speech sample obtained from 20 minutes of child-parent play interaction. By convention, a consonant was considered acquired if it was attempted at least three times in meaningful words and the percentage of correct production was $\geq 75\%$. In the absence of norm-referenced data, we considered six or less acquired consonants as abnormal. This criterion was based on our pilot study, in which all 20 term-born controls had acquired at least seven consonants at 2 years of age, range 7–13, median 10.0, mean 9.9 (Van Noort-van der Spek et al., 2010). Abnormal speech production was defined as six or less acquired consonants based on a spontaneous speech sample of at least 50 different word realizations or a spontaneous speech sample of less than 50 words combined with a delayed word production (i.e., a score less than 1.5 *SD* below the mean) based on the

parent checklist or the standardized test. Non-classifiable speech production was defined as six or less acquired consonants based on analysis of a speech sample of less than 50 words combined with a normal word production score (i.e., a score more than 1 *SD* below the mean) on the parent checklist and the standardized test.

Behavioral function

At age 2, behavioral function was assessed using the Dutch version of the Child Behavior Checklist for ages 1.5–5 (Verhulst, 2000), a validated and norm-referenced parent-report questionnaire, completed by the mother. The following four scales were included in the analysis: Internalizing Problems, Externalizing Problems, Attention Problems and Pervasive Problems. Based on the literature, in particular, symptoms of attention disorder and autism spectrum disorder are often observed in children born VPT. Therefore, the attention problems and pervasive problems scales were added. The scales are normalized using a T-scale with a mean of 50 and a standard deviation of 10. For the internalizing and externalizing problem scale, scores between 60 and 63 are considered borderline and scores of 64 or higher are considered clinical. For the attention problem and pervasive problem scale, scores between 65 and 69 are considered borderline and scores of 70 and higher are considered clinical.

At age 10, behavioral function was measured again by parent reporting of the CBCL/6–18 (Achenbach, 2001). For most cases, the CBCL/6–18 was separately completed by the mother and father. In this study, only the results of the mother were used (except for two teens of whom only the father had completed the questionnaire), as at age 2 also mother's CBCL questionnaires were included. Again, the CBCL-scales' Internalizing Problems, Externalizing Problems and Attention Problems were included, and Total Problems were added as well. Pervasive Problems could not be included since this scale does not exist in the CBCL/6–18. In [Figure 2](#) and [Figure 3](#), these behavioral problem scores are presented as *z*-scores (higher scores refer to less problems), to be easily compared to the cognition and language scores.

Auditory nerve function

At age 2, auditory nerve function was measured by conventional ABR audiometry, using click-evoked stimuli in a soundproof room. No sedation had been given. The waveform obtained at a suprathreshold stimulus level of 70 dB was analyzed by at least two experienced clinical specialists defining the post-stimulus peak latencies I (distal cochlear part of the VIIIth nerve), III (in between cochlear nucleus and the superior olivary complex), and V (between the superior olivary complex and the inferior colliculus) in milliseconds. The I–V and III–V interpeak latencies, as a measure of auditory neural myelination, were included as neurodevelopmental outcomes. Since a strong correlation between the left and right ear can be expected, only the results of one ear, the right ear, were analyzed to prevent statistical overstimulation.

At age 10, pure-tone audiometry (0.5, 1, 2 kHz) and tympanometry were performed to measure hearing thresholds, since hearing function can affect oral language functions directly. All hearing measurements were performed in a soundproof booth and according to the ISO standard 8253–1 (ISO, 2010). A computer-based clinical audiometry system (Decos Technology Group, version 210.2.6 with AudioNigma interface) and TDH-39 headphones were used.

All the above mentioned assessments were taken by certified professionals and were normed and validated for Dutch children (Achenbach, 2001; Semel et al., 2010; Wechsler, 2005). Regarding the standardized tests on cognitive and language function, the raw scores were converted into standard scores based on a mean of 100 and a standard deviation (*SD*) of 15 (Schlichting et al., 1999; Semel et al., 2010; Van der Meulen et al., 1993; Wechsler, 2005). By current clinical standards, mild/moderate delay was defined as a score between 1 and 2 *SD* below the mean (score 84–70) and severe delay as a score of >2 *SD* below the mean (score <70) (Semel et al., 2010; Wechsler, 2005).

Statistical analysis

The statistical analyses were performed using IBM SPSS Statistics version 25 and R version 3.6. Student's *T*-test, Pearson's chi-square test or Fisher's exact test was used to compare perinatal and demographic factors between the study group and the group of nonparticipating children and between each profile. The outcome variables were tested for normality using the Kolmogorov–Smirnov test, with $p < .05$ indicating that the tested variable distribution differed from a normal distribution. Continuous outcome measures were compared across the clusters using univariate analysis of variance with the Tukey post hoc test (for normally distributed data) or the Kruskal–Wallis test with the Dunn–Bonferroni post hoc test (for non-normally distributed data). Normally distributed data are presented as mean \pm standard deviation. Data that were not normally distributed are presented as median with interquartile range.

Regarding the outcome measure for speech production at age 2, inter-rater reliability was established. An independent experienced clinical linguist re-transcribed the spontaneous language of 13 randomly selected children (15%) and measured the number of acquired consonants for each child. A good reliability was found. The average measure ICC was .872 with a 95% confidence interval from .581 to .961; $F(12,12) = 7.817$, $p < .01$. Tukey's test for nonadditivity showed no interaction; $F(1,12) = 1.027$, $p = .33$.

All test scores on cognitive, motor, language and speech function were transformed to *z*-scores. The scores obtained at age 2 were submitted to factor analysis. The *z*-scores of the behavioral and the auditory nerve function outcomes were reversed in order to get the same direction of effect for all outcomes; i.e., a higher *z*-score means a better performance. The extraction method used in the factor analysis was Principal Component Analysis. Kaiser's criterion, eigenvalues >1, was used to define the number of factors to be retained and Varimax rotation was used to determine factor loading. The suitability of our data for factor analysis was evaluated using Kaiser–Meyer–Olkin (KMO) measure of sampling adequacy and Bartlett's test of sphericity.

A cluster analysis with the standardized factor scores was performed based on the data obtained at age 2 to find groups of children that significantly differ from each other on the factors extracted by the factor analysis. First, the optimal number of clusters was determined by means of a hierarchical cluster analysis according to Ward (1963). Second, a K-means cluster analysis over the same factor scores was applied based on the number of clusters indicated by Ward's dendrogram. The cluster centers obtained with the hierarchical cluster analysis were used as the initial values for the K-means cluster analysis.

The Kruskal–Wallis test with the Dunn–Bonferroni post hoc test and chi-square tests were used to determine whether perinatal and demographic factors were associated with clusters.

To ascertain whether the definition of the neurodevelopmental profiles at age 2 improved the prediction of cognitive, language and behavioral outcome measures at school age, compared to the prediction based on single-domain outcome measures, linear regression models were used. More specifically, for each single-domain outcome measure (i.e., receptive language; expressive language; cognitive function; internalizing behavior; externalizing behavior; attention problems) a separate linear regression model was used. An outcome measure at age 2 and profile membership were entered as independent variables and the corresponding outcome measure at age 10 was entered as the dependent variable. Furthermore, different profile trajectories were compared as descriptive statistics as well. To investigate the sensitivity to outliers in a sensitivity analysis, we applied robust regression models using the Huber method, effectively down-weighting outliers in the analyses. All statistical tests were two sided and statistical significance was defined at $p < .05$. Adjustment for multiple testing was performed by using a Bonferroni correction. Since 16 p -values were relevant in the regression models, statistical significance was reached when $p < .05/16$ or $.003$.

