Association of Neonatal Pain-Related Stress and Parent Interaction With Internalizing Behaviors Across 1.5, 3.0, 4.5, and 8.0 Years in Children Born Very Preterm

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Abstract

IMPORTANCE Internalizing (anxiety and/or depressive) behaviors are prevalent in children born very preterm (24-32 weeks’ gestation). Procedural pain-related stress in the neonatal intensive care unit (NICU) is associated with long-term internalizing problems in this population; however, whether positive parenting during toddlerhood attenuates development of internalizing behaviors across childhood is unknown.

OBJECTIVE To investigate whether neonatal pain-related stress is associated with trajectories of internalizing behaviors across 1.5, 3.0, 4.5, and 8.0 years, and whether supportive parenting behaviors and lower parenting stress at 1.5 and 3.0 years attenuate this association.

DESIGN, SETTING, AND PARTICIPANTS In this prospective longitudinal cohort study, preterm neonates (born at 24-32 weeks’ gestation) were recruited from August 16, 2006, to September 9, 2013, with follow-up visits at ages 1.5, 3.0, 4.5, and 8.0 years. The study was conducted at BC Women’s Hospital, Vancouver, Canada, with recruitment from a level III neonatal intensive care unit and sequential developmental assessments performed in a Neonatal Follow-up Program. Data analysis was performed from August to December 2021.

MAIN OUTCOMES AND MEASURES Parental report of child internalizing behaviors on the Child Behavior Checklist at 1.5, 3.0, 4.5, and 8.0 years.

RESULTS A total of 234 neonates were recruited, and 186 children (101 boys [54%]) were included in the current study across ages 1.5 (159 children), 3.0 (169 children), 4.5 (162 children), and 8.0 (153 children) years. After accounting for clinical factors associated with prematurity, greater neonatal pain-related stress was associated with greater internalizing behaviors across ages (B = 4.95; 95% CI, 0.76 to 9.14). Higher parenting stress at age 1.5 years (B = 0.17; 95% CI, 0.11 to 0.23) and a less supportive parent environment (less sensitivity, structure, nonintrusiveness, nonhostility, and higher parenting stress; B = −5.47; 95% CI, −9.44 to −1.51) at 3.0 years were associated with greater internalizing problems across development to age 8.0 years.

CONCLUSIONS AND RELEVANCE In this cohort study of children born very preterm, exposure to repetitive neonatal pain-related stress was associated with persistent internalizing behavior problems across toddlerhood to age 8.0 years. Supportive parenting behaviors during early childhood were associated with better long-term behavioral outcomes, whereas elevated parenting stress was associated with more child anxiety and/or depressive behaviors in this population. These findings reinforce the need to prevent pain in preterm neonates and inform future development of targeted parent-led behavioral interventions.


Key Points

Question Does supportive parenting ameliorate the association between neonatal pain-related stress and child internalizing behaviors in children born very preterm?

Findings In this cohort study of 186 children born very preterm, internalizing behaviors increased across ages 1.5, 3.0, 4.5, and 8.0 years, and more neonatal pain-related stress was associated with greater internalizing behaviors across ages. At 1.5 years, parenting stress was associated with more internalizing behaviors, whereas at age 3.0 years, a more supportive parenting environment was associated with fewer internalizing behaviors across development.

Meaning These findings suggest that supportive parenting is associated with reduced child anxiety and depressive behaviors from toddlerhood through school-age in children born very preterm.
Introduction

Internalizing behavior problems (anxiety and/or depressive symptoms) are prevalent in children born preterm (<37 weeks' gestation). 1-5 Symptoms are evident as early as toddlerhood. 6-9 Those who show more internalizing behaviors in early childhood are likely to show long-term problems through adolescence, 3 often with increases in symptoms 10, 11 impacting social and school functioning, family, and community. 12

As neonates, infants born very preterm (24-32 weeks' gestation) spend their first weeks to months of life in the neonatal intensive care unit (NICU). During a period of neurobiological vulnerability, they are exposed to the stress and pain of frequent invasive procedures. 13-17 Beyond adverse clinical factors related to prematurity (eg, illness severity at NICU admission, analgesics, and infection), we have previously shown that NICU procedural pain-related stress is associated with greater internalizing behaviors at 1.5 years 9 and at school age. 18 Moreover, considerable literature suggests that supportive and structured parenting is associated with improved neurodevelopmental and behavioral outcomes in children born very preterm 19, 20; however, few longitudinal studies have investigated long-term benefits. 6, 21, 22 In an earlier cohort, 9 we found that sensitive and warm (nonhostile) parent interactions partially ameliorated the negative association of neonatal pain-related stress on internalizing behaviors at age 1.5 years, whereas parenting stress was associated with greater prevalence of these behaviors. It is unknown whether a supportive parenting environment (parenting stress and parent behavior) attenuates the association between neonatal pain-related stress and child internalizing behaviors beyond 1.5 years.

