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**eReferences**

This supplemental material has been provided by the authors to give readers additional information about their work.

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Figure 1. Cohort Flowchart

- 619 Very preterm infants eligible from April 2006-September 2013
  - 269 Declined
  - 116 Not approached
    - 54 No study personnel available
    - 62 Refused approach
  - 234 Recruited
    - 7 Deceased
    - 6 Withdrawn from study
      - 21 No CBCL Internalizing score at any age
        - 5 moved away
        - 7 lost to follow up
      - 13 Excluded
        - 6 Major Brain injury
          - 1 Major sensory impairment
          - 2 Major cognitive impairment
          - 2 Major genetic disorder
          - 1 Nonambulatory Cerebral Palsy
          - 1 Severe Autism
    - 186 CBCL-Internalizing data at one or more ages
      - 159 1.5 years
      - 169 3 years
      - 162 4.5 years
      - 155 8 years

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eAppendix 1. Supplemental Methods

Study Population. Of the n = 227 survivors, 21 participants (6 withdrawn, 5 moved away, 7 lost to follow-up) did not have CBCL follow-up data at any age. We excluded 6 infants with severe brain injury on neonatal ultrasound (cystic periventricular leukomalacia [n = 2], intraventricular hemorrhage grade 3 or 4 [n = 4]); at age 4.5 and/or 8 years 1 sensorineural hearing impairment, 1 non-ambulatory cerebral palsy, 2 cognitive impairment with IQ <70, 1 severe autism, 2 genetic abnormality (chromosome 15q11.2 duplication). Exclusion criterion were consistent with our work in a prior, independent cohort. As well, one infant had incomplete (>50%) missing neonatal clinical data (moved hospital during NICU stay) and was therefore excluded.

Parent and Child Interactive Behaviors. At 1.5 and 3 years, the primary caregiver and child engaged in a 5-minute semi-structured teaching session. During the session, the caregiver helped guide the child as they performed two tasks of varying difficulty. At 1.5 years, the easier and more familiar task consisted of the child stacking or nesting cups of varying sizes. In the second task, which was considered novel and more difficult, participants were directed to sort plastic pig and cow figurines into two separate bowls. At 3 years, the first task consisted of arranging a wooden puzzle of a family, while the more challenging task involved sorting plastic shapes by both colour and size. Parents were instructed to interact with their child typically as they would at home.

One primary and two reliability coders rated parent and child EA, blinded to all participant information. Inter-rater reliability assessed via intraclass correlation (ICC) on 20% of the sample was high: Parent Sensitivity, Structuring, Non-intrusiveness, and Non-hostility, and Child Responsiveness and Involvement at 18 months CA ICC’s were 0.87, 0.86, 0.93, 0.84, 0.86, and 0.87 respectively, and at 3 years ICC’s were 0.87, 0.85, 0.90, 0.83, 0.83, and 0.87.
Hypothesis 2: Latent profile analysis. Gaussian mixture modelling estimate model parameters via maximum likelihood estimation. We used the Bayes Information Criteria (BIC), Integrated Complete-data Likelihood (ICL), classification uncertainty, along with Bootstrapped Likelihood Ratio Test Statistic (LRTS) to determine the number of classes that best fit the data. Smaller values of BIC indicate better fit. LRT tests whether an increase in profiles increases fit. We examined plots for uncertainty, favouring models with fewer points of large (> 0.25) uncertainty. Conclusions as to the best fitting model were drawn from all three fit indices, theoretical models of Emotional Availability, and prior empirical work examining interrelationships between parent behavior, parenting stress and child behavior.

Hypotheses 1 and 3: Multilevel models. Multilevel models examining the role of parent environment at 1.5 years used all data across 1.5, 3, 4.5, and 8 years. Subsequent models were run using behaviors from 3, 4.5 to 8 years when considering parenting behaviors and stress at age 3-years.

