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Neurodevelopmental Outcomes at Two Years' Corrected Age of Very Preterm Infants after Implementation of a Post-Discharge Responsive Parenting Intervention Program (TOP Program)

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Objective To compare neurodevelopmental outcomes at 2 years corrected age (CA) between infants born very preterm (VP) who did or did not receive a postdischarge responsive parenting intervention (Transmural developmental support for very preterm infants and their parents [TOP program]) between discharge home and 12 months' CA.

Study design The Systemic Hydrocortisone to Prevent Bronchopulmonary Dysplasia (SToP-BPD) study showed no differences between treatment groups in motor and cognitive development using the Dutch Bayley Scales of Infant Development and behavior using the Child Behavior Checklist at 2 years' CA. During its study period, the TOP program was gradually scaled up nationwide in the same population, providing an opportunity to evaluate the effect of this program on neurodevelopmental outcome, after adjusting for baseline differences.

Results Among 262 surviving VP infants in the SToP-BPD study, 35% received the TOP program. Infants in the TOP group had a significantly lower incidence of a cognitive score <85 (20.3% vs 35.2%; adjusted absolute risk reduction: −14.1% [95% CI: −27.2 to −1.1]; P = .03), and a significantly higher mean cognitive score (96.7 ± 13.8), compared with the non-TOP group (92.0 ± 17.5; crude mean difference: 4.7 [95% CI: 0.3 to 9.2]; P = .03). No significant differences were found on motor scores. For behavior problems, a small but statistically significant effect for anxious/depressive problems was found in the TOP group (50.5 vs 51.2; P = .02).

Conclusions VP infants supported by the TOP program from discharge until 12 months' CA had better cognitive function at 2 years' CA. This study demonstrates a sustained positive effect of the TOP program in VP infants. *(J Pediatr 2023;■:1-7)*.

Improved neonatal care has resulted in increased survival rates of children born very preterm (VP).[1] However, VP birth is still associated with high rates of mild disabilities later in life.[2] To improve neurodevelopmental outcomes, postdischarge parenting intervention programs are recommended by the European Foundation for the Care of Newborn Infants for all VP infants and their families.[3] In the Netherlands, a randomized clinical trial (RCT) evaluating the effect of the Infant Behavioral Assessment and Intervention Program showed improvement of cognitive, motor, and behavioral outcomes at 6 months corrected age (CA).[4] At 24 months' CA, a sustained effect on motor outcomes was found, whereas cognitive outcomes improved in the subgroup of infants with bronchopulmonary dysplasia (BPD).[5] Based on these results, the TOP program (Transmural developmental support for very preterm infants and their parents) was implemented as routine care.[6] The pilot

Bayley-III-NL	Dutch version of the Bayley Scales of Infant Development, Third Edition	GA	Gestational age
		NICU	Neonatal intensive care unit
		RCT	Randomized clinical trial
BPD	Bronchopulmonary dysplasia	SToP-BPD	Systemic Hydrocortisone to Prevent Bronchopulmonary Dysplasia
CA	Corrected age		
CBCL1½−5	Child Behavior Checklist 1.5 to 5 years	TOP	Transmural developmental support for very preterm infants and their parents
CCS	Composite cognitive score		
CMS	Composite motor score	VP	Very preterm
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th Edition		

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The authors declare no conflicts of interest.

Clinical Trial Registration: The SToP-BPD study was registered with the Netherlands Trial Register (NTR2768; registered on 17 February 2011; https://www.trialregister.nl/trial/2640) and the European Union Clinical Trials Register (EudraCT, 2010-023777-19; registered on 2 November 2010; https://www.clinicaltrialsregister.eu/ctr-search/trial/2010-023777-19/NL).

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implementation started in 2010, and since 2014, the TOP program is reimbursed by all Dutch Health Care Insurers and, consequently, is increasingly offered in the Netherlands to VP infants born before 32 weeks of gestation and/or with a birth weight below 1500 g, irrespective of social context. In 2018, 70% of the Dutch target population was supported in the TOP program.[6]

The SToP-BPD (Systemic Hydrocortisone to Prevent Bronchopulmonary Dysplasia) study was a randomized placebo-controlled trial conducted between November 2011 and December 2016 investigating the efficacy and safety of systemic hydrocortisone treatment initiated in the second week of life in ventilator-dependent preterm infants born before 30 weeks' gestation.[7] Follow-up at 2 years' CA showed no difference in the composite outcome death or neurodevelopmental impairment between the hydrocortisone and placebo group.[8]

The current study gave us the opportunity to evaluate the effect of the TOP program during its implementation in the real-world setting, as the pilot and full implementation phases of the TOP program corresponded with the study period of the SToP-BPD study. The objective of the current study was to compare the cognitive, motor, and behavioral outcomes of VP infants at 2 years' CA who did and did not receive the TOP program.