In the present study, in an independent cohort of children born very preterm, we addressed the hypotheses that (1) greater neonatal pain-related stress is associated with more internalizing behaviors across ages 1.5, 3.0, 4.5, and 8.0 years; (2) multiple aspects of the parenting environment co-occur, such that a supportive parenting environment would encompass low parenting stress, greater sensitivity, nonintrusiveness, greater structuring, and nonhostile parent behaviors; and (3) a more supportive parenting environment at ages 1.5 and 3.0 years attenuates the negative association of neonatal pain-related stress with internalizing behaviors across development.

Methods

The University of British Columbia and BC Women's Hospital Clinical Research Ethics Board approved this study. Parental written informed consent was obtained at study enrollment and again at each follow-up visit. This study follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for cohort studies.

Study Population

In a prospective longitudinal cohort study, infants born very preterm (24-32 weeks' gestational age) were recruited from the level III NICU at BC Women's Hospital in Vancouver Canada from August 6, 2006, to September 9, 2013. Inclusion criteria included being born at 24 to 32 weeks' gestational age; no major congenital malformation or syndrome; no antenatal toxoplasmosis, cytomegalovirus, rubella, or herpes virus infection; and/or no large periventricular hemorrhagic infarction (>2 cm) on clinical ultrasonography (eFigure 1 and eAppendix 1 in the Supplement).

Participant Demographics

Parent(s) reported on demographics including maternal and paternal education level and years, age, and ethnicity. Ethnic background options (ie, Black, East/Southeast Asian, East Indian, Filipino, First Nations, White, and any other) were defined by investigators and were assessed in this study to provide detailed demographic information about the study sample.
Neonatal Clinical Factors
Prospective daily medical and nursing medical record reviews were conducted by neonatal research nurses to obtain data on clinical factors from birth to NICU discharge or term-equivalent age, whichever came first (Table 1). Clinical factors were selected to be consistent with our prior work examining pain and/or stress, parenting, and child behavior. Cumulative pain and/or stress was defined as the number of invasive procedures from birth to NICU discharge or term equivalent age, whichever came first, as in our previous studies.

Parenting Stress
At ages 1.5 and 3.0 years, caregivers reported on their level of parenting stress using the Parenting Stress Index (PSI). The PSI is a 120-item questionnaire, for which each item was rated by parents via a 6-point Likert scale from 1 (strongly agree) to 6 (strongly disagree). We used the total raw score for the Parent Domain in the current study, which sums scores on 54 items across 7 subscales measuring stress related to parenting characteristics: Competence (13 items), Isolation (6 items), Attachment (7 items), Role Restriction (7 items), Depression (9 items), Spouse/Parenting Partner Relationship (7 items), and Health (5 items). Scores on the Parent Domain range from 54 to 270; higher scores indicate greater parenting stress.

Parent and Child Interactive Behaviors
Parent and child interactions during a 5-minute semistructured teaching task (described in eAppendix 1 in the Supplement) were filmed and then rated separately by independent coders (1 primary and 2 reliability; not coauthors of this article) who were blinded to all information, using the Emotional Availability (EA) Scale–IV. Parent behaviors included sensitivity (appropriateness and authenticity of affect), nonhostility (nonthreatening, warm), nonintrusiveness (lack of overprotection, allows autonomy), and structuring (guidance); child behaviors included responsiveness (affect, organization of behavior, attention) and involvement (physical and verbal, initiation of play). Scores on each dimension range from 7 to 29, with scores of 26 to 29 considered optimally emotionally available, scores of 18 to 25 considered inconsistently emotionally available, and scores of 7 to 17 considered nonoptimally emotionally available per clinical cutoff criterion. Dimensions of EA have been widely used to study parent-child interaction in normative and preterm dyads. We summed child involvement and responsiveness to create an EA dimensional sum of child interactive behavior at each age. To account for child-associated parent behaviors, we