Multilevel models are ideal for analysis of repeated measures within observational study designs where data is missing at random. For analysis with complete data, we fitted models using restricted maximum likelihood estimation which estimates parameters of analysis model by maximizing the observed-data likelihood. Model significance of effects was tested using the Satterthwaite approximations for degrees of freedom. These methods have been found to produce acceptable bias parameter estimates and Type 1 error rates even for smaller samples. However, in multilevel models, missing data on the dependent variable is dealt with, while missing data on explanatory variables are not accounted for. Using a joint modelling imputation approach, imputations were simultaneously generated from specified models and the clustered structure of the data was accounted for. This approach has been shown to produce less biased parameter estimates than other multiple imputation techniques particularly in the case of categorical and non-normally distributed longitudinal data collected at unevenly spaced time-points.

Child age at visit (time-depdenant measure) was specified as a first level variable and participant-specific measures (e.g. gestational age, neonatal pain-related stress, parent behavior, parenting stress) as second level variables. First an intercept-only model was established by allowing the intercept to enter as a random effect in order to examine the amount of variance in internalizing behaviors that is accounted for within and between individuals and to ensure the data required multi-level modelling analysis. Next, we tested whether internalizing behaviors were predicted by child age by adding this variable to the model (Model 1). We then examined whether the effect of age on internalizing behaviors differed between participants, entering age of the child as a random effect. If the random effect of age did not improve model fit, it was removed from the model prior to entering second-level variables. Next, second-level variables were entered into the model. First, we added gestational age at birth to confirm established reports of degree of prematurity in relation to internalizing behaviors (Model 2). Next, to test Hypothesis 1, we added clinical factors associated with prematurity, neonatal pain-related stress and child sex to the models (Model 3). We entered the interaction terms of neonatal pain-related stress and age into the model, and explored whether this interaction was subsequently dependant on child sex, or gestational age. To test Hypothesis 3, parent environment (parent behavior and parent stress) at each age were included as predictors in separate models, and subsequent models tested whether parenting factors interacted with neonatal pain-related stress in relation to internalizing behaviors across age (2-way interaction of Parenting X neonatal pain-related stress and 3-way interaction of Parenting X neonatal pain-related stress X Child Age). Finally, we tested whether effects were independent of child interactive behaviors and maternal education level (index of socioeconomic status) when examining relationships between parent interactive behaviors and child internalizing behaviors.

Reported models met all assumptions of multilevel models.
eFigure 2. Patterns of Missing Data

Note: Each row in the matrix represents a pattern of missing data in pink and complete data in blue, across the study variables (columns); 55.91% of participants had valid data across all study variables.
eTable 1. Missing Data for Each Study Variable

| Study Variable                                    | Missing Data (%) |
|--------------------------------------------------|------------------|
| Child age 8y                                      | 18               |
| Internalizing behaviors 8y                        | 18               |
| Parent sensitivity 1.5y                          | 16               |
| Parent structuring 1.5y                          | 16               |
| Parent non-intrusiveness 1.5y                     | 16               |
| Parent non-hostility 1.5y                         | 16               |
| Child interactive behavior 1.5y                   | 16               |
| Parenting stress 1.5y                            | 15               |
| Internalizing behaviors 1.5y                      | 15               |
| Internalizing behaviors 4.5y                      | 13               |
| Parent sensitivity 3y                             | 11               |
| Parent structuring 3y                            | 11               |
| Parent non-intrusiveness 3y                       | 11               |
| Parent non-hostility 3y                           | 11               |
| Child interactive behavior 3y                     | 11               |
| Parenting stress 3y                               | 11               |
| Child age 4.5y                                   | 1                |
| Internalizing behaviors 3y                        | 0.9              |
| Child age 3y                                      | 0.5              |
| Child age 1.5y                                   | 0.3              |
| Cumulative morphine                              | 0.1              |
| Infection                                         | 0.1              |
| Days on mechanical ventilation/oscillation        | 0.05             |
| Gestational age at birth                          | 0                |
| Neonatal pain/stress                             | 0                |
| Number of surgeries                               | 0                |
| Child sex                                         | 0                |
eAppendix 3. Supplemental Results