Missing data at age 2 were replaced for the purpose of the factor-analysis by means of Expectation Maximization (Little's MCAR test: Chi-square = 74.536, DF = 71, $p = .364$). Missing data resulted from either examiner error or child noncompliance. The proportion of missing values was 6.0% ($n = 5$) for cognitive function; 4.8% ($n = 4$) for word production; 3.6% ($n = 3$) for behavioral function; 17.9% ($n = 15$) for motor function; and 13.1% ($n = 11$) for auditory nerve function.

Results

The 84 children assessed at age 2 had a mean birth weight of 1173 ± 392 g and mean gestational age of 29 ± 2 weeks. The characteristics of the study group did not significantly differ from the nonparticipating group, $n = 41$ (Table S1, online supplement). Besides, the characteristics of the participating group at age 10, $n = 61$, did not significantly differ from the group lost to follow-up at age 10, $n = 23$ (Table S1, online supplement). The neurodevelopmental outcomes at age 2 are presented in Table S2 (online supplement). The mean scores on these outcomes were within the normal range, except for speech production, which was abnormal in almost half of the children.

Factor and cluster analysis at age 2

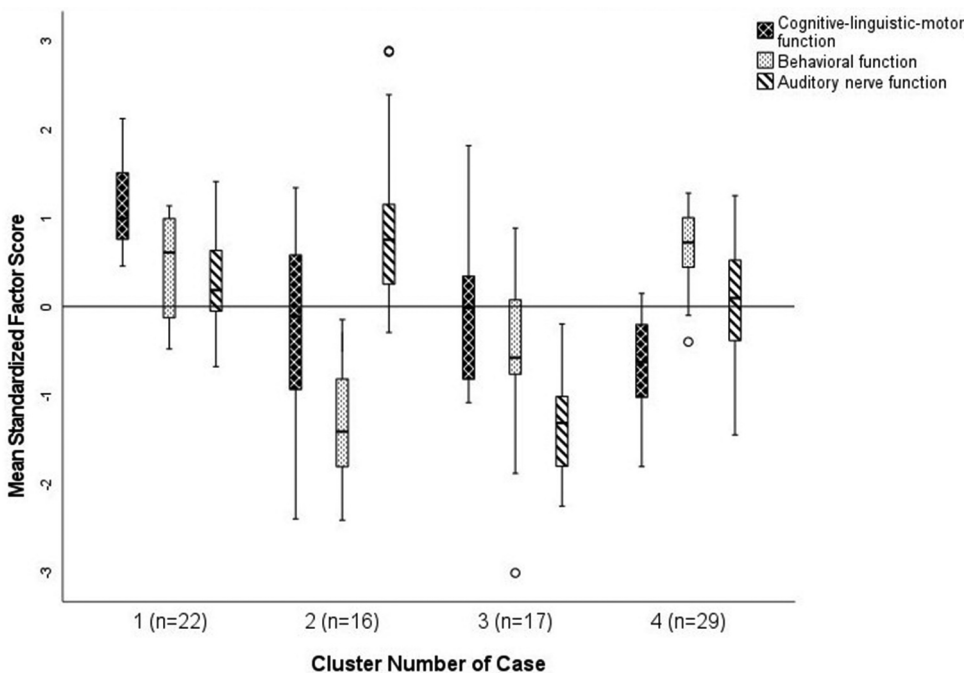
A scree plot and eigenvalue analyses indicated that three factors could be extracted which explained 69% of the total variance in the neurodevelopmental outcomes of the children born VPT. The eigenvalues for the three factors were respectively 3.9, 2.7 and 1.7. Therefore, the number of factors was set to three for the subsequent varimax rotation analysis. The factor matrices were then examined and factors defined in terms of variables with a loading of .5 or larger. The KMO value was 0.74, which is above the acceptable lower value 0.5, and the Bartlett' test of sphericity significance value was 0.000 which is less than the lower range value 0.005. This indicates that the correlation matrix was suitable for factor analysis. The results of the factor analysis with Varimax rotation are presented in Table 1.

Table 1. Factor-analysis with Varimax rotation on neurodevelopmental outcomes in children born very preterm at 2 years of corrected age ($n = 84$).

Outcomes	Factor 1	Factor 2	Factor 3
Cognitive composite score	.81	.13	-.04
Receptive language quotient	.78	.11	-.13
Word production quotient	.85	.07	.01
Lexi list quotient	.83	.09	-.07
Spontaneous speech production score	.84	-.07	-.04
Motor composite score	.60	-.05	-.50
Internalizing problems score	.06	.82	-.31
Externalizing problems score	.10	.89	-.03
Attention problems score	-.13	.76	-.05
Pervasive problems score	.28	.78	.19
I-V interval latency in ms	-.06	-.01	.85
III-V interval latency in ms	-.08	-.12	.76

The first factor included cognitive, motor, language, and speech outcomes and was labelled “cognitive-motor-language function.” The second factor was labelled “behavioral function” because it was clearly defined by aspects of behavioral function. The third factor was labelled “auditory nerve function” because the I–V and III–V interval latencies were found to load high on this factor.

A dendrogram of the Ward’s hierarchical cluster analysis based on the three factors of the factor analysis showed that the neurodevelopmental outcomes clustered into four groups. A K-means cluster analysis was then conducted with a restriction to four clusters.

**Figure 2.** Boxplot illustrating the results of K-means cluster analysis for the children born very preterm based on their neuro-developmental outcomes.

The z-scores of the behavioral and the auditory nerve function outcomes were reversed in order to get the same direction of effect for all outcomes, i.e., a higher z-score means a better performance.

Figure 2 displays boxplots of these four clusters. The units on the vertical axis are standard deviations from the mean of the standardized factor scores ($M = 0$ and $SD = 1$). A high mean factor score indicates that the cluster of children had a relatively good performance on this specific factor.

Table 2. Neurodevelopmental outcomes for each of the four profiles of children born very preterm at 2 years of corrected age ($n = 84$).