| Table 1. Neonatal Clinical Factors |
| Variable | Mean (SD) | Median (IQR) [range] |
| Gestational age at birth, wk | 28.0 (2.2) | 27.71 (26.0-29.9) [24.0-32.3] |
| Sex, neonates, No. (%) | | |
| Male | 101 (54) | NA |
| Female | 85 (46) | NA |
| Total time in neonatal intensive care unit, d | 62 (47) | 48 (20-101) [3-221] |
| Neonatal pain-related stress, No. of invasive procedures from birth to term | 120.6 (78.9) | 96.0 (64.0-168.0) [14.0-385.0] |
| Score for Neonatal Acute Physiology–II | 12.7 (12.8) | 9.0 (0.0-17.0) [0.0-57.0] |
| Morphine exposure, cumulative dose adjusted for daily body weight, mg | 4.3 (10.3) | 0.1 (0.0-2.7) [0.0-58.3] |
| Time receiving mechanical ventilation and/or oscillation, d | 48.8 (36.4) | 44.0 (12.0-84.0) [0.0-111.0] |
| Surgical procedures, No. (%) | | |
| 0 | 134 (72) | NA |
| 1 | 30 (16) | NA |
| 2-4 | 22 (12) | NA |
| Culture-confirmed postnatal infection, No. (%) | 89 (48) | NA |

Abbreviation: NA, not applicable.
controlled for child interactive behaviors when examining relationships between parent interactive behaviors and child internalizing behaviors.

**Child Internalizing Behaviors**

The Child Behavior Checklist (CBCL) 1.5 to 5 years\textsuperscript{28} questionnaire was completed by the primary caregiver (85\% mothers) at ages 1.5, 3.0, and 4.5 years; at age 8.0 years, the CBCL for years 6 to 18 was completed.\textsuperscript{29} Here, we used the CBCL-Internalizing (Withdrawn, Somatic Complaints, Anxious/Depressed) subscale T-score (mean [SD], 50 [10]). Higher scores represent greater problems; a T-score of 64 or higher is the clinical problem cutoff, and a score of 60 or higher is the subclinical problem cutoff.

**Statistical Analysis**

Data analysis was performed from August to December 2021. Analyses were conducted in R statistical software version 4.1.0 (R Project for Statistical Computing).\textsuperscript{30} Participant characteristics were compared across visit ages using analysis of variance and 2-sided $\chi^2$ tests, with significance set at $P < .05$. Because of nonnormal distributions, cumulative morphine exposure and neonatal pain-related stress were log-transformed, and a square-root transformation was applied to days on mechanical ventilation and/or oscillation. Pearson correlations among study variables were performed. Latent profile analysis via gaussian mixture modeling was used to identify profiles of parent environment at ages 1.5 and 3.0 years from continuous measures of parent behaviors and parenting stress via the mclust\textsuperscript{31} package (hypothesis 2). To examine hypotheses 1 and 3, multilevel models were conducted with time-dependent data (CBCL Internalizing at each age) nested within individuals using lme4\textsuperscript{32} and lmerTest\textsuperscript{33} R packages. Across ages, missing data were found to be random (eFigure 2 and eTable 1 in the Supplement). We optimized model fit while accounting for missing participant-level data across assessment ages using the multilevel joint modeling multiple imputation,\textsuperscript{34} lme4,\textsuperscript{35} and mitmi\textsuperscript{36} R packages. We report estimated coefficients and SEs pooled across 100 imputed data sets for multilevel models. Likelihood ratio tests (LRTs) for multiply imputed data sets\textsuperscript{37} were used to compare models at each stage to establish the most parsimonious explanatory model. See eAppendix 2 in the Supplement for further details.

**Results**

**Cohort Description**

A total of 234 neonates were recruited. After exclusions, 186 participants (101 boys [54\%]) had valid neonatal clinical data (Table 1) and CBCL Internalizing scores at 1 or more assessment age: 159 children at 1.5 years, 169 children at 3.0 years, 162 children at 4.5 years, and 153 children at 8.0 years, with 120 (65\%) having parental report of behaviors at all 4 study ages (Table 2). Demographic indicators of participants who attended did not differ across visits (Table 2). At 1.5 years, 3 children met the cutoff for clinical problems, and 24 of 153 children (16\%) met this criterion at 8.0 years. See eAppendix 3 and eTable 2 in the Supplement for study variable intercorrelations. Attrition analyses are provided in eTable 3 in the Supplement.