Intercorrelations

Children born at lower gestational age were exposed to higher neonatal cumulative pain/stress; $r = -.78, P < 0.001$. Lower gestational age at birth was associated with greater internalizing behaviors, with differences most detectable at ages 4 ($r = -.16, P = .04$) and 8 years ($r = -.18, P = .02$).
### eTable 2. Intercorrelations Among CBCL Internalizing T-Scores, Parent and Child During Semistructured Teaching Task Within and Across Ages 1.5 and 3 Years

| Study Variable | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 |
|----------------|---|---|---|---|---|---|---|---|---|----|----|----|----|
| Internalizing 1.5y | .58 | <.001 | | | | | | | | | | |
| Internalizing 3y | | | | | | | | | | | | |
| Parent sensitivity 1.5y | .02 | .78 | -.05 | .51 | | | | | | | | |
| Parent structuring 1.5y | .07 | .38 | .03 | .75 | .73 | <.001 | | | | | | |
| Parent non-intrusiveness 1.5y | -.01 | .88 | -.1 | .24 | .85 | <.001 | .52 | <.001 | | | | |
| Parent non-hostility 1.5y | .07 | .38 | -.05 | .55 | .92 | <.001 | .66 | <.001 | .80 | <.001 | | |
| Child interactive behaviors 1.5y | -.02 | .85 | -.11 | .21 | .71 | <.001 | .59 | <.001 | .65 | <.001 | .62 | <.001 |
| Child interactive behaviors 3y | -.14 | .1 | -.22 | .005 | .26 | .002 | .15 | .08 | .21 | .08 | .21 | .01 | .29 | <.001 |
| Parent sensitivity 3y | -.13 | .12 | -.2 | .01 | .31 | <.001 | .21 | .01 | .32 | .01 | .28 | <.001 | .23 | .006 | .74 | <.001 |
| Parent structuring 3y | -.09 | .31 | -.18 | .03 | .25 | .003 | .19 | .03 | .23 | .03 | .22 | .009 | .17 | .04 | .63 | <.001 | .79 | <.001 |
| Parent non-intrusiveness 3y | -.17 | .04 | -.28 | <.001 | .29 | <.001 | .16 | .06 | .31 | .06 | .26 | .001 | .20 | .02 | .68 | <.001 | .86 | <.001 | .63 | <.001 |
| Parent non-hostility 3y | -.08 | .35 | -.18 | .02 | .29 | <.001 | .19 | .02 | .29 | .02 | .26 | .002 | .21 | .01 | .67 | <.001 | .93 | <.001 | .76 | <.001 | .85 | <.001 |
| Parenting stress 1.5y | .36 | <.001 | .26 | .001 | .20 | .02 | .14 | .09 | .17 | .09 | .20 | .02 | .22 | .009 | .01 | .87 | -.03 | .75 | -.08 | .35 | .00 | .98 | -.04 | .60 | <.001 |
| Parenting stress 3y | .23 | .006 | .36 | <.001 | .10 | .23 | .11 | .21 | .06 | .21 | .02 | .83 | .14 | .10 | -.05 | .55 | -.05 | .50 | -.10 | .20 | -.06 | .45 | -.02 | .81 | .78 | <.001 |
eTable 3. Demographic Comparison of Children With Complete Versus Incomplete Data