Methods

Study Design and Participants

Sixteen neonatal intensive care units (NICU) in the Netherlands and Belgium participated in the SToP-BPD study (NTR2768; EudraCT 2010-023777-19). Infants born at a gestational age (GA) <30 weeks and/or with a birth weight <1250 g, who were ventilator-dependent between 7 and 14 days after birth, were eligible.[9] For the current cohort study, survivors of the SToP-BPD study who attended the 2-year follow-up visit were included.

All survivors of the SToP-BPD study fulfilled the inclusion criteria for the TOP program and participated if a TOP interventionist was available. Written informed consent was obtained from both parents before randomization in the SToP-BPD trial. The study protocol of the SToP-BPD study was approved by the human research ethics committees of the Academic Medical Center in Amsterdam, the Netherlands (reference number: 2010_297), and at each participating center.[7] The birth characteristics from the SToP-BPD database were used to identify infants in the TOP database. No additional consent was required for this procedure. The SToP-BPD study was registered with the Netherlands Trial Register (NTR2768; registered on 17 February 2011; https://www.trialregister.nl/trial/2640) and the European Union Clinical Trials Register (EudraCT, 2010-023777-19; registered on 2 November 2010; https://www.clinicaltrialsregister.eu/ctr-search/trial/2010-023777-19/NL).

Intervention

The TOP program aims to enhance the developmental opportunities for VP infants at a critical time of their life by targeting parental responsiveness toward their child.[6] Key goals of the program are to assist parents to observe, understand, and interpret the behavioral cues of the child and to use adequate responsive reactions. The theoretical framework for the TOP program was further developed based on outcomes and insights obtained in the RCT. Adaptations to the protocol were made to tailor the intervention to a real-world setting, such as extending the intervention to 12 months' CA. Since 2014, the TOP program is increasingly becoming part of routine care in the Netherlands and consists of 12 one-hour intervention sessions at home, starting after discharge from hospital until 12 months' CA. The intervention has a defined Theory of Change, and the intervention protocol is carried out by pediatric physical therapists who are additionally trained to execute the TOP program.[6]

Chain of Care in which TOP Takes Place

All VP infants were invited for standardized follow-up visits in their NICU center during the first year of life at 6 and 12 months' CA, and thereafter, at two and 5 years' CA. In addition, infants regularly visited their regional pediatricians at least until the age of 15-18 months. If deemed necessary, a referral to a pediatric physical therapist was done by the regional pediatrician or follow-up clinic when families did not participate in the TOP program.

Outcomes

The follow-up at 2 years' CA was performed between April 18, 2014, and June 27, 2019. Participants were evaluated by trained professionals in one of the NICU follow-up clinics.

The main outcome measures of this study were the cognitive, motor, and behavioral outcomes at 2 years' CA. Neurodevelopmental assessment was performed using the Dutch version of the Bayley Scales of Infant Development, Third Edition (Bayley-III-NL) yielding the composite cognitive score (CCS) and composite motor score (CMS). CMS consisted of the gross motor and fine motor scales. In the majority of infants (94%), the Bayley-III-NL was used. When the American version of the Bayley-III or the Dutch version of the Bayley Scales of Infant Deveopment, Second Edition was used, scores were converted to the Bayley-III-NL, as described previously.[10,11] A CCS or CMS below 85 (which corresponds to 1 SD below the mean) was considered as a clinically relevant neurodevelopmental delay.

Prior to the 2-year follow-up visit, parents completed the Child Behavior Checklist 1.5 to 5 years (CBCL1½ −5) to assess the child's behavior problems.[12] The CBCL consists of 100 questions in which parents can indicate to what extent behavior problems are present, during the preceding 2 months. A standardized T score was calculated for each scale. A higher score reflects more behavioral problems.[13] The rate of infants with a T score above 55 was also reported, as scores above 55 were indicative for serious behavioral problems in need of intervention.[14]

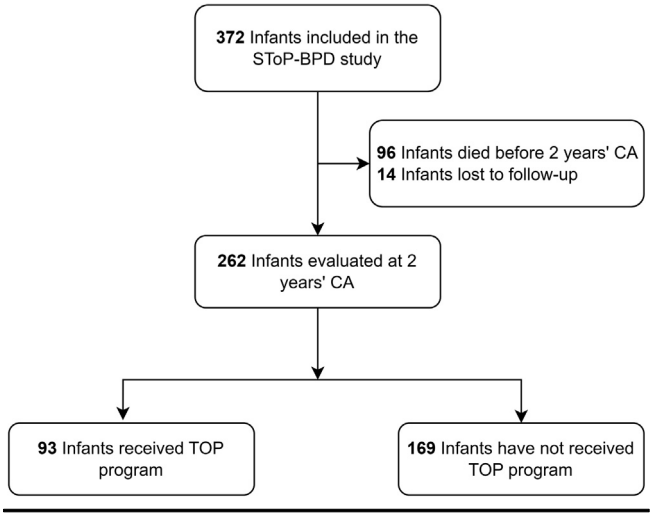

Figure. Consolidated standards of reporting trials flow diagram.