**Hypothesis 1: Trajectories of Internalizing Behaviors**

In Table 3 the final multilevel models are provided. The data were suited to multilevel analysis, with 44\% of the variance in CBCL-Internalizing behaviors attributed to interchild differences. At 1.5 years (intercept), internalizing behavior scores were within normal range (mean [SD] T-score, 45.47 [7.50]). On average, as child age increased, CBCL-Internalizing scores were higher (Table 3, model 1), with the model estimates showing an increase of 8.5 T-score points across ages 1.5 through 8.0 years. Next, gestational age at birth was added in model 2. Higher internalizing behaviors were associated with lower gestational age at birth (a T-score increase of 0.6 per week born earlier) (Table 3, model 2). Above and beyond clinical factors related to prematurity and gestational age at birth, greater
exposure to neonatal pain-related stress was associated with increased internalizing behaviors across age (B = 4.95; 95% CI, 0.76 to 9.14) (Table 3, model 3). Neonatal pain-related stress did not vary by child age at assessment in relation to internalizing behaviors.

**Hypothesis 2: Profiles of Parent Environment**

**Age 1.5 Years**

At this age, when considering parenting stress and parent behaviors together in latent profile analyses, statistically, the bayesian information criterion (BIC) index identified 1 profile of parent environment. However, the uncertainty plots of classification and bootstrapped sequential LRTs indicated considerable variability in parent behaviors and parenting stress at this age (Table 2). Therefore, we only included parenting behaviors in subsequent latent profile analysis and considered parenting stress as a separate factor in models. The 3 profiles are displayed in [Figure 1A](higher support, 24%; average support, 69%; lower support, 16%). Although a 2-factor model demonstrated slightly better fit (BIC, −1203.8; integrated complete-data likelihood [ICL], −1221.8) than the 3-factor model (BIC, −1219.0; ICL, −1268.0), inspection of uncertainty of classification plots revealed better model convergence with the 3-factor model. Bootstrapped sequential LRTs confirmed suitability of the 3-factor vs 2-factor model (LRT, 43.35; \( P = .001 \)). Moreover, the 3 profiles better differentiated between established EA Parent Dimension subscales and, thus, theoretical models of emotional availability.25 Parents demonstrating low and average support behavior profiles displayed inconsistent EA, with profiles differing primarily in their levels of nonintrusiveness, with low support parents demonstrating nonoptimal behaviors (interfering, directing, and driving play). In subsequent