Outcomes	Profile 1 $n = 22$	Profile 2 $n = 16$	Profile 3 $n = 17$	Profile 4 $n = 29$
Cognitive composite score, mean (<i>SD</i>)	113.7 (6.1)	100.5 (12.3)	103.4 (8.7)	98.9 (8.9)
Receptive language quotient, mean (<i>SD</i>)	109.1 (10.3)	86.1 (18.2)	89.8 (13.2)	84.1 (17.0)
Word production quotient, mean (<i>SD</i>)	107.4 (9.6)	90.3 (9.7)	92.8 (10.6)	85.6 (8.6)
Lexilist quotient, mean (<i>SD</i>)	103.9 (10.6)	83.1 (13.3)	90.4 (12.3)	79.9 (12.1)
Spontaneous speech production score, mean (<i>SD</i>)	9.9 (2.5)	6.2 (3.6)	6.2 (2.8)	4.3 (2.6)
Motor composite score, median (IQR)	107 (104–113)	98 (86–103)	110 (96–126)	98 (94–104)
Internalizing problems score, ^a median (IQR)	51 (50–53)	63 (58–66)	53 (51–56)	50 (50–51)
Externalizing problems score, ^a median (IQR)	37 (36–45)	60 (56–62)	51 (45–58)	41 (37–45)
Attention problems score, ^a median (IQR)	52 (50–62)	62 (54–70)	56 (52–60)	51 (50–52)
Pervasive problems score, ^a median (IQR)	50 (50–51)	59 (52–68)	56 (52–63)	51 (50–52)
I–V interval latency in ms, median (IQR)	4.2 (4.1–4.2)	4.1 (3.9–4.2)	4.4 (4.3–4.4)	4.2 (4.0–4.3)
III–V interval latency in ms, median (IQR)	1.9 (1.8–2.0)	1.8 (1.7–2.0)	2.1 (2.1–2.2)	1.9 (1.9–2.0)

^aThe behavioral problems scale is inverse, so a higher score indicates more reported behavior problems.

Table 2 presents a detailed picture of the neurodevelopmental outcome scores for each profile. Profile 1 ($n = 22$; 26%) consisted of children with high-average mean scores on all domains, the highest scores in all neurodevelopmental domains among the different profiles. We named this group: neurodevelopmental high performers. Profile 2 ($n = 16$; 19%) consisted of children with average mean scores for cognition, motor, and language function. However, they stand out in abnormal behavioral function, below-average speech production as well as the shortest mean ABR interval latencies, indicating accelerated auditory nerve function. We named this group: very low behavioral function and markedly accelerated auditory nerve function. Profile 3 ($n = 17$; 20%) consisted of children with mean scores in the high-average to low-average range for cognitive, motor, language and behavioral function. This profile, however, had the longest mean ABR interval latencies, indicating delayed auditory nerve function, and below-average speech production. We named this group: mild neurodevelopmental delay with delayed auditory nerve function. Profile 4 ($n = 29$; 35%) consisted of children with low to below-average mean scores specifically for language and speech function, normal behavioral and auditory nerve function. We named this group: poor neurodevelopmental functioning but no behavioral problems.

Perinatal and demographic characteristics for each profile at 2 years of corrected age are shown in Table 3. Only total days of invasive mechanical ventilation was statistically significantly different among the profiles at 2 years of corrected age (Kruskal–Wallis $X^2 [4] = 9.679$; $p = .021$) since cluster 2 showed a higher number of total days of invasive mechanical ventilation than cluster 1 ($p = .019$). However, after Bonferroni-correction because of the 16 comparisons, no significant difference among the profiles was found.

Table 3. Perinatal and demographic characteristics for each of the four neurodevelopmental profiles of children born very preterm at 2 and 10 years of age.

	Profile 1		Profile 2		Profile 3		Profile 4	
	Age 2 n = 22	Age 10 n = 16	Age 2 n = 16	Age 10 n = 11	Age 2 n = 17	Age 10 n = 10	Age 2 n = 29	Age 10 n = 24
Gestational age, weeks, mean (SD)	29.6 (1.5)	29.7 (1.5)	28.0 (1.9)	27.7 (2.0)	29.8 (1.4)	30.0 (1.2)	28.6 (2.4)	28.6 (2.4)
Birth weight, grams, mean (SD)	1234.1 (431.1)	1281.6 (425.5)	1020.6 (349.6)	1001.8 (313.3)	1282.9 (335.8)	1312.0 (391.8)	1147.1 (402.0)	1148.3 (421.0)
Male sex, n (%)	11 (50)	8 (50)	12 (75)	7 (64)	10 (59)	6 (60)	18 (62)	15 (62)
Neonatal brain injury, ^a n (%)	1 (5)	1 (6)	2 (13)	2 (18)	1 (6)	1 (10)	2 (7)	2 (8)
Perinatal inflammation, ^b n (%)	9 (41)	6 (38)	7 (44)	4 (36)	10 (59)	6 (60)	17 (59)	12 (50)
Total days of invasive mechanical ventilation, mean (SD)	2.0 (3.4)	2.2 (3.9)	11.3 (13.2)	10.5 (9.6)	3.5 (5.7)	2.6 (3.7)	8.2 (12.7)	8.4 (13.5)
Total days of stay in neonatal care unit, mean (SD)	19.2 (15.0)	17.5 (16.0)	27.3 (20.4)	26.6 (15.5)	16.4 (14.3)	15.0 (11.9)	28.9 (30.2)	30.1 (31.8)
Neighborhood socioeconomic status, ^c mean (SD)	-0.17 (-0.94- -0.19)	-0.31 (0.88)	-0.17 (-0.54-0.55)	0.46 (1.60)	.01 (-0.55-0.65)	-0.04 (1.23)	-0.03 (-0.51-0.93)	0.01 (1.09)
Educational level mother (parent-reported at age 10), low to high, n (%) ^d		3 (19)		2 (18)		1 (10)		5 (21)
1: High school	-	4 (25)	-	7 (64)	-	1 (10)	-	9 (37)
2: Intermediate vocational education	-	8 (50)	-	0	-	7 (70)	-	4 (17)
3: Higher vocational education	-	0	-	0	-	1 (10)	-	4 (17)
4: University level	-	1 (6)	-	2 (18)	-	0	-	2 (8)
Unknown	-	-	-	-	-	-	-	-
Receptive vocabulary parent, mean (SD) ^e	-	98 (7.9)	-	84.1 (12.0)	-	91.8 (10.8)	-	96.7 (11.4)
Hearing threshold of one ear above 20 dB – wearing hearing aids, n (%)	-	1 (6)	-	0	-	0	-	3 (13)-1 (4)
Hearing threshold of both ears above 20 dB – wearing hearing aids, n (%)	-	0	-	1 (9) – 1 (9)	-	0	-	1 (4)
(measured at age 10)	-	-	-	4 (36)	-	2 (20)	-	3 (13)
ADHD diagnosis (parent-reported at age 10), n (%)	-	1 (6)	-	2 (18)	-	2 (20)	-	7 (29)
Left-handed (parent-reported at age 10), n (%)	-	3 (19)	-	2 (18)	-	1 (10)	-	4 (17)
Special school services (parent-reported at age 10), n (%)	-	0	-	7 (64)	-	4 (40)	-	17 (71)
Received speech-language therapy (parent-reported at age 10), n (%)	-	4 (25)	-	-	-	-	-	-

^aNeonatal brain injury (i.e., intraventricular hemorrhage grade II–IV and infarction). None of the children included in this study had cystic periventricular leukomalacia (c-PVL). Since the detection of less severe grades of PVL is difficult, we did not include this prenatal factor in the group of “neonatal brain injury”; ^bperinatal inflammation (i.e., neonatal proven sepsis, premature rupture of the membranes or chorioamnionitis); ^cneighborhood socioeconomic status (SES; Knol et al., 2012). This score ranges from +3.4 to -5.2 and is based on income, occupation, and education. Scores >0 are considered high SES and scores ≤0 low SES. ^dThere were missing values for two variables: “Educational level mother” (displayed in table) and “Receptive vocabulary parent” (i.e., missing values Profile 1: n = 4; Profile 2: n = 1; Profile 3: n = 0; Profile 4: n = 3), p-Values were calculated with univariate analysis of variance or Pearson’s chi-square test. All comparisons were p > .05.



