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Cumulative Risk, Protection, and Early Intervention: Neurodevelopment in Sibling Groups Exposed Prenatally to Substances

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ABSTRACT

Mothercraft's Breaking the Cycle is an early intervention program for substance-exposed children with neurodevelopmental vulnerabilities. Within three substance-exposed sibling groups (N = 8; 0–6 years), we 1) described longitudinal neurodevelopmental trajectories, 2) explored the balance of cross-domain cumulative risk and protection on neurodevelopment, and 3) generated hypotheses on how cumulative risk, protection, and early intervention impact neurodevelopment. Neurodevelopment is potentially shaped by the balance of risk and protection. Postnatal risk (birth/post natal, child, parent-child interaction) and relational protection (family, parent-child interaction) appear to have the most salient impact on neurodevelopment. Early intervention is thought to be important as soon as possible and before age 3 years.

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Prenatal substance exposure is a serious public health concern given that such exposure is associated with deficits across many domains of functioning (Huizink, 2015; McQueen, Murphy-Oikonen, & Desaulniers, 2015). Specifically, children with prenatal substance exposure are considered at high risk for a range of biological, neurodevelopmental, and behavioral problems, as well as psychopathology (Bandstra, Morrow, Mansoor, & Accornero, 2010). Research has shown that the adverse effects of prenatal substance exposure can be exacerbated by risk factors across various domains in the perinatal environment (Carta et al., 2001; Conners et al., 2004). The accumulation of protective factors also occurs across domains and attenuates the negative effects of cumulative risk, promoting positive development (Ackerman, Schoff, Levinson, Youngstrom, & Izard, 1999; Ostaszewski & Zimmerman, 2006; Spencer, 2005).

Mothercraft's Breaking the Cycle (BTC) is a child maltreatment prevention and early intervention program for pregnant and parenting women who use substances and their young children aged 0–6 years in Toronto, Canada (Espinet, Motz, Jeong, Jenkins, & Pepler, 2016). This is the final paper in a four-paper set examining cumulative risk, protection, and neurodevelopment in substance-exposed sibling groups at BTC. Our previous papers overview: 1) the establishment of clinically and theoretically grounded, cross-domain cumulative risk and protection measures (see PAPER 1 for published measures; Bondi, Pepler, Motz, & Andrews, 2020b), 2) for use with a sample of substance-exposed sibling groups (see PAPER 2 for overview of measure development and quantiative profile scores; Bondi, Pepler, Motz, & Andrews, 2020c), alongside 3) a qualitative case study of cumulative risk and protective factors in this sample which yielded insights into how contexts of risk and protection contribute to clinical progress in substance-exposed families accessing early intervention services (see

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Supplemental data for this article can be accessed on the publisher's website.

PAPER 3 for qualitiative case studies; Bondi et al., 2021). There has been minimal investigation, however, into the impact of cumulative risk, protection, and early intervention, on *neurodevelopment* specifically in this population. The current mixed-method study integrates and builds upon our previous work to explore and generate hypotheses surrounding how previously described profiles of cumulative risk and protection, and early intervention, may impact the *neurodevelopment* of young substance-exposed children.

Neurodevelopmental profiles of substance-exposed children

Children with prenatal substance exposure are at high risk for neurodevelopmental deficits (Bandstra et al., 2010; Black, Schuler, & Nair, 1993). Prenatal alcohol and marijuana exposure have long-term adverse effects on neurodevelopment, specifically attentional skills, with marijuana exposure associated with Attention-Deficit/Hyperactivity Disorder (Fried, Watkinson, & Gray, 1992). Prenatal alcohol exposure affects academic achievement and executive functioning, suggesting global adverse effects (Williams & Ross, 2007). Prenatal alcohol exposure is the etiology of Fetal Alcohol Spectrum Disorder, characterized by congenital abnormalities, cognitive, behavioral, emotional, and adaptive functioning deficits (Williams & Ross, 2007). Prenatal cocaine exposure negatively impacts arousal regulation, auditory comprehension, language abilities, and academic achievement (Koren et al., 1998; Landi, Avery, Crowley, Wu, & Mayes, 2017; Mayes, Grillon, Granger, & Schottenfeld, 1998; Morrow et al., 2006; Nulman et al., 2001; Singer et al., 2004; Williams & Ross, 2007), while prenatal opiate exposure is associated with cognitive and psychomotor deficits (Hunt, Tzioumi, Collins, & Jeffery, 2008). Prenatal tobacco exposure affects academic achievement and memory (Williams & Ross, 2007). Prenatal polysubstance exposure, however, has been less studied but is thought to impact overall cognitive development (Moe, 2002; Slinning, 2004; van Baar, Soepatmi, Gunning, & Akkerhuis, 1994). In summary, exposure to various substances prenatally has diverse adverse effects on neurodevelopment. This study provides additional understanding around the neurodevelopment of young children exposed prenatally to polysubstance exposure, thus addressing a notable gap in the literature.