<table>
<thead>
<tr>
<th>Variable (N = 186)</th>
<th>1.5 y Corrected age</th>
<th>3.0 y</th>
<th>4.5 y</th>
<th>8.0 y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age at birth, mean (SD) [range], y</td>
<td>33.0 (5.2) [22.1-45.9]</td>
<td>32.8 (5.1) [21.8-45.9]</td>
<td>32.9 (5.2) [21.8-45.9]</td>
<td>32.6 (5.2) [21.8-45.9]</td>
</tr>
<tr>
<td>Maternal education level, mothers, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary or secondary school graduation</td>
<td>24 (15)</td>
<td>21 (13)</td>
<td>25 (16)</td>
<td>23 (15)</td>
</tr>
<tr>
<td>Partial or complete undergraduate degree</td>
<td>101 (64)</td>
<td>114 (68)</td>
<td>105 (66)</td>
<td>98 (65)</td>
</tr>
<tr>
<td>Postgraduate university degree</td>
<td>32 (20)</td>
<td>32 (19)</td>
<td>29 (18)</td>
<td>29 (19)</td>
</tr>
<tr>
<td>Parent sensitivity score</td>
<td>Mean (SD) [range]</td>
<td>20.2 (4.0) [10.0-29.0]</td>
<td>21.4 (3.6) [12.5-29.0]</td>
<td>NA</td>
</tr>
<tr>
<td>Missing, No.</td>
<td>29</td>
<td>21</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Parent nonhostility score</td>
<td>Mean (SD) [range]</td>
<td>21.7 (3.5) [12.0-29.0]</td>
<td>22.4 (3.1) [15.0-29.0]</td>
<td>NA</td>
</tr>
<tr>
<td>Missing, No.</td>
<td>29</td>
<td>21</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Parent nonintrusiveness score</td>
<td>Mean (SD) [range]</td>
<td>19.1 (4.9) [8.0-29.0]</td>
<td>20.7 (4.4) [10.0-29.0]</td>
<td>NA</td>
</tr>
<tr>
<td>Missing, No.</td>
<td>29</td>
<td>21</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Parent structuring score</td>
<td>Mean (SD) [range]</td>
<td>20.9 (3.4) [13.0-28.5]</td>
<td>22.4 (3.6) [13.5-29.0]</td>
<td>NA</td>
</tr>
<tr>
<td>Missing, No.</td>
<td>29</td>
<td>21</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Child interactive behavior score</td>
<td>Mean (SD) [range]</td>
<td>38.3 (6.4) [14.0-55.5]</td>
<td>41.3 (6.5) [26.0-57.0]</td>
<td>NA</td>
</tr>
<tr>
<td>Missing, No.</td>
<td>29</td>
<td>21</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Parenting stress score</td>
<td>Mean (SD) [range]</td>
<td>111.8 (21.0) [66.0-181.0]</td>
<td>115.2 (22.9) [66.0-187.0]</td>
<td>NA</td>
</tr>
<tr>
<td>Missing, No.</td>
<td>27</td>
<td>20</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Child age, mean (SD) [range], y</td>
<td>1.6 (0.1) [1.2-2.2]</td>
<td>3.2 (0.2) [2.8-4.0]</td>
<td>4.9 (0.2) [4.4-5.5]</td>
<td>8.4 (0.5) [7.9-11.9]</td>
</tr>
<tr>
<td>Internalizing behaviors score</td>
<td>Mean (SD) [range]</td>
<td>44.9 (9.3) [29.0-83.0]</td>
<td>48.0 (9.9) [29.0-78.0]</td>
<td>49.0 (12.0) [29.0-78.0]</td>
</tr>
<tr>
<td>Clinical problems, No.</td>
<td>3</td>
<td>11</td>
<td>20</td>
<td>24</td>
</tr>
<tr>
<td>Missing, No.</td>
<td>27</td>
<td>17</td>
<td>24</td>
<td>33</td>
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</tbody>
</table>
modeling, we tested both the additive and interactive effects of our profiles (herein termed "parent support") and parenting stress at 1.5 years in association with internalizing behaviors.

Age 3.0 Years
Using the BIC index for model fit, the best fitting model (BIC, $-1568.0$; ICL, $1586.0$) identified a 2-factor model for parent environment at age 3.0 years. Similar to our findings at age 1.5 years, inspection of uncertainty of classification plots revealed better model convergence with the 3-factor than 2-factor model. Bootstrapped LRTs further confirmed suitability of the 3-factor vs 2-factor model ($LRT, 43.36; P = .001$). The 3 parenting profiles identified at age 3.0 years are presented in Figure 1B (high supportive parenting behaviors, low parenting stress, 22%; average supportive parenting behaviors and average parenting stress levels, 62%; low supportive parenting behaviors and high parenting stress, 16%). Parents in the high support, low stress profile displayed optimal parenting across all behaviors (EA scores of approximately 26), and typical stress (24th percentile).

Table 3. Final Models of Factors Associated With Increased Child Internalizing Behaviors Across Ages 1.5, 3.0, 4.5, and 8.0 Years