| Study Variable                           | Complete data (n=103) | Incomplete data (n=83) | P     |
|-----------------------------------------|----------------------|------------------------|-------|
| Gestational age at birth (wks)          |                      |                        | .355  |
| Mean (SD)                               | 28.1 (2.4)           | 27.8 (2.0)             |       |
| Range (min - max)                       | 24.0 - 32.3          | 24.4 - 31.7             |       |
| Child sex, No. (%)                      |                      |                        | .233  |
| Boy                                     | 60 (58)              | 41 (49)                |       |
| Maternal age at birth (years)           |                      |                        | .60   |
| Mean (SD)                               | 32.9 (5.3)           | 32.4 (5.3)             |       |
| Range (min - max)                       | 22.1 - 45.9          | 21.8 - 45.1             |       |
| Maternal marital status                 |                      |                        | .81   |
| Married/Common Law                      | 95 (92)              | 73 (91)                |       |
| Single/Divorced/Separated               | 8 (8)                | 7 (9)                  |       |
| Maternal ethnicity, No. (%)             |                      |                        | .08   |
| Black                                   | 0 (0)                | 0 (0)                  |       |
| East/Southeast Asian                    | 12 (11.5)            | 11 (13)                |       |
| East Indian                             | 3 (3)                | 8 (10)                 |       |
| Filipino                                | 5 (5)                | 10 (12)                |       |
| First Nations                           | 1 (1)                | 3 (3.5)                |       |
| White Caucasian                         | 70 (68)              | 42 (51)                |       |
| Other*                                  | 11 (10.5)            | 6 (7)                  |       |
| Did not report                          | 1 (1)                | 3 (3.5)                |       |
| Maternal education (years)              |                      |                        | .07   |
| Mean (SD)                               | 16.3 (2.9)           | 15.6 (2.8)             |       |
| Range (min - max)                       | 10.0 - 23.0          | 10.0 - 27.0             |       |
| Maternal Level of Education, No. (%)    |                      |                        | .1010 |
| Primary or Secondary School Graduation   | 14 (14)              | 14 (18)                |       |
| Partial or Complete Undergraduate Degree| 64 (63)              | 57 (71)                |       |
| Post-Graduate University degree          | 24 (24)              | 9 (11)                 |       |
| Paternal age at birth (years)           |                      |                        | .822  |
| Mean (SD)                               | 34.8 (5.7)           | 34.6 (5.7)             |       |
| Range (min - max)                       | 22.0 - 48.7          | 20.9 - 48.9             |       |
| Paternal marital status, No. (%)        |                      |                        | .044  |
| Married/Common Law                      | 84 (82)              | 53 (68)                |       |
| Single/Divorced/Separated               | 19 (18)              | 25 (32)                |       |
| Paternal ethnicity, No. (%)             |                      |                        | .02   |
| Black                                   | 0 (0)                | 1 (1)                  |       |
| East/Southeast Asian                    | 8 (8)                | 7 (8.5)                |       |
| East Indian                             | 3 (3)                | 8 (10)                 |       |
| Filipino                                | 3 (3)                | 8 (10)                 |       |
| First Nations                           | 2 (2)                | 1 (1)                  |       |
| White Caucasian                         | 85 (82)              | 50 (60)                |       |
| Other*                                  | 2 (2)                | 1 (1)                  |       |
| Did not report                          | 0 (0)                | 7 (8.5)                |       |
| Paternal education (years)              |                      |                        | .933  |
| Mean (SD)                               | 15.3 (2.8)           | 15.3 (3.5)             |       |
| Range (min - max)                       | 10.0 - 23.0          | 9.0 - 27.0              |       |
| Paternal level of education, no. (%)    |                      |                        | .733  |
| Primary or Secondary School Graduation   | 22 (22)              | 20 (26)                |       |
| Partial or Complete Undergraduate Degree| 66 (65)              | 45 (59)                |       |
| Post-Graduate University degree          | 14 (14)              | 11 (14)                |       |

*aLatino, Melanesian, Metis, Mixed race; bMelanesian, Slavic
## eTable 4. Final Models of Factors Related to Increased Child Internalizing Behaviors Across 3, 4.5, 8 Years Using Imputed Data