The first objective of this study was to describe the neurodevelopmental trajectories of children with prenatal polysubstance exposure longitudinally; specifically, across early development. Exploring neurodevelopmental trajectories during the infancy and early childhood period is essential to enhance understanding of how early intervention can be maximized during this dynamic period of neurodevelopment. Notably, description of the moderating role of risk and protective factors on the relationship between polysubstance exposure and neurodevelopment is also essential in informing targeted interventions for this vulnerable population.

Cumulative risk and protection and neurodevelopment

Research on prenatal substance exposure has revealed risk factors across perinatal domains (e.g., factors related to the mother, secondary parent, family, pregnancy, birth, child, parent-child interactions) that exacerbate the adverse effects of prenatal substance exposure on neurodevelopment. For instance, the effects of prenatal marijuana exposure on neurodevelopment are heightened with maternal age (Williams & Ross, 2007). The neurodevelopmental risks associated with prenatal alcohol exposure are heightened with increased maternal age, a history of alcohol use, high-level maternal binge drinking prenatally (Williams & Ross, 2007), and minimal cognitive stimulation for the child (Bailey et al., 2004; Jacobson, Jacobson, Sokol, Chiodo, & Corobana, 2004). Maternal intelligence and quality of care in the home are determinants of neurodevelopment in children exposed prenatally to cocaine (Singer, 2002; Singer et al., 1997, 2001, 2004). Relative to controls, children with prenatal cocaine exposure are more likely to be victims of emotional and physical neglect, have minimal contact with their biological fathers, have fewer toys, have less adequate housing, and live in chaotic home environments; mothers consuming cocaine prenatally are more likely to be depressed, have fewer recourses, lack social support, spend less time with their children, and make frequent moves (Nulman

et al., 2001). Cocaine and opiate exposure are thought to have little effect in utero, with their effects on neurodevelopment most likely mediated through maternal psychosocial functioning, outlining the need to consider the exacerbating role of perinatal environmental risks (Lester et al., 2002; Williams & Ross, 2007). Prenatal tobacco exposure relates to the quality of the early caregiving environment, including maternal mental state, attitudes, personality, socioeconomic status, and education level (Wakschlag & Hans, 2002). In a review of cumulative risk and child development, Evans, Li, and Whipple (2013) discussed the need to combine multiple risk factors into domains. Most children exposed to a single risk factor suffer minimal enduring consequences (Evans et al., 2013; Rutter, 1981). In contrast, children exposed to multiple risk factors are at high risk for poor neurodevelopmental outcomes and psychological disorders (Kessler, Davis, & Kendler, 1997; Kessler et al., 2010; Rutter, 1979, 1981; Sameroff, 2006), emphasizing the importance of considering cumulative rather than individual risks. Further, risk exposure across multiple domains presents more challenging adaptive demands on children relative to intense but concentrated risk exposure within a single domain (Ackerman et al., 1999; Brennan, Hall, Bor, Najman, & Williams, 2003; Evans et al., 2013; Whipple, Evans, Barry, & Maxwell, 2010), emphasizing the importance of considering cumulative risks across domains.