Table 4. Language, cognitive, and behavioral outcomes at age 2 and 10 for each of the four profiles of the children born very preterm.

	Profile 1 (<i>n</i> = 16), Mean (SD)		Profile 2 (<i>n</i> = 11), Mean (SD)		Profile 3 (<i>n</i> = 10), Mean (SD)		Profile 4 (<i>n</i> = 24), Mean (SD)		Total (<i>n</i> = 61), Mean (SD)	
	2 years	10 years	2 years	10 years	2 years	10 years	2 years	10 years	2 years	10 years
<i>Language</i>										
Receptive language quotient, mean (SD)	110.3 (10.5)	92.9 (15.1)	88.0 (19.2)	85.2 (13.1)	86.3 (12.5)	92.0 (12.4)	85.7 (17.4)	88.1 (13.9)	92.7 (18.5)	89.5 (13.8)
Word production quotient, mean (SD)	108.4 (9.4)	97.2 (16.0)	90.1 (7.9)	84.7 (14.8)	87.0 (9.1)	91.3 (14.0)	85.3 (8.6)	87.5 (14.9)	92.5 (13.0)	90.2 (15.4)
Expressive language quotient, mean (SD)	-	-	-	-	-	-	-	-	-	-
<i>Cognition</i>										
Cognitive composite score, mean (SD)	113.3 (6.6)	-	99.8 (11.1)	85.2 (13.1)	101.4 (8.3)	96.2 (11.7)	100.4 (7.6)	94.6 (12.3)	103.9 (9.8)	95.7 (13.3)
Verbal IQ, mean (SD)	-	101.0 (14.2)	-	89.6 (13.9)	-	96.2 (11.7)	-	94.6 (12.3)	-	95.7 (13.3)
Performance IQ, mean (SD)	-	94.3 (15.1)	-	87.7 (11.7)	-	86.1 (14.6)	-	89.7 (15.3)	-	90.0 (14.5)
Total IQ, mean (SD)	-	97.6 (14.1)	-	87.2 (10.7)	-	90.3 (13.8)	-	91.3 (12.8)	-	92.1 (13.2)
<i>Behavior</i>										
Total problems score, mean (SD)	46.4 (10.6)	52.7 (12.1)	60.7 (8.1)	62.3 (12.6)	53.7 (5.1)	60.5 (10.0)	41.2 (9.5)	49.7 (9.3)	48.1 (11.5)	54.5 (11.8)
Internalizing problems score, mean (SD)	51.1 (11.2)	54.5 (11.9)	62.2 (5.7)	59.3 (8.9)	56.3 (6.3)	61.0 (10.4)	50.8 (1.7)	48.7 (9.7)	53.9 (5.7)	54.1 (11.2)
Externalizing problems score, mean (SD)	38.8 (6.5)	46.1 (11.4)	60.3 (3.3)	53.4 (8.3)	53.3 (7.9)	55.0 (12.6)	40.0 (6.3)	45.3 (10.5)	45.5 (10.6)	48.5 (11.3)
Attention problems score, mean (SD)	55.5 (7.3)	59.5 (9.7)	62.6 (9.1)	66.3 (13.2)	59.9 (9.6)	60.6 (9.1)	41.2 (9.5)	58.0 (7.2)	56.3 (8.1)	60.3 (9.7)
Receptive language quotient < -1 SD, <i>n</i> (%)	0	3 (25)	5 (45)	6 (55)	5 (50)	2 (20)	10 (42)	9 (38)	20 (33)	20 (33)
Expressive language quotient < -1SD, <i>n</i> (%)	0	4 (25)	4 (36)	6 (55)	6 (60)	3 (30)	12 (50)	9 (38)	22 (36)	22 (36)
VIQ < -1 SD, <i>n</i> (%)	-	2 (13)	-	2 (18)	-	2 (20)	-	4 (17)	-	10 (16)
PIQ < -1 SD, <i>n</i> (%)	-	4 (25)	-	4 (36)	-	5 (50)	-	10 (42)	-	23 (38)
Cognitive composite score < -1 SD, <i>n</i> (%)	0	-	1 (9)	-	0	-	0	-	1 (2)	-
Disharmonic IQ profile, <i>n</i> (%)	-	7 (44)	-	4 (36)	-	3 (30)	-	10 (43)	-	-
<i>Total behavior problems score</i>										
Clinical range, <i>n</i> (%)	0	4 (25)	4 (36)	4 (36)	0	4 (40)	0	2 (8)	4 (7)	14 (23)
Borderline range, <i>n</i> (%)	2 (13)	2 (13)	1 (9)	0	1 (10)	2 (20)	0	1 (4)	4 (7)	5 (8)
<i>Internalizing problems score</i>										
Clinical range, <i>n</i> (%)	0	5 (31)	3 (27)	4 (36)	1 (10)	4 (40)	0	2 (8)	4 (7)	15 (25)
Borderline range, <i>n</i> (%)	0	1 (6)	4 (36)	3 (27)	1 (10)	2 (20)	0	1 (4)	5 (8)	7 (11)
<i>Externalizing problems score</i>										
Clinical range, <i>n</i> (%)	0	1 (6)	1 (9)	3 (27)	1 (10)	2 (20)	0	3 (13)	2 (3)	9 (15)
Borderline range, <i>n</i> (%)	0	1 (6)	5 (45)	0	1 (10)	1 (10)	0	0	6 (10)	2 (3)
<i>Attention problems score</i>										
Clinical range, <i>n</i> (%)	1 (6)	2 (13)	3 (27)	3 (27)	2 (20)	2 (20)	1 (4)	1 (4)	7 (11)	8 (13)
Borderline range, <i>n</i> (%)	2 (13)	3 (25)	1 (9)	2 (18)	0	2 (20)	1 (4)	3 (13)	4 (7)	10 (16)

Profile trajectories

From the children born VPT who participated at 2 and 10 years of age ($n = 61$), there were 16 children with profile 1 (73% of original 22), 11 children with profile 2 (69% of original 16), 10 children with profile 3 (59% of original 17) and 24 with profile 4 (83% of original 29). Table 3 also presents the perinatal and demographic characteristics of the children born VPT included at follow-up at age 10. No significant differences were found between the four profiles on birth weight (BW), male sex, neighborhood socioeconomic status (SES), total days of stay in the NICU, and total days of invasive mechanical ventilation. However, GA ($F(3,49) = 3.382, p = .024$) and parent's receptive vocabulary score did significantly differ among the profiles ($F(3,49) = 3.982, p = .013$). A Tukey post hoc test revealed that in the study group of the current study ($n = 61$) mean GA was significantly lower in profile 2 children (27.7 ± 2.0) compared to profile 3 children ($30.0 \pm 1.3, p = .042$), while there were no significant differences between GA of the four profiles at the original cohort at age 2 ($n = 84$). Mean parent's receptive vocabulary score was significantly lower in profile 2 children (84 ± 12.0) compared to profile 1 children ($98 \pm 8.0, p = .020$) as well as compared to profile 4 children ($97 \pm 11.4, p = .018$). Furthermore, mother's educational level was also significantly different among profiles ($\chi^2(9, n = 56) = 21.49, p = .011$). However, after Bonferroni-correction because of the 16 comparisons, no significant difference among the profiles was found.