Statistical Analysis

Descriptive statistics are used to summarize the clinical and parental characteristics and outcome parameters. Statistical uncertainty is expressed in 95% confidence intervals (95% CIs). Crude mean differences, absolute risk differences, and odds ratios were calculated for the effect of the TOP program on cognitive, motor, and behavioral outcomes using linear regression models for continuous outcomes and a generalized linear model with a binomial distribution and identity link and logistic regression models for binary outcomes. In addition, multivariable regression models were used to adjust the outcomes for selected baseline differences between both groups (severe retinopathy of prematurity and parental education) and factors known to influence neurodevelopmental outcomes (GA, BPD severity, and severe brain injury).

For the CBCL scores, 30% of checklists were missing. In addition, 43% of the data of the syndrome scales and 52% of the *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition* (DSM-IV)-oriented subscales were missing. Assuming that these data were missing at random, we used multiple imputation with chained equations to impute missing outcome data for the CBCL scores prior to data analysis.[15] Baseline variables (GA, birth weight, sex, and multiple birth), postrandomization variables (BPD diagnosis and severe brain injury), 2-year neurodevelopmental variables (CCS and CMS on the Bayley Scales of Infant and Toddler Development-III, Dutch version), and parental characteristics (parental education and multilingual environment) were used as predictor variables within the imputation approach. Fifty imputed datasets were generated with 50 iterations. Predictive mean matching was used as the imputation routine for continuous data. The analyses were pooled based on Rubin's rules.[16] Furthermore, we performed a sensitivity analysis on cases with complete questionnaire data only. Results based on multiple imputed data were compared with those based on complete-case analysis.

All analyses were performed using 2-sided tests, and $P < .05$ was regarded as statistically significant. No formal adjustments for multiple comparisons were made. Statistical analysis was performed in IBM SPSS Statistics for Windows, version 28.0 (IBM Corp, Armonk).

Table I. Characteristics of infants and parents who attended the TOP program and who did not

Characteristics	TOP program yes (n = 93)	TOP program no (n = 169)	*P* value
Infant birth characteristics			
Gestational age at birth, median (IQR), wk	25.1 (24.4 – 26.0)	25.9 (25.0 – 26.6)	<.001*
Birth weight, median (IQR), g	780 (648 – 865)	760 (660 – 870)	.93
Male sex	50 (53.8)	96 (56.8)	.70
Small for gestational age†	11 (11.8)	25 (14.8)	.58
Multiple birth	36 (38.7)	51 (30.2)	.17
Neonatal morbidities			
Moderate and severe bronchopulmonary dysplasia	64 (68.8)	104 (61.5)	.78
Severe brain injury‡	9 (9.7)	27 (16.0)	.19
Infection§	49 (52.7)	85 (50.3)	.80
Severe retinopathy of prematurity, >grade 2	32 (34.4)	38 (22.5)	.04*
Parental characteristics¶			
Parental education**			.07
Low level	16 (17.2)	48 (28.4)	
Middle level	32 (34.4)	45 (26.6)	
High level	40 (43.0)	59 (34.9)	
Unknown	5 (5.4)	17 (10.1)	
Dutch as main language spoken at home	84 (90.3)	140 (83.3)	.14
Multilingual environment	16 (17.2)	33 (19.6)	.74

Data are expressed as n (%) unless stated differently.
IQR, interquartile range.
*$P < .05$ was regarded as statistically significant.
†Defined as less than the 10th percentile on the Fenton growth chart.
‡Includes infants with intraventricular hemorrhage > grade 2, cystic periventricular leukomalacia, and post hemorrhagic ventricular dilation during admission at the neonatal intensive care unit.
§Includes infants with culture-proven sepsis and necrotizing enterocolitis > stage 2a according to Bell classification during admission at the neonatal intensive care unit.
¶Parental characteristics at baseline are at the infant level (ie, parents were counted multiple times if they had multiple infants).
**Parental educational level is defined as low if one or both parents have attended lower professional school or less or one parent low and the other middle; middle if both parents have attended medium professional school or one low and the other high; and high if one or both parents have attended higher professional school or university or one parent high and the other middle.