<table>
<thead>
<tr>
<th>Study variable</th>
<th>B (95% CI)</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
<th>Model 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child age at visit</td>
<td>1.29 (1.05 to 1.52)</td>
<td>1.29 (1.06 to 1.52)</td>
<td>1.29 (1.06 to 1.52)</td>
<td>1.31 (1.07 to 1.54)</td>
<td></td>
</tr>
<tr>
<td>Gestational age at birth</td>
<td>NA</td>
<td>−0.63 (−1.17 to −0.08)</td>
<td>−0.39 (−1.42 to 0.64)</td>
<td>−1.08 (−2.08 to −0.07)</td>
<td></td>
</tr>
<tr>
<td>Child sexa</td>
<td>NA</td>
<td>NA</td>
<td>2.03 (−0.42 to 4.49)</td>
<td>1.56 (−0.79 to 3.91)</td>
<td></td>
</tr>
<tr>
<td>Illness severity (day 1)</td>
<td>NA</td>
<td>NA</td>
<td>0.09 (−0.01 to 0.19)</td>
<td>0.11 (0.02 to 0.21)</td>
<td></td>
</tr>
<tr>
<td>Neonatal pain-related stress</td>
<td>NA</td>
<td>4.95 (0.76 to 9.14)</td>
<td>2.92 (−1.09 to 6.94)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cumulative morphine exposure</td>
<td>NA</td>
<td>NA</td>
<td>−0.73 (−5.11 to 3.66)</td>
<td>−2.98 (−7.79 to 1.84)</td>
<td></td>
</tr>
<tr>
<td>Days receiving mechanical ventilation and/or oscillation</td>
<td>NA</td>
<td>NA</td>
<td>−0.69 (−1.54 to 0.16)</td>
<td>−0.96 (−1.98 to 0.05)</td>
<td></td>
</tr>
<tr>
<td>Culture-positive infectionb</td>
<td>NA</td>
<td>NA</td>
<td>−1.42 (−4.74 to 1.90)</td>
<td>−1.50 (−4.73 to 1.72)</td>
<td></td>
</tr>
<tr>
<td>No. of surgical procedures</td>
<td>NA</td>
<td>NA</td>
<td>0.19 (−1.55 to 1.94)</td>
<td>0.39 (−1.27 to 2.04)</td>
<td></td>
</tr>
<tr>
<td>Parenting stress at 1.5 y</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>0.74 (−2.79 to 4.26)</td>
<td></td>
</tr>
<tr>
<td>Parent environment at 1.5 y</td>
<td></td>
<td>NA</td>
<td>NA</td>
<td>1.31 (−3.73 to 6.35)</td>
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</tr>
<tr>
<td>Low support</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>−0.29 (−0.56 to −0.04)</td>
<td></td>
</tr>
<tr>
<td>High support</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Child interactive behavior at 1.5 y</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Male = 0.

b Confirmed infection = 1.

Reference group was parent environment 1.5 years: average support.

Figure 1. Profiles of Parent Environment

Scores are mean standardized scores at 1.5 years considering only parent behaviors (A) and at 3.0 years considering parenting stress and parent behaviors (B). The scales across Parenting Stress Index and Emotional Availability Scale–IV measures vary.
In contrast, parents who displayed a low support, average high stress profile displayed, on average, nonoptimal parenting behaviors and elevated, albeit typical stress (50th percentile). Similar to profiles at 1.5 years, parent nonintrusiveness played a key role in construction of the low support, high stress parent behavior profile.

**Hypothesis 3**

**Parenting at 1.5 Years**

Higher parenting stress at age 1.5 years ($B = 0.17$; 95% CI, 0.11 to 0.23), but not parent support, was associated with higher internalizing behaviors across childhood (Table 3, model 4). After consideration of parenting stress at 1.5 years, neonatal pain-related stress was no longer significantly associated with internalizing behaviors. Profiles of parent support and parenting stress did not interact in association with internalizing behaviors ($P$ for interaction = .08). Model 4 accounted for 51% of variance in child internalizing behaviors (21% within-participant differences including child age; 30% between-participant variables). Parenting stress and parent support at 1.5 years did not differ by neonatal pain-related stress or gestational age at birth across child age at assessment in association with internalizing behaviors.

**Parenting at 3.0 Years**

To examine associations of parenting at 3.0 years with internalizing behaviors and neonatal factors associated with prematurity, models were rerun considering only internalizing behaviors from 3.0 through 8.0 years (eTable 4 in the Supplement). Parent environment at 3.0 years was significantly associated with trajectories of internalizing behaviors, such that child internalizing behaviors were highest for those children exposed to a low interaction support, high stress parent environment at age 3.0 years (higher support, lower stress, $B = −5.47$, 95% CI, −9.44 to −1.51) (Figure 2 and eTable 4, model 4 in the Supplement). After considering profiles of parent environment at 3.0 years, neonatal pain-related stress was no longer significantly associated with child internalizing behaviors. The final model accounted for 59% of the variance in child internalizing behaviors (44% attributable to between-individual differences in internalizing at 3.0 years, 15% accounted for by model variables). Importantly, the association between parent environment and internalizing behaviors across development held after accounting for child interactive behaviors during semistructured play and maternal education (eTable 5 [model 5] and eTable 6 [model 4] in the Supplement).