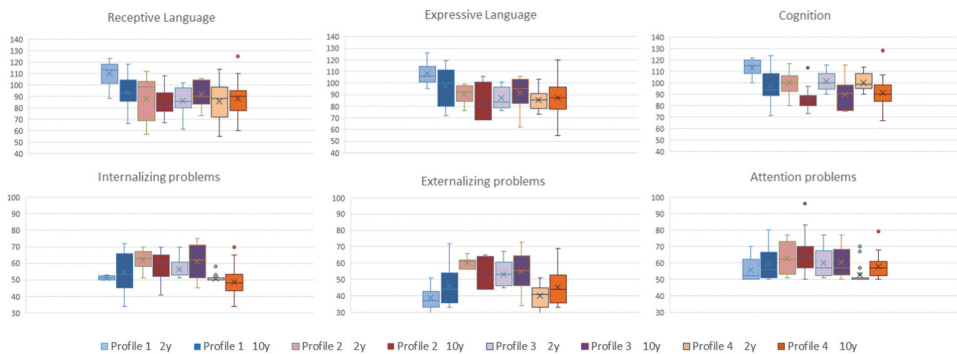


Figure 3. Box plots of the neurodevelopmental outcomes at 2 and 10 years of age for each of the four profiles.

Mean scores = "x"; median = midline boxes; first and third quartile = outline of boxes; minimum score = bottom of line "┴"; maximum score = top of line "T." Outliers = "o." Outliers were defined as values lower than the lower quartile minus 1.5 times the interquartile range or higher than the upper quartile plus 1.5 times the interquartile range.

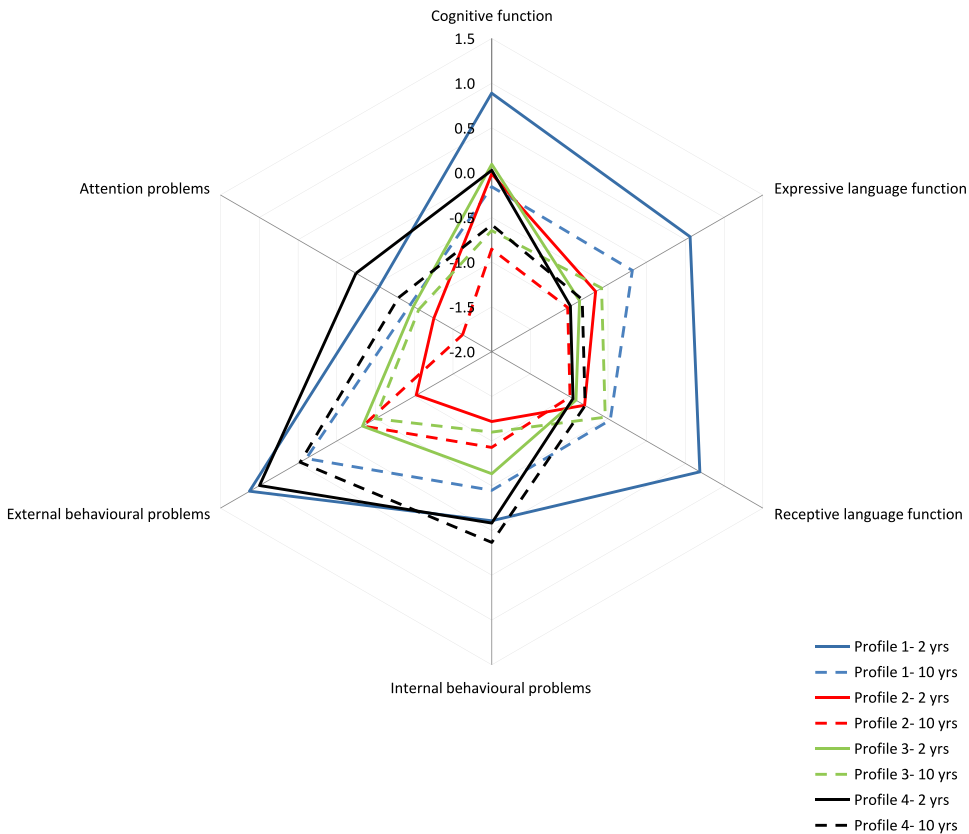


Figure 4. Radar chart of the neurodevelopmental outcomes at 2 and 10 years of age for each of the four profiles.

Data are presented in standardized mean-scores for all variables; high scores refer to favorable results for all outcome measures.

Regarding the second research question, descriptive statistics indicated different neurodevelopmental trajectories for each profile (Table 4, Figure 3 and Figure 4). Children with *profile 1* showed a sharp decrease in the language and cognitive outcomes, which was not expected from their favorable scores at the age of 2. They maintained neurodevelopmental scores within normal limits at 10 years of age, but overall, at 10 years of age, their scores were approximately 1 *SD* lower than the mean score at age 2. Children with *profile 2*, who were characterized by behavioral problems and accelerated auditory nerve function at age 2, showed the expected worse development, showing the lowest scores at the age of 10 for all outcome measures, of all four profiles. Their mean behavior problem score remained in the borderline range, however their attention problem score increased from the normal to the borderline range. In contrast, children with *profile 3*, who were characterized by mild neurodevelopmental delay with delayed auditory nerve function, unexpectedly showed the most increasing trajectory of all four profiles. At age 10, children with profile 3 had a better outcome compared to children with profiles 2 and 4 and even approached the outcomes of profile 1, at 10 years of age. However, their mean total behavioral problems score increased from the normal to the

borderline range. The trajectories of the children with *profile 4* showed the largest variation, compared to the other profiles, but mean language scores remained almost 1 *SD* below the mean. They showed severely increased mean attention problem score and mean total behavior problem score (41% and 21%, respectively).

Mean cognition scores decreased in all profiles, however, the largest difference (16 Q-points, 14%) occurred in children with profile 1, the neurodevelopmental high performers, compared to 13%, 11% and 9% in profile 2, 3 and 4, respectively.

Regarding the third research question, all neurodevelopmental outcome scores at age 10 were regressed on those at age 2 and profile membership. Profile membership was not statistically significant for any of the outcomes. This result did not change when robust regression was used.

Additionally, taken together all 61 children, boys performed worse than girls at the age of 2, specifically on receptive language outcome (mean receptive language score boys: 86.1 (*SD* 19.1), girls: 102.2 (*SD* 12.7), independent samples *t*-test: $p = .001$). However, boys, more often than girls, have a neurodevelopmental profile with a catch-up trajectory. Moreover, girls had diminishing receptive language outcomes at the age of 10 (mean receptive language score girls: 92.2 (*SD* 13.9), paired samples *t*-test: $p = .007$), resulting in equal receptive language outcomes for boys and girls at age 10 (mean receptive language score boys age 10: 87.6 (*SD* 13.7)).