Research has revealed protective factors across perinatal domains that ameliorate the adverse effects of prenatal substance exposure on neurodevelopment. Parental intelligence and the quality of the caregiving environment are important protective factors (Williams & Ross, 2007). Many protective factors are linked to positive outcomes in children exposed to substances including: support from school, immediate and extended family, the presence of a stable adult, a positive relationship with a caregiver, minimal separation from the primary caregiver in the first year of life, and individuals and services outside the family (Velleman & Templeton, 2007). Specifically, an optimal home environment is positively related to neurodevelopmental performance, buffering the adverse effects of prenatal cocaine exposure (Black et al., 1993).

There is, therefore, evidence that both risk and protective factors in the perinatal environment can impact children's neurodevelopmental outcomes beyond prenatal substance exposure alone, thus warranting further consideration. Research on the impact of cumulative risk and protective factors on neurodevelopment requires integration across the perinatal domains within which they occur (e.g., factors relating to the mother versus the child) in order to inform our understanding of contexts of risk and protection, and early intervention planning. As such, the second objective of this study was to illustrate the patterns of cumulative risk and protection across perinatal domains (as outlined in our prior work within this paper set) as they relate to neurodevelopment in infancy and early childhood.

Cross-domain cumulative risk and protection and neurodevelopment

The clinically and theoretically grounded, cross-domain cumulative risk and protection measures previously established at BTC (PAPER 1; Bondi et al., 2020b) conceptualize salient perinatal domains of both risk and protection for substance-exposed sibling groups based on the Developmental Model of Transgenerational Transmission of Psychopathology (Figure 1; Hosman, van Doesum, & van Santvoort, 2009). Cross-domain (i.e., risk and protective factors categorized within domains) and overall (i.e., total risk and protective factors) profiles of cumulative risk and protection, and the number of clinically notable domains of risk relative to protection, were reported, thus enabling consideration of intra- and inter-domain risk and protection within and between sibling groups (PAPER 2; Bondi et al., 2020c). For instance, one child may have clinically notable risk in specific domains (e.g., mother domain: teenage mother; other parent domain: other parent substance use; family domain: domestic violence in parental relationship), but may also have more protective factors across other clinically notable domains (e.g., family domain: extended family supports; child domain: child in daycare; parent-child interaction domain: high parental empathy; social networks and professional services domain: financial allowances). This combination of both risk and protective factors across domains can uniquely impact child outcomes. We then used a case study approach to