Table II. Neurodevelopmental outcomes at 2 years' corrected age

Neurodevelopmental outcomes at 2 years' CA	TOP program yes	TOP program no	Mean difference (95% CI)*	OR (95% CI)†	*P* value
Bayley-III-NL‡					
Composite cognitive score (n = 223)	96.7 (±13.8)	92.0 (±17.5)	4.7 (0.3 to 9.2)		.04
Composite cognitive score <85, n (%) (n = 223)	18/81 (22.2)	51/142 (35.9)			
Crude analysis			−13.7 (−25.7 to −1.7)§	0.51 (0.27 to 0.95)	.03¶
Adjusted analysis** (n = 209)			−14.1 (−27.2 to −1.1)§	0.44 (0.22 to 0.91)	.03¶
Composite motor score (n = 202)	94.9 (±13.2)	92.5 (±16.7)	2.3 (−2.2 to 6.9)		.32
Composite motor score <85, n (%) (n = 202)	16/70 (22.9)	36/132 (27.3)			
Crude analysis			−4.4 (−16.8 to 8.0)§	0.79 (0.40 to 1.56)	.49¶
Adjusted analysis** (n = 189)			−2.1 (−13.3 to 9.1)§	0.91 (0.43 to 1.96)	.71¶
Fine motor score, mean scaled score (n = 198)	10.3 (±2.5)	9.7 (±3.5)	0.6 (−0.3 to 1.5)		.19
Gross motor score, mean scaled score (n = 190)	8.1 (±2.6)	7.8 (±2.8)	0.2 (−0.6 to 1.1)		.55

Data are expressed as the mean (SD) unless stated differently.
CA, corrected age; *Bayley-III-NL*, Bayley Scales of Infant and Toddler Development, Third Edition, Dutch version.
*Data are mean difference unless otherwise indicated. Crude data are given unless otherwise indicated.
†Logistic regression analysis. Crude data are given unless otherwise indicated.
‡Normed mean of Bayley-III-NL of 100 and a standard deviation of 15.
§Absolute risk reduction with 95% CI.
¶Generalized linear model with a binomial distribution and identity link.
**Absolute risk reduction and odds ratio are adjusted for gestational age, BPD diagnosis (no/mild BPD vs moderate/severe BPD), parental education (low vs middle and high educational level), severe retinopathy of prematurity > grade 2 (yes vs no), and severe brain injury (yes vs no).

Results

Of the 372 VP infants enrolled in the SToP-BPD trial, 96 infants died before 2 years' CA, and 14 infants were lost to follow-up. A total of 262 infants were evaluated at 2 years' CA, of which 93 infants received the TOP program during its implementation process (**Figure**). Clinical characteristics of the 262 infants and their parents did not differ between the groups, with the exception of a lower GA, a higher proportion of severe retinopathy of prematurity, and an overall higher level of parental education in the TOP group (**Table I**).

The TOP program was provided by 46 TOP interventionists, each of whom supported 1 to 7 infants that participated in this study. Infants participating in the TOP program received a mean of 10.7 intervention sessions (range: 2 to 13), and 59 infants (83%) had more than 8 intervention sessions. Of the infants in the non-TOP group, 76.9% (130/169) received physical therapy in the first year. In the second year of life, infants in the non-TOP group received significantly more physical therapy than infants in the TOP group (59% vs 41%, respectively, difference: −17.9% [95% CI: −30.4% to −5.4%], $P = .005$).

At 2 years' CA, infants in the TOP group had a significantly lower incidence of a CCS below 85 (20.3% vs 35.2%; adjusted

Table III. Behavioral outcomes assessed by CBCL 1.5-5 year at 2 years' corrected age

	Multiple imputation analysis					
CBCL	TOP program yes (n = 93)	TOP program no (n = 169)	Mean difference (95% CI)*	Adjusted mean difference (95% CI)†	*P* value	Adjusted *P* value
Total problems	46.3 (9.9)	48.2 (10.6)	−1.91 (−4.48 to 0.66)	−1.70 (−4.51 to 1.11)	.15	0.24
Internalizing problems	45.2 (10.1)	46.9 (11.8)	−1.73 (−4.52 to 1.06)	−1.60 (−4.63 to 1.44)	.22	0.30
Externalizing problems	49.3 (10.6)	49.8 (11.0)	−0.56 (−3.24 to 2.13)	−0.06 (−2.97 to 2.85)	.69	0.97
CBCL syndrome scales						
Emotionally reactive	52.8 (5.8)	52.5 (5.5)	0.28 (−1.14 to 1.70)	0.49 (−1.02 to 2.01)	.70	0.52
Anxious/depressive	50.5 (1.6)	51.2 (3.1)	−0.73 (−1.39 to −0.08)	−0.83 (−1.51 to −0.15)	.03	0.02
Somatic complaints	53.7 (6.7)	55.6 (8.8)	−1.87 (−3.91 to 0.17)	−2.07 (−4.26 to 0.13)	.07	0.07
Withdrawn behavior	53.9 (6.2)	54.0 (6.1)	−0.07 (−1.64 to 1.50)	0.11 (−1.53 to 1.76)	.93	0.89
Sleep problems	52.3 (5.0)	53.5 (7.8)	−1.20 (−2.84 to 0.45)	−1.57 (−3.35 to 0.20)	.16	0.08
Attention problems	56.6 (8.5)	56.0 (9.4)	0.52 (−1.67 to 2.72)	0.43 (−1.85 to 2.70)	.64	0.71
Aggressive behavior	53.1 (5.9)	53.2 (6.5)	−0.11 (−1.65 to 1.43)	0.43 (−1.22 to 2.08)	.89	0.61
CBCL DSM-IV-oriented subscales						
Affective problems	53.0 (4.6)	54.4 (7.1)	−1.36 (−2.85 to 0.13)	−1.36 (−2.90 to 0.17)	.07	0.08
Anxiety problems	51.2 (3.3)	52.4 (5.7)	−1.17 (−2.37 to 0.04)	−1.31 (−2.64 to 0.02)	.06	0.05
Pervasive developmental	54.4 (7.2)	54.0 (6.9)	0.36 (−1.44 to 2.15)	0.52 (−1.40 to 2.45)	.70	0.59
Oppositional defiant problems	53.7 (6.5)	53.9 (6.6)	−0.13 (−1.74 to 1.48)	0.16 (−1.58 to 1.90)	.87	0.86
Attention deficit/hyperactivity problems	54.3 (6.8)	54.2 (7.3)	0.12 (−1.64 to 1.87)	0.46 (−1.41 to 2.33)	.90	0.63