Discussion

This preliminary study showed that a multidisciplinary profile-oriented approach might be important in children born VPT to gain insight in which of these children are at risk for long-term adverse neurodevelopmental outcomes and to improve counseling and provide targeted treatment for at risk children. A factor and cluster analysis based on a broad array of neurodevelopmental outcomes obtained at 2 years CA revealed four distinctive profiles of children born VPT. The longitudinal course of these multidisciplinary profiles from 2 to 10 years of age, as well as the profile differences on single-domain outcome trajectories is presented. Despite very preterm birth, about one quarter of the children performed well on all investigated neurodevelopmental outcomes, cognitive-language-motor, behavioral, and auditory nerve function – the profile 1 children. However, these children showed an unexpected serious decline up to 10 years of age. Since they had the most favorable cognitive-language-motor function scores at age 2, the results at age 10 could be reflecting a regression to the mean. Another explanation, however, might be the relatively high vocabulary scores of the parents of children with this profile. At age 2, these children may have benefited from living in an environment with relatively rich language input. At school age, neurodevelopmental functioning becomes more complex, entailing integration across different neurocognitive domains. This increasing complexity might have led to diminishing developmental scores over time, resulting in a “growing into deficits effect.” This effect has been defined as cumulative, increasing neurodevelopmental problems throughout childhood due to early brain damage (Aarsen et al., 2006). If this trend could be validated in larger samples, such a declining development would be critical to clinical practice. Then, it would be highly relevant to study whether extra cognitive-linguistic stimulation (by parents or a treatment program) will sustain their favorable early development. Another explanation might be that these children cannot keep up with

their head start, due to altered brain development. Children born VPT have been suggested to have delayed language lateralization (Murner-Lavanchy et al., 2014), which might explain the “growing into deficits effect” for children with favorable scores at age 2.

All other children had below-average mean scores in at least one neurodevelopmental domain at the age of 2 – profile 2, 3 and 4 children. However, based on visual inspection of the data in graphs (Figure 4), these children showed different trajectories dependent on their profile membership. Profile 2 children were mainly characterized by behavioral problems at age 2. Interestingly, this aspect goes together with shorter ABR latencies, which has no known clinical implications but may be a marker of abnormal neural function (Stipdonk et al., 2016). A possible reason for shortened ABR latencies may be a shorter neural trajectory due to smaller head size (Trune et al., 1988). However, in the present study, the shorter latencies could not be explained by a significantly shorter head circumference at 2 years of age in profile 2 children (mean \pm SD; 48.3 ± 1.9) compared to the children in the three other profiles (respectively, 48.4 ± 1.6 ; 47.8 ± 1.3 ; 48.1 ± 1.5). The trajectory of profile 2 children showed a decline, while children with mild neurodevelopmental delay with delayed auditory nerve function (profile 3) showed a catch-up, and children with poor neurodevelopmental functioning (without behavioral problems or delayed auditory nerve function, profile 4) showed the widest variation in their trajectory.

A possible explanation for the favorable development of profile 3 children might be that these children represent “slow starters.” Their delayed auditory nerve function at age 2 might reflect delayed, but not disordered, brain maturation, followed by a catch-up development in the following years. Thus, delayed auditory nerve function might be associated with low performance at age 2, but might reflect increased performance at school-age.

Another explanation for the different trajectories of profile 2 and profile 3 children might be found in behavioral problems at age 2, since behavior scores differed significantly between children with profile 2 and 3 at age 2. More behavioral problems, as children with profile 2 were found to have, might have negatively impacted their language development, since their language scores declined the most. Accordingly, less behavioral problems, as profile 3 children were found to have, might have been favorable for their language development. This is in line with previous research suggesting that early behavioral problems have a negative impact on long-term cognitive and language outcome in VPT children (Burnett et al., 2018; Wong et al., 2016). The difference in language development between profile 2 and 3 children might also be explained by perinatal factors. Mean GA was significantly lower in profile 2 children than in profile 3 children.

Children with profile 4 showed the widest variation on all outcome measures at the age of 10 years. This might be explained by the fact that neonatal factors such as GA and neonatal illness varied the most in profile 4 children. Children with lower GA or more severe neonatal illness are expected to have a stable low trajectory, while children with a more favorable neonatal base are expected to have increasing development (Burnett et al., 2018; Linsell et al., 2015).

Regarding cognitive function, our preliminary data showed diminishing scores between 2 and 10 years of age in all four profiles, suggesting a growing into deficits effect. This had not been expected, since longitudinal studies have shown stable cognitive development throughout childhood (Mangin et al., 2017; Stalnacke et al., 2019). However, Wong et al. showed that early developmental assessments such as the BSID have poor sensitivity for long-term cognitive development, which is in accordance with our results showing

a majority of children with lower cognitive scores at school age (assessed with WISC-III) than at age 2 (assessed with BSID) (Wong et al., 2016). The results of the current study also provided evidence for the idea that the BSID may not be sensitive enough to detect cognitive deficits at age 2. Since the BSID is regularly used in clinical practice, these findings are alarming and show the importance of longitudinal follow-up of all children born.

Previous research has repeatedly shown boys born VPT to have lower neurocognitive scores, including language scores, than girls born VPT (Burnett et al., 2018; Hintz et al., 2006; Wolke et al., 2008). Therefore, an additional analysis was performed, which showed that boys performed worse than girls at the age of 2, specifically on receptive language outcome. Interestingly, however, boys, more often than girls, have a neurodevelopmental profile with a catch-up trajectory. This is in accordance with results of Doyle et al. (2015). The diminishing receptive language outcomes of girls at the age of 10, resulting in equal receptive language outcomes for boys and girls at age 10, therefore show that boys may have a “*slow to warm up*” development, while girls show a “*head start*,” but do not maintain this more advanced development when they reach school age.

Strengths and limitations

This study is the first to use factor- and cluster-analysis based on a broad array of included neurodevelopmental outcomes obtained from domain-specific tests. The method of longitudinally analyzing these multiple neurodevelopmental outcomes within the framework of four distinctive neurodevelopmental profiles is unique. This “profile-view” is a person-oriented approach, where the child and his coherent neurodevelopment are centralized, instead of one specific scientific field. The main limitation of this study is its small sample size. Since we followed-up four profiles, the power of each individual profile remained insufficient for adequate statistical analysis. Unfortunately, due to the small sample size, it was not possible to study sex differences within each profile, for example. Furthermore, we studied a wide timeline, from 2 to 10 years of age, which covers a period in which a child is exposed to many different influencing factors, at home and school, in an academic and social way, leading to an enormous amount of environmental variety. Also, a control group could have provided more insight in the specificity of the developmental patterns, although our main aim was to better understand the developmental differences *within* children born VPT.