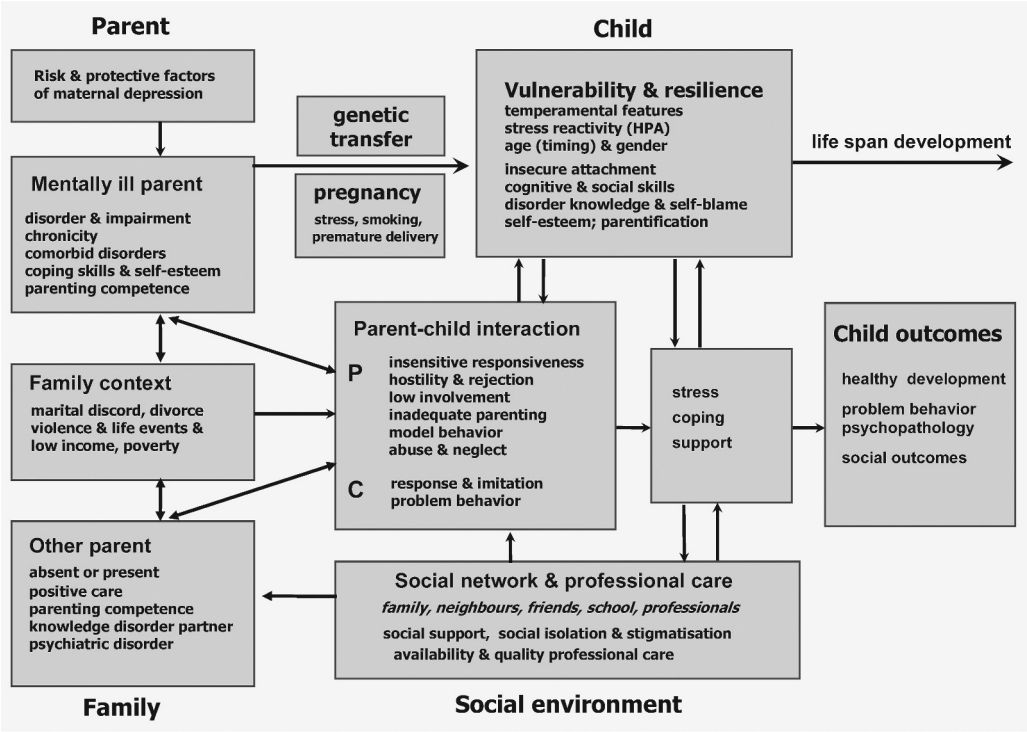

Figure 1. Theoretical model. Reprinted from Hosman, C. M. H., van Doesum, K. T. M., & Santvoort, F. (2009). Prevention of emotional problems and psychiatric risks in children of parents with a mental illness in the Netherlands. I. The scientific basis to a comprehensive approach. *Australian e-journal for the advancement of mental health, 8*(3), 250–63. Copyright 2009 by the Taylor & Francis Ltd (https://www.tandfonline.com). Reprinted with permission.

qualitatively examine cumulative risk and protection, as well as neurodevelopment, yielding insights into how contexts of cumulative risk and protection may contribute to child-specific neurodevelopment and family-specific clinical progress (PAPER 3; Bondi et al., 2021). For example, a child with more notable protective domains than risk domains fared better in their clinical progress and neurodevelopment (cognitive and social-emotional development), whereas a child with many notable risk domains and few protective domains fared worse in their clinical progress and neurodevelopment (cognitive and social-emotional development). The final objective of the present study was to integrate and build upon these mixed-method frameworks (i.e., [i] quantitative cumulative risk and protection measures and [ii] qualitative case study descriptions of cumulative risk and protection and neurodevelopment) to generate hypotheses surrounding how quantitative profiles of cumulative risk and protection, and early intervention, impact quantitative neurodevelopmental profiles of substance-exposed sibling groups.

Current study

This study focused on substance-exposed infants and young children in the context of the mother-child relationship across their time receiving early intervention services at BTC. This study included the same sibling groups that were involved in the three prior studies conducted at BTC. Programming at BTC supports the development of substance-exposed young children through a comprehensive, integrated, cross-sectoral model, highlighting protective factors and their potential impact on neurodevelopment within the context of early intervention (Motz, Leslie, & Pepler, 2016). In this study, we thus explored cumulative risk and protection (with reference to our prior work) alongside

neurodevelopment in young children with prenatal polysubstance exposure. Specifically, we endeavored to: 1) described each child's longitudinal neurodevelopmental trajectory, 2) explore the balance of cross-domain cumulative risk and protection (as previously reported) as they relate to children's neurodevelopment, and 3) generate hypotheses regarding how cumulative risk, protection, and early intervention impact neurodevelopment.

Materials and methods

Study design and setting

This study was conducted at BTC in Toronto, Canada in accordance with the ethical standards of the American Psychological Association and was approved by York University's Ethics Review Board. BTC supports the development of children with prenatal substance exposure by providing maternal services (e.g., addiction counseling) and child services (e.g., early intervention services, yearly developmental assessments), in addition to relationship-focused services specifically designed to foster the mother-child relationship (e.g., mother-child interactional support groups, home-based dyadic developmental services). Through a single access model, BTC operates in formal partnership with nine agencies addressing services related to child protection, addiction treatment, health, community corrections and probation, and child mental health and development (Espinet et al., 2016).

Sample characteristics

Three pediatric (0–6 years) sibling groups with substance exposure histories were included in this study (as well as all prior studies in this paper set): two sibling dyads and one sibling quadrad (N = 8). We selected families that included sibling groups in order to compare cumulative risk and protection between and within sibling groups. Evaluation of sibling groups also allowed us to compare children within a family with similar risk exposures but differential time of entry into early intervention programming. All sibling groups had participated in treatment at BTC for a minimum of 2.5 years, with developmental assessments at multiple time points. The three families, herein referred to as family A (dyad), family B (quadrad), and family C (dyad), were selected based on their clinical progress, which lead clinicians at BTC classified as good, fair, and poor, respectively. Clinicians assessed the families' overall clinical progress based on the families' participation in programming at BTC, child apprehensions from parental care during their involvement at BTC, as well as their situation and progression toward individual therapeutic goal attainment at the time of ending services at BTC. Families with variable levels of clinical progress were included to capture the range of clients seen at BTC. Although several families met this inclusion criteria, only three families were selected as the mixed-method nature of this study necessitated extensive chart review. The three families that were selected had the longest involvement time at BTC and were deemed by clinicians to represent the clearest depiction of each clinical progress status, respectively. Individual children within each sibling group are referred to according to family letter (e.g., A, B, C) and birth order (e.g., 1–4). B1 and B2 were identical twins. Informed consent was obtained from all mothers included in the study and mothers consented on behalf of their young children.