Data are expressed as the mean (SD).
*Mean difference with 95% CI was calculated using linear regression.
†Mean difference adjusted for gestational age, BPD diagnosis (no/mild BPD vs moderate/severe BPD), parental education (low vs middle and high educational level), severe retinopathy of prematurity > grade 2 (yes vs no), and severe brain injury (yes vs no) using linear regression.

absolute risk reduction: −14.1% [95% CI: −27.2 to −1.1]; P = .03), with a significantly higher mean CCS (96.7, SD ± 13.8) than those in the non-TOP group (mean: 92.0, SD ± 17.5; crude mean difference: 4.7 [95% CI: 0.3 to 9.2]; P = .04). No significant differences were found between the TOP and non-TOP group for CMS, fine motor score, and gross motor score (crude mean difference: 2.3 [95% CI: −2.2 to 6.9] for CMS, 0.6 [95% CI: −0.3 to 1.5] for fine motor score, and 0.2 [95% CI: −0.6 to 1.1] for gross motor score) (**Table II**).

Of the 183 completed checklists, the CBCL syndrome scales were calculated for 150 infants and the CBCL DSM-IV-oriented subscales for 126 infants. When multiple imputation was used to account for missing data, the T scores for total problems, internalizing problems, and externalizing problems were not significantly different between both groups (**Table III**). In addition, the CBCL syndrome and DSM-IV-oriented subscales were not significantly different between both groups, except for a small but statistically significant difference in T score for anxious/depressive problems in the TOP group compared with the non-TOP group (50.5 vs 51.2, respectively; adjusted mean difference: −0.83 [95% CI: −1.51 to −0.15]; P = .02) (**Table III**). The proportion of infants with a T score above 55 was not significantly different between both groups (**Table IV**; available at www.jpeds.com).

The sensitivity analyses limiting analyses to cases with complete CBCL questionnaire data revealed significant lower mean T scores in the TOP group and lower proportion of infants in the TOP group with a T score above 55 for somatic complaints, sleep, and affective and anxiety problems than those in the non-TOP group (**Table V** and **VI**; available at www.jpeds.com).

Discussion

This study evaluated the effect of the TOP program, during its nationwide implementation, on the neurodevelopmental and behavioral outcomes of VP infants included in the STOP-BPD study. The STOP-BPD study showed high rates of infants with moderate to severe BPD and, consequently, a high risk for adverse neurodevelopmental outcomes.[7,8] Therefore, this cohort was used to perform a secondary analysis. We found that VP infants supported by the TOP program had better cognitive function and a small but statistically significant decrease in anxious/depressive behaviors at 2 years' CA than those not supported by the TOP program.

Our results correspond with the prior outcomes of the RCT investigating the effect of the Infant Behavioral Assessment and Intervention Program, which showed improved cognitive outcomes over a time frame of 5 years.[17] In that study, the cognitive improvements at 2 years' CA were most pronounced in the subgroup of children with BPD,[5] and these effects were sustained at 5 years' follow-up.[18] Additionally, the Cochrane Review on early intervention programs for preterm infants showed positive influences on cognitive and motor outcomes during infancy and benefits on cognitive outcomes persisting into preschool age.[19] An important difference between an RCT and a postimplementation study is that an RCT is conducted under ideal conditions in a highly selected patient population which may limit generalizability, whereas an observational cohort study reflects the intervention in the real-world setting.[20] The current study is the first study comparing neurodevelopmental outcomes of VP infants following implementation of a postdischarge intervention program, outside the setting of an RCT. The STOP-BPD study was conducted at the start of the scaling-up process of the TOP program. There was a gradual increase in capacity of trained interventionists since the TOP education program for pediatric physical therapists lasts 1 year. This explains the 35% uptake in the current study sample. In the subsequent years, the reach of the program continued to increase, with uptake currently exceeding 80% in the target population in the Netherlands. Consequently, a prospective study comparing infants with and without the support of the TOP program is no longer feasible.