| Study Variable                                      | B (95% CI)       |
|-----------------------------------------------------|------------------|
|                                                     | Model 1 | Model 2 | Model 3 | Model 4 |
| Child age at visit                                  | 1.29    | 1.28    | 1.28    | 1.28    |
|                                                     | (0.98, 1.60)   | (0.97, 1.59) | (0.98, 1.59) | (0.97, 1.59) |
| Gestational age at birth                            | NA      | -0.69   | -0.61   | -0.35   |
|                                                     | (-1.28, -0.11) | (-1.72, 0.50) | (-1.42, 0.72) | |
| Child sexa                                          | NA      | NA      | 1.82    | 1.99    |
|                                                     | (-0.85, 4.50) | (-0.59, 4.57) | |
| Illness severity (day 1)                            | NA      | NA      | 0.10    | 0.09    |
|                                                     | (-0.01, 0.21) | (-0.02, 0.20) | |
| Neonatal pain-related stress                        | NA      | NA      | 4.99    | 3.88    |
|                                                     | (0.47, 9.50)  | (-0.51, 8.27) | |
| Cumulative morphine exposure                        | NA      | NA      | 0.12    | 1.71    |
|                                                     | (-4.62, 4.87) | (-2.98, 6.39) | |
| Days on mechanical ventilation/oscillation          | NA      | NA      | -0.72   | -0.59   |
|                                                     | (-1.63, 0.18) | (-1.47, 0.28) | |
| Culture positive infectionb                         | NA      | NA      | -2.39   | -3.12   |
|                                                     | (-6.04, 1.26) | (-6.65, 0.42) | |
| Number of surgeries                                 | NA      | NA      | 0.14    | 0.04    |
|                                                     | (-1.72, 2.00) | (-1.77, 1.85) | |
| Parent environment 3 years: Low Support, High Stress | NA      | NA      | NA      | -5.47   |
|                                                     | (-9.44, -1.51) | |
| Parent environment 3 years: High Support, Low Stress | NA      | NA      | NA      | 4.66    |
|                                                     | (0.54, 8.77)  | |
| Child interactive behavior 3 years                  | NA      | NA      | NA      | 0.08    |
|                                                     | (-0.19, 0.35) | |

Note: a Male = 0 b Confirmed infection = 1 c Reference group = Parent Environment 3 years: Average Support, Average Stress
Table 5. Estimated Multilevel Models of Internalizing Behaviors Across 1.5, 3, 4.5, 8 Years Using Listwise Deletion for Missing Data

| Study Variable | Model 1  | Model 2  | Model 3  | Model 4  | Model 5  | B (95% CI) |
|----------------|---------|---------|---------|---------|---------|----------|
| Child age at visit | 1.29    | 1.29    | 1.28    | 1.30    | 1.37    | (1.06, 1.52) |
|                | (1.05, 1.52) | (1.05, 1.56) | (1.12, 1.62) |
| Gestational age at birth | NA     | -0.63   | -0.40   | -1.04   | -0.24   | (-1.17, -0.09) |
|                | (-1.46, 0.66) | (-2.16, 0.08) | (-1.27, 0.79) |
| Child sex⁸ | NA     | NA     | 2.21    | 1.21    | 0.63    | (-0.33, 4.75) |
|                | (-1.41, 3.82) | (-1.93, 3.18) |
| Illness severity (day 1) | NA     | NA     | 0.09    | 0.12    | 0.07    | (-0.01, 0.20) |
|                | (0.01, 0.22) | (-0.03, 0.18) |
| Neonatal pain-related stress | NA     | NA     | 4.82    | 2.14    | 3.50    | (0.53, 9.10) |
|                | (-2.44, 6.71) | (-0.63, 7.63) |
| Cumulative morphine exposure | NA     | NA     | -0.64   | -2.98   | 1.01    | (-5.22, 3.93) |
|                | (-7.79, 1.84) | (-3.52, 5.53) |
| Days on mechanical ventilation/oscillation | NA     | NA     | -0.71   | -0.96   | -0.57   | (-1.58, 0.16) |
|                | (-1.98, 0.05) | (-1.41, 0.28) |
| Culture positive infection⁹ | NA     | NA     | -1.33   | -1.41   | -1.94   | (-4.74, 2.08) |
|                | (-4.90, 2.08) | (-5.32, 1.44) |
| Number of surgeries | NA     | NA     | 0.16    | 0.88    | 0.16    | (-1.63, 1.94) |
|                | (-0.97, 2.73) | (-1.58, 1.89) |
| Parenting stress 1.5 years | NA     | NA     | NA     | 0.17    | NA      | (0.10, 0.24) |
| Parent environment 1.5 years*: Low Support | NA     | NA     | NA     | -0.06   | NA      | (-3.89, 3.76) |
| Parent environment 1.5 years*: High Support | NA     | NA     | NA     | 1.28    | NA      | (-4.18, 6.73) |
| Child interactive behavior 1.5 years | NA     | NA     | NA     | -0.29   | NA      | (-0.56, -0.01) |
| Parent environment 3 years*: Low Support, High Stress | NA     | NA     | NA     | NA      | 4.92    | (1.15, 8.69) |
| Parent environment 3 years*: High Support, Low Stress | NA     | NA     | NA     | NA      | NA      | (-5.31, -2.82) |
|                      |     |     |     |     |            |
|----------------------|-----|-----|-----|-----|------------|
|                      | NA  | NA  | NA  | NA  | 0.06       |
| Child interactive behavior 3 years |     |     |     |     | (-8.97, -1.66) |
| Maternal education (years) |     |     |     |     | -0.50      |
|                      | NA  | NA  | NA  | NA  | (-0.97, -0.04) |