To ensure participant privacy and confidentiality, the sex of the children and other highly identifiable participant characteristics are omitted. A1 did not have prenatal substance exposure. A2 had prenatal polysusbstance exposure across all three trimesters (i.e., nicotine, opioids, opiates, prescribed and non-prescribed methadone, cocaine). B1 and B2 were exposed to prenatal polysubstance use across all three trimesters (i.e., nicotine, alcohol, prescribed methadone). B3 (i.e., consistent nicotine, few occasions of alcohol and cocaine use) and B4 (i.e., consistent nicotine and cocaine, few occasions of alcohol use) were also exposed to prenatal polysubstance use across all three trimesters. C1 was exposed to prenatal polysubstance use within the first trimester (i.e., nicotine, alcohol, cannabis, ecstasy). C2 was reportedly only exposed to nicotine within the first

trimester. For comprehensive case studies and qualitative descriptions of each child's clinical progress, see PAPER 3; Bondi et al., 2021). Notably, the women and children at BTC are highly vulnerable (Motz, Leslie, Pepler, Moore, & Freeman, 2006), making BTC a unique context to evaluate perinatal cumulative risk and protective factors as they relate to neurodevelopment. All three mothers in the sample engaged in prenatal substance use, 67% had a diagnosed mental health illness, 100% had a history of child abuse/neglect, 67% had a history of interpersonal violence/complex trauma, 100% had a primary relationship with a substance user, 100% had a dysfunctional or abusive relationship with the other parental figure, 67% underwent a separation/divorce from the other parental figure while at BTC, and 33% were teenage parents while at BTC. This sample was uniquely situated within a relationally focused early intervention program that has demonstrated improved maternal mental health and relationship capacity (Espinet et al., 2016).

Procedures

This study utilized archival BTC data collected under a nationally funded, multi-year study (Espinet et al., 2016). Existing quantitative (PAPER 1 AND 2; Bondi et al., 2020b, 2020c) and qualitative (PAPER 3; Bondi et al., 2021) descriptions of cross-domain cumulative risk and protection for the target sibling groups (see respective studies for further method specifications) were integrated in this study. Novel quantitative neurodevelopmental data unique to this study were obtained from clients' charts, using annual developmental assessment measures and reports that spanned social-emotional and cognitive developmental domains. Multiple measures were used for each construct, as appropriate for child age, given the nuanced and dynamic nature of developmental capacities in early childhood. The three families differed in their use of services and their length of involvement with BTC; therefore, available assessment time points varied somewhat across children. The children differed in age at entry into BTC programming and the proportion lifetime in programming.

Measures

Cross-domain cumulative risk and protection

Previously established clinically and theoretically grounded, cross-domain cumulative risk and protection measures were used (see PAPER 1 for published measures; Bondi et al., 2020b). The cumulative risk and protection measures encompassed domains based on Hosman and colleagues' (2009) theoretical model, which aligned with BTC staff's clinical understanding of these substance-exposed children undergoing intervention (Figure 1). Measures of both cumulative risk and protection included factors categorized within the following domains: mother, secondary parent, family, pregnancy, birth, child, parent-child interactions, social networks, and professional services (see PAPER 2 for a comprehensive overview of how the measures were established; Bondi et al., 2020c). Risk factors were extracted from clients' charts and were based on: 1) items from a cumulative risk measure utilized in prior BTC research, 2) measures used clinically at BTC to assess maternal mental health, addiction, and parenting capacity, 3) a measure utilized in studies on adverse childhood experiences, and 4) the Diagnostic Classification of Mental Health and Developmental Disorders of Infancy and Early Childhood, specifically Axis IV on Psychosocial Stressors (Anda et al., 2006; Mothander, 2016; Motz et al., 2011). Protective factors were based on: 1) service components at BTC that families attended, 2) clinical measures assessing maternal mental health, addiction, and parenting capacity, and 3) additional known protective factors outlined in the literature. An example risk factor was 'mother has history of child abuse/neglect,' and protective factor was 'mother in recovery for substance use,' both within the 'mother' domain (PAPER 1; Bondi et al., 2020b). Risk and protection measures were scored via client chart review and total and domain-specific cumulative risk and protection percentages were calculated (based on the number of positive factors). Domain-specific percentages > 25% were