While we did find the expected improvement on 2-year cognitive outcome, we did not find differences in motor domains as reported in the initial RCT.[4,5,18] Within the non-TOP group, 77% received home physical therapy during the first year after discharge. In the second year of life, more infants in the non-TOP group (59%) received physical therapy at home, compared with the TOP group (41%). Although the TOP program is also executed by pediatric physical therapists,[6] there are essential differences between the interventions. The TOP program is a preventive intervention, whereas physical therapy supports those infants who are referred for an observed motor problem. Furthermore, the TOP program aims to increase parental responsiveness for behavioral cues of the infant in order to create conditions to improve all domains of development, including motor development. Physical therapy directly and specifically targets motor development. The higher referral for physical therapy in the second year of life in the non-TOP group may indicate more motor problems after 1 year of CA. In addition, this more extensive motor intervention could explain the limited differences observed on motor domains between both groups at 2 years' CA.

Parental responsiveness is strongly associated with cognitive development and behavioral outcomes in VP infants.[21,22] This is consistent with the clinically significant cognitive improvement observed in the TOP group at 2 years' CA. While reports from the previously conducted RCT also investigated the effect of the intervention on behavioral outcomes of the child and found a positive effect of the intervention at 6 months' CA,[4] at 2 years' CA, the CBCL scores showed no differences between the intervention and control group.[5] In the current study, we found similar mean T scores for internalizing, externalizing, and total problems as in the RCT, without significant differences between both groups. However, we found a small positive effect on anxious/depressive problems in infants supported by the TOP intervention

program. This positive effect might be caused by increased self-regulatory capacities, more sense of security, and knowledge of the parents about their infant's needs.[23,24] Although the observed positive effect is small and therefore possibly of limited clinical relevance, behavioral problems are frequently present in infants born very prematurely.[2] For this reason, behavioral problems are important to address when evaluating postdischarge intervention programs. The positive effects on cognitive and behavior outcomes of the child should be further evaluated at 5 years, as the predictive value of a 2-year follow-up assessment for later neurodevelopment outcome is limited.[18]

In our study, parents of infants who received the TOP program had overall significantly higher education levels than those who did not receive TOP. However, our multivariable regression model adjusted for parental education and other factors associated with neurodevelopment and confirmed the robustness of the effect of the TOP program on cognitive function.

As mentioned previously, we evaluated the intervention effect of the TOP program during the scaling-up period. Implementation of such a process-oriented program is complex and may vary across settings.[25] The positive effects found in a controlled environment may decrease during scaling up, described as the scale-up penalty.[26,27] The implementation process of the TOP program followed three consecutive phases and was done through careful planning and monitoring to maintain the positive effects.[6] With this study, we were able to demonstrate cognitive improvements in VP infants following real-world implementation of a postdischarge responsive parenting intervention program. This demonstrates the importance of integration and further development of early intervention programs for VP infants with high risk for adverse neurodevelopmental outcomes.[28]

Our study has some limitations. First, we performed a secondary analysis of the original SToP-BPD study in a nonrandomized setting. Few differences in perinatal and sociodemographic variables were found, and our analysis was adjusted for these confounding factors. However, in a nonrandomized setting unmeasured differences can exist between both groups for which analysis were not adjusted, resulting in residual confounding.[29] By evaluating the effect of the TOP program in a large cohort of infants with high rates of moderate to severe BPD, we are able to demonstrate the effects of an early intervention program following implementation. Second, in 6% of infants the neurodevelopmental status at 2 years' CA could not be assessed or the assessments were performed using the Dutch version of the Bayley Scales of Infant Development, second edition, resulting in the need to convert scores to Bayley-III-NL-equivalent scores. Since the number of these infants was small and equally distributed between both groups, it is unlikely that this has biased our results.[8] We note, however, the wide confidence intervals observed for the CCS and CMS, raising uncertainty in the point estimate reported. As the TOP program is now widely distributed across the Netherlands, performing prospective evaluation in a larger population is currently not feasible. Third, up to 30% of the parents did not complete the CBCL 1½-5 checklist and for some children the subscale scores were not registered. We found some differences analyzing only cases with complete questionnaire data compared with the multiple imputation analysis, which emphasizes the need for multiple imputation in populations with many missing data to accurately evaluate the impact of missing data on study findings. Fourth, to understand fully the lack of a difference in the motor domain between the TOP group and non-TOP group, more detailed information about the number of sessions, content and execution of the regular physical therapy treatment would be necessary. This information was not available in our database. Last, this study period encompasses both the pilot implementation of the TOP program when small adaptations in the intervention protocol and the TOP education program were made, as well as the full implementation phase.[6] For the current study, no information or measuring tools were available to evaluate the pathway of change.