*Note:* a Male = 0, b Confirmed infection = 1, c Reference group = Parent Environment 1.5 years: Average Support, d Reference group = Parent Environment 3 years: Average Support, Average Stress
## eTable 6. Estimated Multilevel Models of Internalizing Behaviors Across 3, 4.5, 8 Years Using Listwise Deletion for Missing Data

| Study Variable                                      | B (95% CI)       | Model 1   | Model 2   | Model 3   | Model 4   |
|-----------------------------------------------------|------------------|-----------|-----------|-----------|-----------|
| Child age at visit                                  | 1.28 (0.97, 1.59)  | 1.28 (0.97, 1.59)  | 1.27 (0.96, 1.58)  | 1.31 (0.99, 1.64)  |
| Gestational age at birth                            | NA (-1.28, -0.11) | -0.69 (-1.85, 0.37) | -0.74 (-1.65, 0.58) | (-1.11, 4.20) |
| Child sex <sup>a</sup>                               | NA 1.55 (0.96, 1.58) | NA (0.97, 1.59)   | -0.01 (0.37)       | (-2.22, 3.29) |
| Illness severity (day 1)                            | NA (0.13, 9.19)   | NA (0.13, 9.19)   | 0.12 (0.13, 9.19)  | -1.02 (7.91) |
| Neonatal pain-related stress                        | NA (-4.62, 4.87)  | NA (-4.62, 4.87)  | -0.72 (-4.62, 4.87) | (-3.21, 6.53) |
| Culture positive infection <sup>b</sup>              | NA (-6.64, 1.26)  | NA (-6.64, 1.26)  | -2.39 (-6.64, 1.26) | (-1.59, 0.22) |
| Number of surgeries                                 | NA (-1.72, 2.00)  | NA (-1.72, 2.00)  | 0.14 (0.14, 2.00)  | (-1.65, 2.08) |
| Parent environment 3 years: Low Support, High Stress| NA (-9.56, -1.68) | NA (-9.56, -1.68) | NA (4.88)          | NA (4.88)          |
| Parent environment 3 years: High Support, Low Stress| NA (0.82, 8.95)   | NA (0.82, 8.95)   | NA (0.07)          | (0.82, 8.95)       |
| Child interactive behavior 3 years                  | NA (-0.20, 0.34)  | NA (-0.20, 0.34)  | NA (0.57)          | (-1.07, 0.07) |
| Maternal education (years)                          | NA (-0.20, 0.34)  | NA (-0.20, 0.34)  | NA (0.57)          | (-1.07, 0.07)     |

<sup>Note:</sup> <sup>a</sup> Male = 0 <sup>b</sup> Confirmed infection = 1 <sup>c</sup> Reference group = Parent Environment 3 years: Average Support, Average Stress

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