Further research and implications

We strongly recommend other researchers to study larger samples of children born VPT and use profile analysis based on at least language, cognitive and behavioral outcome to describe the longitudinal, multidisciplinary development of children born VPT adequately. Besides, it may be of interest to study this development also in other subgroups of children born preterm, i.e., extremely preterm (GA less than 28 weeks) and moderate to late preterm (GA 32–37 weeks). Future studies with larger sample sizes are also needed to explore the idea of a mediated effect by other domains on language development as well as the impact of neonatal factors, such as GA and birth weight on clustered neurodevelopmental trajectories. In addition, with a larger sample, it might be possible to explain the wide variability as found in profile 4 children (i.e.,

poor neurodevelopmental functioning but normal behavioral and auditory nerve function) in this study, by studying the impact of GA and neonatal illness on their development. It may also be relevant to include sex as an interacting factor that may add to a better prediction of the neurodevelopmental trajectories. If our results could be confirmed in larger samples, this wide variability would suggest that these children have to be monitored intensively. Future research may also reveal more specific important environmental factors that may influence neurocognitive development during childhood, such as number of siblings, type of education and certain stressors. Furthermore, it is recommended to compare the development of the profiles of children born VPT to those of term-born peers to find out whether the different developmental patterns are typically for children born VPT only. If our preliminary results could be validated in other, larger studies, these results could be indicative for parent-counseling protocols. Developmental perspectives and advice may be profile-dependent. For example, children with below average language scores in combination with behavioral problems (profile 2 children) might have a worse prognosis regarding language outcome at school-age, than children with below average language scores but no behavioral problems (profile 3 children). In addition, if our preliminary results can be validated in further studies, these could lead to more appropriate early intervention as well. For example, children with profile 2 with deteriorated language development and increased attention problems over time might benefit from a structured parent-based early language intervention combined with intervention focused on improvement executive function and self-regulation skills.

Conclusions

In conclusion, our preliminary study demonstrated that a multidisciplinary, profile-oriented approach may be relevant in children born VPT to improve parent counseling and to enable early intervention and targeted treatment for those who are truly at risk. It should not be expected that high performers at age 2 continue to maintain their favorable development without further follow-up or treatment. Besides, behavioral problems at age 2 appear to negatively impact language development, and delayed auditory nerve function at age 2 suggests a “slow start” in language development followed by a catch-up.

Acknowledgments

We thank K.A.L. Mauff for statistical assistance and J. Hagoort for English language editing of the manuscript. We also thank all the children and their parents who participated in the study for their continuous effort and support.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

ORCID

Inge L. van Noort-van der Spek  <http://orcid.org/0000-0003-3853-7228>

References

- Aarnoudse-Moens, C. S., Smidts, D. P., Oosterlaan, J., Duivenvoorden, H. J., & Weisglas-Kuperus, N. (2009). Executive function in very preterm children at early school age. *Journal of Abnormal Child Psychology*, 37(7), 981–993. <https://doi.org/10.1007/s10802-009-9327-z>
- Aarsen, F. K., Paquier, P. F., Reddingius, R. E., Streng, I. C., Arts, W. F., Evera-Preesman, M., & Catsman-Berrevoets, C. E. (2006). Functional outcome after low-grade astrocytoma treatment in childhood. *Cancer*, 106(2), 396–402. <https://doi.org/10.1002/cncr.21612>
- Achenbach, T. (2001). *Child behavior checklist (CBCL) Nederlandse vertaling*. Aseba.
- Arpi, E., & Ferrari, F. (2013). Preterm birth and behaviour problems in infants and preschool-age children: A review of the recent literature. *Developmental Medicine & Child Neurology*, 55(9), 788–796. <https://doi.org/10.1111/dmcn.12142>
- Barre, N., Morgan, A., Doyle, L. W., & Anderson, P. J. (2011). Language abilities in children who were very preterm and/or very low birth weight: A meta-analysis. *Journal of Pediatrics*, 158(5), 766–774.e761. <https://doi.org/10.1016/j.jpeds.2010.10.032>
- Beers, M. (1995). *The phonology of normally developing and language-impaired children. (Studies in Language and Language Use no. 20)*. IFOTT.
- Burnett, A. C., Cheong, J. L. Y., & Doyle, L. W. (2018). Biological and social influences on the neurodevelopmental outcomes of preterm infants. *Clinics in Perinatology*, 45(3), 485–500. <https://doi.org/10.1016/j.clp.2018.05.005>
- Doyle, L. W., & Anderson, P. J. (2010). Adult outcome of extremely preterm infants. *Pediatrics*, 126(2), 342–351. <https://doi.org/10.1542/peds.2010-0710>
- Doyle, L. W., Cheong, J. L., Burnett, A., Roberts, G., Lee, K. J., & Anderson, P. J., & Victorian Infant Collaborative Study, G. (2015). Biological and social influences on outcomes of extreme-preterm/low-birth weight adolescents. *Pediatrics*, 136(6), e1513–1520. <https://doi.org/10.1542/peds.2015-2006>
- Hintz, S. R., Kendrick, D. E., Vohr, B. R., Kenneth Poole, W., & Higgins, R. D., Nichd Neonatal Research, N. (2006). Gender differences in neurodevelopmental outcomes among extremely preterm, extremely-low-birthweight infants. *Acta Paediatrica*, 95(10), 1239–1248. <https://www.iso.org/standards.html>
- International Organization for Standardization (2010). *Acoustics - Audiometric Test Methods*. (ISO Standard No. 8253-1:2010). <https://www.iso.org/standard/43601.html>
- Jary, S., Whitelaw, A., Walloe, L., & Thoresen, M. (2013). Comparison of Bayley-2 and Bayley-3 scores at 18 months in term infants following neonatal encephalopathy and therapeutic hypothermia. *Developmental Medicine & Child Neurology*, 55(11), 1053–1059. <https://doi.org/10.1111/dmcn.12208>
- Knol, F., Boelhouwer, J., & Veldheer, V. (2012). Status development of districts in the Netherlands 1998-2010. The Netherlands Institute for Social Research.
- Lean, R. E., Paul, R. A., Smyser, T. A., Smyser, C. D., & Rogers, C. E. (2018). Social adversity and cognitive, language, and motor development of very preterm children from 2 to 5 years of age. *Journal of Pediatrics*, 203(Dec), 177–184.e1. <https://doi.org/10.1016/j.jpeds.2018.07.110>