In conclusion, at 2 years' CA, high risk VP infants following the TOP program as part of routine care had better cognitive function. This finding confirms the previous findings in our RCT and demonstrates the benefits of the TOP program in improving neurodevelopmental outcomes in VP infants in the clinical setting. ■

Author Contributions.

Nienke Halbmeijer performed the statistical analyses, prepared the data tables, drafted the initial manuscript, and revised the manuscript. Martine Jeukens-Visser and Monique Flierman made substantial contributions to the interpretation of data and reviewed and revised the manuscript.

Wes Onland and Anton van Kaam are local investigators, made substantial contributions to the concept and design of the study, and critically reviewed the manuscript for important intellectual content.

Aleid Leemhuis is a local investigator, made substantial contributions to the concept and design of the study, critically reviewed the manuscript for important intellectual content, had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Data Statement

Data sharing statement available at www.jpeds.com.

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Table IV. Proportions of infants with behavioral problems needing intervention, T score above 55, assessed by CBCL 1.5-5 years at 2 years' corrected age

	Multiple imputation analysis			
CBCL	TOP program yes (n = 93)	TOP program no (n = 169)	Difference, % (95% CI)*	*P* value
Total problems	20 (21.5)	39 (23.1)	−1.6 (−13.3 to 10.1)	.79
Internalizing problems	14 (15.1)	36 (21.3)	−6.5 (−17.3 to 4.4)	.24
Externalizing problems	24 (25.8)	53 (31.3)	−5.9 (−18.6 to 5.8)	.36
CBCL syndrome scales				
Emotionally reactive	16 (17.2)	29 (17.2)	0.5 (−10.7 to 11.6)	.93
Anxious/depressive	3 (3.2)	19 (11.2)	−7.5 (−14.8 to −0.3)	.04
Somatic complaints	28 (30.1)	62 (36.7)	−8.1 (−21.9 to 5.8)	.25
Withdrawn behavior	36 (38.7)	66 (39.1)	−0.5 (−15.7 to 14.7)	.95
Sleep problems	19 (20.4)	48 (28.4)	−8.1 (−20.7 to 4.5)	.21
Attention problems	42 (45.2)	72 (42.6)	3.3 (−12.7 to 19.3)	.69
Aggressive behavior	18 (19.4)	36 (21.3)	−2.1 (−13.4 to 9.2)	.71
CBCL DSM-IV-oriented subscales				
Affective problems	27 (29.0)	62 (36.7)	−7.8 (−22.4 to 6.9)	.30
Anxiety problems	9 (9.8)	28 (16.6)	−7.1 (−17.3 to 3.1)	.17
Pervasive developmental	28 (30.1)	49 (29.0)	1.3 (−12.8 to 15.4)	.86
Oppositional defiant problems	19 (20.4)	40 (23.7)	−3.6 (−16.3 to 9.2)	.58
Attention deficit/hyperactivity problems	27 (29.0)	49 (29.0)	−0.2 (−14.1 to 13.8)	.98

Data are expressed as n (%).
*Absolute risk difference was calculated using a generalized linear model using a binomial distribution with identity link.

Table V. Behavioral outcomes assessed by CBCL 1.5-5 years at 2 years' corrected age in cases with complete outcome data