Associations of parent environment at 3.0 years with internalizing behaviors across ages were not moderated by neonatal pain-related stress or gestational age at birth across child age at assessment. The final model considering parenting behaviors at 3.0 years held when rerun considering internalizing behaviors across 1.5, 3.0, 4.5, and 8.0 years (eTable 5 [model 5] in the Supplement). Model estimates were comparable when using complete data (eTable 5 and eTable 6 in the Supplement).

**Discussion**

In this prospective, longitudinal cohort study, we identified environmental factors across the first 3 years of life associated with trajectories of early internalizing behaviors in children born very preterm.

![Figure 2. Parent Environment at Age 3.0 Years Associated With Internalizing Behaviors Across Ages 3.0, 4.5, and 8.0 Years](https://jamanetwork.com/)

Error bars denote 95% CIs. The model (model 4) is reported in eTable 4 in the Supplement. CBCL indicates Child Behavior Checklist.
We found that parent-reported internalizing behaviors increased from 1.5, 3.0, 4.5, to 8.0 years. First, we showed that, above and beyond gestational age at birth and neonatal clinical factors, greater pain-related stress was associated with greater internalizing behaviors across this period. In subsequent models in which we considered the more proximal parent environment, neonatal pain-related stress was no longer associated with outcomes. Instead, elevated internalizing behaviors were associated with greater parenting stress at 1.5 years, whereas a more supportive parent environment at age 3.0 years was associated with fewer internalizing behaviors across 1.5 through 8.0 years. Our findings have implications for follow-up monitoring of children born very preterm and delivery of interventions in pediatric care.

Our finding of increasing internalizing behavior symptoms across 1.5, 3.0, 4.5, and 8.0 years is in line with prior work examining trajectories through childhood\textsuperscript{38} to adolescence\textsuperscript{1,3} in children born very preterm. In the current study, the majority of children displayed parent-reported internalizing behaviors within the normative range at 1.5 years; however, by 8.0 years, almost 1 in 7 children displayed behaviors in the clinically abnormal range. Internalizing problems are related to poorer school\textsuperscript{39,40} and social\textsuperscript{41} functioning and, later, psychiatric illness.\textsuperscript{1} Our findings support the continued monitoring of children born very preterm through early childhood.

When considering only the early NICU environment, we found that exposure to neonatal pain-related stress was associated with higher internalizing symptoms across 1.5, 3.0, 4.5, and 8.0 years, after accounting for clinical risk factors. This association was stable across early childhood. These findings extend our prior work in an independent cohort in which we demonstrated that NICU pain-related stress is associated with greater internalizing behaviors at ages 1.5 years\textsuperscript{9} and 8.0 years.\textsuperscript{18} Alterations to brain development in key stress-related limbic regions as early as the neonatal period\textsuperscript{42,43} and evident at school age\textsuperscript{44} may underlie poorer behavioral outcomes independently of, or in interaction with, stress dysregulation (hypothalamic pituitary adrenal axis),\textsuperscript{7,45-47} which is also related to internalizing behaviors.\textsuperscript{7,45} Across cohorts of children born very preterm, we have demonstrated that exposure to neonatal pain-related stress is associated with widespread difficulties in neurobehavioral outcomes, including cognition, motor skills, and behavior across childhood.\textsuperscript{15}

Our most novel and important finding in the present study is that a supportive parent environment reflecting more positive parent behaviors and lower stress was associated with a reduction in the development of internalizing behaviors across early childhood in children born very preterm. These findings are in concert with prior work\textsuperscript{9,20-22,48,49} largely limited to cross-sectional study designs investigating specific parent behaviors without considering the related influence of parenting stress. Extending on evidence from an experimental animal model of neonatal pain\textsuperscript{50} and our prior work,\textsuperscript{9,45,51} here we show that a positive postnatal environment, inclusive of supportive, structured maternal behaviors and mood may attenuate, whereas negative environments may maintain, adverse outcomes associated with neonatal pain-related stress exposure and other factors associated with prematurity.