- Linsell, L., Malouf, R., Morris, J., Kurinczuk, J. J., & Marlow, N. (2015). Prognostic factors for poor cognitive development in children born very preterm or with very low birth weight: A systematic review. *JAMA Pediatrics*, 169(12), 1162–1172. <https://doi.org/10.1001/jamapediatrics.2015.2175>
- Lowe, J. R., Erickson, S. J., Schrader, R., & Duncan, A. F. (2012). Comparison of the Bayley II mental developmental index and the Bayley III cognitive scale: Are we measuring the same thing? *Acta Paediatrica*, 101(2), e55–58. <https://doi.org/10.1111/j.1651-2227.2011.02517.x>
- Lundequist, A., Bohm, B., & Smedler, A. C. (2013). Individual neuropsychological profiles at age 5 (1/2) years in children born preterm in relation to medical risk factors. *Child Neuropsychology*, 19(3), 313–331. <https://doi.org/10.1080/09297049.2011.653331>
- Luu, T. M., Vohr, B. R., Allan, W., Schneider, K. C., & Ment, L. R. (2011). Evidence for catch-up in cognition and receptive vocabulary among adolescents born very preterm. *Pediatrics*, 128(2), 313–322. <https://doi.org/10.1542/peds.2010-2655>
- Mainemer, A., & Rosenblatt, B. (1996). Evoked potentials as predictors of outcome in neonatal intensive care unit survivors: Review of the literature. *Pediatric Neurology*, 14(3), 189–195. [https://doi.org/10.1016/0887-8994\(96\)00049-5](https://doi.org/10.1016/0887-8994(96)00049-5)
- Mangin, K. S., Horwood, L. J., & Woodward, L. J. (2017). Cognitive development trajectories of very preterm and typically developing children. *Child Development*, 88(1), 282–298. <https://doi.org/10.1111/cdev.12585>
- Marlow, N. (2004). Neurocognitive outcome after very preterm birth. *Archives of Disease in Childhood - Fetal and Neonatal Edition*, 89(3), F224–228. <https://doi.org/10.1136/adc.2002.019752>
- Murner-Lavanchy, I., Steinlin, M., Kiefer, C., Weisstanner, C., Ritter, B. C., Perrig, W., & Everts, R. (2014). Delayed development of neural language organization in very preterm born children. *Developmental Neuropsychology*, 39(7), 529–542. <https://doi.org/10.1080/87565641.2014.959173>
- Nguyen, T. N., Spencer-Smith, M., Zannino, D., Burnett, A., Scratch, S. E., Pascoe, L., Ellis, R., Cheong, J., Thompson, D., Inder, T., Doyle, L. W., & Anderson, P. J. (2018). Developmental trajectory of language from 2 to 13 years in children born very preterm. *Pediatrics*, 141(5), 5. <https://doi.org/10.1542/peds.2017-2831>
- Pascal, A., Govaert, P., Oostra, A., Naulaers, G., Ortibus, E., & Van den Broeck, C. (2018). Neurodevelopmental outcome in very preterm and very-low-birthweight infants born over the past decade: A meta-analytic review. *Developmental Medicine & Child Neurology*, 60(4), 342–355. <https://doi.org/10.1111/dmnc.13675>
- Ross, G. S., Foran, L. M., Barbot, B., Sossin, K. M., & Perlman, J. M. (2016). Using cluster analysis to provide new insights into development of very low birthweight (VLBW) premature infants. *Early Human Development*, 92(Jan), 45–49. <https://doi.org/10.1016/j.earlhumdev.2015.11.005>
- Schlichting, J., Lutje, S., Spelberg, H., van der Meulen, S., & van der Meulen, B. (1999). *Schlichting Test voor Taalproductie. Test voor Woordontwikkeling. [Schlichting test for language production, word production test]*. Swets & Zeitlinger BV.
- Schlichting, J., & Spelberg, H. (2002). *Lexilijst Nederlands. [Dutch Lexilist]*. Pearson Assessment and Information B.V.
- Schlichting, L. (2005). *Peabody picture vocabulary test-III-NL*. Harcourt Test Publishers.
- Semel, E., Wiig, E. H., & Secord, W. H. (2010). *Clinical evaluation of language fundamentals 4 - NL*. Pearson.
- Stalnacke, J., Lundequist, A., Bohm, B., Forssberg, H., & Smedler, A. C. (2015). Individual cognitive patterns and developmental trajectories after preterm birth. *Child Neuropsychology*, 21(5), 648–667. <https://doi.org/10.1080/09297049.2014.958071>
- Stalnacke, S. R., Tessma, M., Bohm, B., & Herlenius, E. (2019). Cognitive development trajectories in preterm children with very low birth weight longitudinally followed until 11 years of age. *Frontiers in Physiology*, 10(Apr 2), 307. <https://doi.org/10.3389/fphys.2019.00307>
- Steenis, L., Verhoeven, M., & Van Baar, L. (2012). The Bayley III: The instrument for early detection of developmental delay. In *Advances in psychology research* (pp. 133–141). Nova Science Publishers.

- Stipdonk, L. W., Dudink, J., Utens, E., Reiss, I. K., & Franken, M. J. P. (2020). Language functions deserve more attention in follow-up of children born very preterm. *European Journal of Paediatric Neurology*, 26(May), 75–81. <https://doi.org/10.1016/j.ejpn.2020.02.004>
- Stipdonk, L. W., Weisglas-Kuperus, N., Franken, M. C., Nasserinejad, K., Dudink, J., & Goedegebure, A. (2016). Auditory brainstem maturation in normal-hearing infants born preterm: A meta-analysis. *Developmental Medicine & Child Neurology*, 58(10), 1009–1015. <https://doi.org/10.1111/dmcn.13151>
- Trune, D. R., Mitchell, C., & Phillips, D. S. (1988). The relative importance of head size, gender and age on the auditory brainstem response. *Hearing Research*, 32(2–3), 165–174. [https://doi.org/10.1016/0378-5955\(88\)90088-3](https://doi.org/10.1016/0378-5955(88)90088-3)
- Van der Meulen, B., Spelberg, H., & Smrkovsky, M. (1993). *Handleiding Bayley scales of infant development-Nederlandse versie (BSID-II-NL)*. Swets & Zeitlinger.
- Van Eldik, M., Spelberg, H., van der Meulen, B., & van der Meulen, S. (2004). *Handleiding Reynell Test voor Taalbegrip. [Reynell test for language comprehension manual]* (Fourth ed.). Harcourt Assessment BV.
- Van Noort-van der Spek, I. L., Franken, M. C., & Weisglas-Kuperus, N. (2012). Language functions in preterm-born children: A systematic review and meta-analysis. *Pediatrics*, 129(4), 745–754. <https://doi.org/10.1542/peds.2011-1728>
- Van Noort-van der Spek, I. L., Franken, M. C., Wieringa, M. H., & Weisglas-Kuperus, N. (2010). Phonological development in very-low-birthweight children: An exploratory study. *Developmental Medicine & Child Neurology*, 52(6), 541–546. <https://doi.org/10.1111/j.1469-8749.2009.03507.x>
- Verhulst, F. (2000). Gedragsvragenlijst voor kinderen 1½-5 jaar. Dutch version of the Children's Behavior Questionnaire. Erasmus MC Sophia Children's Hospital.
- Wang, X., Carroll, X., Wang, H., Zhang, P., Selvaraj, J. N., & Leeper-Woodford, S. (2020). Prediction of delayed neurodevelopment in infants using brainstem auditory evoked potentials and the Bayley II scales. *Frontiers in Pediatrics*, 8(Aug 21), 485. <https://doi.org/10.3389/fped.2020.00485>
- Ward, J. (1963). Hierarchical grouping to optimize an objective function. *Journal of the American Statistical Association*, 58(301), 236–244. <https://doi.org/10.1080/01621459.1963.10500845>
- Wechsler, D. (2005). *WISC-III-NL Handleiding*. Harcourt Assessment.
- Wolke, D., Samara, M., Bracewell, M., Marlow, N., & Group, E. P. S. (2008). Specific language difficulties and school achievement in children born at 25 weeks of gestation or less. *Journal of Pediatrics*, 152(2), 256–262. <https://doi.org/10.1016/j.jpeds.2007.06.043>
- Wong, H. S., Santhakumaran, S., Cowan, F. M., & Modi, N., & Medicines for Neonates Investigator, G. (2016). Developmental assessments in preterm children: A meta-analysis. *Pediatrics*, 138(2), e20160251. <https://doi.org/10.1542/peds.2016-0251>
- Zimmerman, E. (2018). Do infants born very premature and who have very low birth weight catch up with their full term peers in their language abilities by early school age? *Journal of Speech Language, and Hearing Research*, 61(1), 53–65. https://doi.org/10.1044/2017_jslhr-l-16-0150