	Cases with complete outcome data					
CBCL	TOP program yes	TOP program no	Mean difference (95% CI)*	Adjusted mean difference (95% CI)†	*P* value	Adjusted *P* value
Total problems (n = 183)	45.9 (9.6)	48.6 (9.7)	−2.71 (−5.58 to 0.16)	−2.30 (−5.34 to 0.73)	.06	0.14
Internalizing problems (n = 183)	44.7 (9.3)	47.3 (10.6)	−2.61 (−5.61 to 0.39)	−2.27 (−5.47 to 0.92)	.09	0.16
Externalizing problems (n = 183)	48.9 (10.4)	50.1 (10.2)	−1.17 (−4.22 to 1.88)	−0.48 (−3.70 to 2.73)	.45	0.77
CBCL syndrome scales						
Emotionally reactive (n = 150)	52.9 (5.3)	53.4 (5.6)	−0.49 (−2.26 to 1.28)	−0.01 (1.87 to 1.85)	.58	0.99
Anxious/depressive (n = 150)	50.4 (1.1)	51.5 (3.0)	−1.10 (−1.86 to −0.34)	−1.17 (−1.95 to −0.39)	.005	0.004
Somatic complaints (n = 150)	53.6 (5.6)	56.4 (7.8)	−2.87 (−5.11 to −0.63)	−2.93 (−5.34 to −0.52)	.01	0.02
Withdrawn behavior (n = 150)	53.9 (5.1)	54.7 (6.0)	−0.87 (−2.70 to 0.95)	−0.29 (−2.16 to 1.59)	.35	0.76
Sleep problems (n = 149)	52.2 (4.2)	53.9 (6.5)	−1.70 (−3.52 to 0.13)	−2.20 (−4.19 to −0.20)	.07	0.03
Attention problems (n = 150)	56.7 (7.8)	56.4 (7.8)	0.25 (−2.30 to 2.80)	0.29 (−2.42 to 3.00)	.85	0.83
Aggressive behavior (n = 150)	53.1 (5.5)	54.0 (7.0)	−0.89 (−2.96 to 1.19)	−0.09 (−2.29 to 2.11)	.40	0.94
CBCL DSM-IV-oriented subscales						
Affective problems (n = 126)	52.8 (3.7)	55.8 (6.2)	−2.95 (−4.80 to −1.09)	−2.98 (−4.86 to −1.11)	.002	0.002
Anxiety problems (n = 126)	51.1 (2.5)	53.2 (5.5)	−2.11 (−3.68 to −0.54)	−2.34 (−4.12 to −0.56)	.01	0.01
Pervasive developmental (n = 126)	54.0 (6.2)	55.2 (6.7)	−1.21 (−3.50 to 1.08)	−0.80 (−3.33 to 1.72)	.30	0.53
Oppositional defiant problems (n = 126)	53.6 (6.2)	54.6 (5.6)	−0.94 (−3.03 to 1.14)	−0.72 (−3.03 to 1.59)	.37	0.54
Attention deficit/hyperactivity problems (n = 126)	54.2 (6.3)	54.8 (6.4)	−0.61 (−2.87 to 1.65)	−0.39 (−2.73 to 1.94)	.60	0.74

Data are expressed as the mean (SD).
*Mean difference with 95% CI was calculated using a t test.
†Mean difference adjusted for gestational age, BPD diagnosis (no/mild BPD vs moderate/severe BPD), parental education (low vs middle and high educational level), severe retinopathy of prematurity > grade 2 (yes vs no), and severe brain injury (yes vs no) using linear regression.

Table VI. Proportions of infants with behavioral problems needing intervention (T score above 55) assessed by CBCL 1.5-5 years at 2 years' corrected age in cases with complete outcome data

	Cases with complete outcome data			
CBCL	TOP program yes No./total (%)	TOP program no No./total (%)	Difference, % (95% CI)*	*P* value
Total problems	16/74 (21.6)	27/109 (24.8)	−3.1 (−15.5 to 9.2)	.62
Internalizing problems	10/74 (13.5)	25/109 (22.9)	−9.4 (−20.5 to 1.7)	.10
Externalizing problems	18/74 (24.3)	36/109 (33.0)	−8.7 (−21.9 to 4.5)	.20
CBCL syndrome scales				
Emotionally reactive	12/66 (18.2)	20/84 (23.8)	−5.6 (−18.6 to 7.4)	.40
Anxious/depressive	2/66 (3.0)	12/84 (14.3)	−11.3 (−19.8 to −2.7)	.01
Somatic complaints	19/66 (28.8)	34/84 (40.5)	−11.7 (−26.3 to 3.5)	.13
Withdrawn behavior	25/66 (37.9)	37/84 (44.0)	−6.2 (−22.0 to 9.6)	.44
Sleep problems	13/66 (19.7)	26/83 (31.3)	−11.6 (−25.5 to 2.2)	.10
Attention problems	30/66 (45.5)	36/84 (42.9)	2.6 (−13.4 to 18.6)	.75
Aggressive behavior	12/66 (18.2)	22/84 (26.2)	−8.0 (−21.2 to 5.2)	.24
CBCL DSM-IV-oriented subscales				
Affective problems	16/56 (28.6)	32/70 (45.7)	−17.1 (−33.8 to −0.5)	.04
Anxiety problems	5/56 (8.9)	15/70 (21.4)	−12.5 (−24.7 to −0.3)	.04
Pervasive developmental	15/56 (26.8)	26/70 (37.1)	−10.4 (−26.6 to 5.8)	.21
Oppositional defiant problems	10/56 (17.9)	20/70 (28.6)	−10.7 (−25.3 to 3.9)	.15
Attention deficit/hyperactivity problems	15/56 (26.8)	22/70 (31.4)	−4.6 (−20.5 to 11.3)	.57

*Absolute risk difference was calculated using a generalized linear model using a binomial distribution with identity link.