Beyond effects of preterm birth, children exposed to more neonatal pain-related stress display behavioral dysregulation, poorer physiological stress regulation, sensory processing problems,\textsuperscript{52} and early attentional problems associated with poorer executive functioning.\textsuperscript{15} Sensitive, warm, and nonintrusive parents who provide structured guidance may attenuate the development of children's internalizing behavior by helping their child cope with feelings of anxiety and the tendency to withdraw in threatening situations.\textsuperscript{53,54} Promote child attention and engagement in tasks,\textsuperscript{55} support healthy physiological stress regulation,\textsuperscript{7} and promote behavioral regulatory skills. However, poor parent well-being and parenting stress, which are common in parents of preterm infants,\textsuperscript{56} make providing a supportive environment challenging for parents\textsuperscript{55} and impede appropriate modeling of anxiety-related behaviors.\textsuperscript{57,58} Of note, disentangling the directionality of parent-child associations is difficult. Poorer neurodevelopment\textsuperscript{37-39} and difficult temperaments\textsuperscript{59} in preterm born children are associated with persistent parenting stress\textsuperscript{59,60} and are challenging for parenting.\textsuperscript{61} Although there is evidence that parents experience more stress when their child is challenged developmentally,\textsuperscript{62}
other research suggests that parent contribution is independent of child developmental challenge.\textsuperscript{21,63} Our findings more likely support the latter, as the association between parenting and child internalizing behaviors across development was evident after accounting for child behavior when assessing parent behavior during parent-child semistructured teaching interaction.

At 3.0 years, but not 1.5 years, children displayed lower parent-reported internalizing behaviors related to supportive parenting interactions, after accounting for observed child behavior during parent-child semistructured teaching task. Although prior work demonstrates that positive parenting in the NICU through the first 3 years has immediate benefits,\textsuperscript{9} few have examined the sustained benefits of early parenting behaviors as they align with developmental timing.\textsuperscript{21,64} We postulate that parenting behaviors in the context of teaching tasks may be most beneficial for long-term behavioral outcomes in late toddlerhood, when children shift from emotional coregulation strategies dependent on their primary caregiver toward activities of exploration and independent learning.\textsuperscript{65} Around age 3.0 years, self-regulatory skills\textsuperscript{66} and related executive functioning (eg, attentional shifting and inhibition) abilities are emerging.\textsuperscript{55} At this age, preterm born children may benefit from structured guidance that encourages autonomy. Our findings have implications for integration of parent support intervention in neonatal follow-up. Parent-led interventions that target parent psychosocial support and supportive training in multiple developmentally appropriate behaviors may prove beneficial. Importantly, such interventions may help prepare parents and children for the evolving developmental needs and environmental changes into the school years.\textsuperscript{67}

Significant participant retention across all 4 developmental visits is a clear strength of our study. By excluding children with severe brain injury and/or major impairments, our findings represent outcomes for the broad majority of children born very preterm. Modeling accounted for clinical confounders in an attempt to disentangle the role of pain and/or stress from the reasons why procedures are performed (eg, infection). Future research could look to examine other between-participant factors related to the onset and development of internalizing behaviors in this population, including potential genetic susceptibility.

Limitations

Our study has several limitations. The parents in our cohort had high education levels, with universal access to health care. Importantly, despite this, the associations between parenting and child internalizing behaviors remained after accounting for parent education. We did not collect data on individual early allied health interventions, access to which varies by region in British Columbia. We examined parenting in the context of semistructured teaching tasks only; however, given the high need for structuring for children born very preterm, we chose this a key context for parent factors to be examined. The lack of parent-child interaction and parenting stress data at ages 4.5 and 8.0 years did not allow for examination of potential bidirectional parent-child relationships across development; this is an important question for future research.

Conclusions

In a prospective cohort study of children born very preterm, we demonstrate associations among aspects of the early environment and development of internalizing behaviors across childhood. We found that neonatal pain-related stress is related to the early emergence of these behaviors, and parents play a pivotal role in attenuating child behavior problems across development. Importantly, our novel findings highlight parenting as a modifiable factor related to better outcomes for this vulnerable population, not only in the short term but with continued benefits as children develop. Our findings warrant support of parents of children born very preterm across the early years and development and implementation of efficacious parent-child intervention strategies that promote optimal behavior in this population.
ARTICLE INFORMATION
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REFERENCES


eTable 5. Estimated Multilevel Models of Internalizing Behaviors Across 1.5, 3, 4.5, 8 Years Using Listwise Deletion for Missing Data

eTable 6. Estimated Multilevel Models of Internalizing Behaviors Across 3, 4.5, 8 Years Using Listwise Deletion for Missing Data

eReferences