considered clinically notable (PAPER 2; Bondi et al., 2020c). The number of clinically notable protective domains was subtracted from clinically notable risk domains to quantify the balance of cross-domain cumulative risk and protection (i.e., Net Risk Score; positive numbers indicating more notable risk domains relative to protection domains; PAPER 2; Bondi et al., 2020c).

Longitudinal neurodevelopmental trajectories

Social-emotional functioning. Emotional and behavioral problems were assessed using the Child Behavior Checklist (CBCL), a well-established standardized parent/caregiver and teacher questionnaire (Achenbach, 2000). Separate versions of the CBCL were used for children aged 1.5 to 5 years old and 6 to 18 years old (Achenbach, 2000). The CBCL was completed using parent/caregiver and/or teacher/daycare worker report; notably, different teachers/daycare workers provided ratings at each time period. Emotion regulation and behavior were assessed using the Infant-Toddler Social Emotional Assessment (ITSEA) measure for young children aged 1 to 3 years old (Carter & Briggs-Gowan, 2006). The ITSEA was completed by a parent/caregiver. ITSEA and CBCL ratings were compared to same-aged peers using the measure-specific classification schemes shown in (Table 1) (Achenbach, 2000; Carter & Briggs-Gowan, 2006). T-scores were used to describe each child's ratings relative to age-matched population norms. Social-emotional development was considered clinically concerning if scores fell within the borderline clinical range or the clinical range. The borderline clinical range was classified as clinically concerning given the young age and high-risk nature of the sample. When considering neurodevelopment longitudinally, the proportion of clinically concerning scores (across respondents) was reported at each assessment time point. Proportions above 25% were designated as clinically concerning. These quantitative multi-informant reports of social-emotional functioning were

Table 1. Neurodevelopmental assessment measures classification schemes.

ITSEA Classification Scheme	
Domains	
Classification	**Range of T-Scores**
Of-Concern	≥ 63
Normal	< 63

CBCL Classification Scheme			
Syndrome Scales DSM-Oriented Scales		**Behavioral Concerns**	
Classification	**Range of T-scores**	**Classification**	**Range of T-scores**
Clinical	≥70	Clinical	≥64
Borderline Clinical	65–69	Borderline Clinical	60–63
Normal	<65	Normal	<60

BAYLEY-III Classification Scheme WPPSI-IV Classification Scheme	
Full-Scale IQ Domains	
Classification	**Range of Percentiles**
Very Superior	≥98th percentile
Superior	92nd – 97th percentile
High Average	76th – 91st percentile
Average	25th – 75th percentile
Low Average	9th – 24th percentile
Impaired	≤8th percentile

compared to the previously outlined qualitative case study description (PAPER 3; Bondi et al., 2021) of each child's neurodevelopmental profile. Additional qualitative clinical information was provided if there was a discrepancy between the quantitative and qualitative profiles.

Intellectual and cognitive functioning. Intellectual and cognitive functioning were assessed using the Bayley Scales of Infant and Toddler Development-Third Edition (BAYLEY-III) for children 1 to 3.5 years old, and the Wechsler Preschool and Primary Scale of Intelligence-Fourth Edition (WPPSI-IV) for children 2.5 to 7.6 years old (Bayley, 2006; Wechsler, 2012). Performance was compared to same-aged peers age using the measure-specific classification schemes shown in (Table 1; Bayley, 2006; Wechsler, 2012). Percentile ranks were used to describe each child's performance relative to age-matched population norms. Cognitive development was considered clinically concerning if scores fell within the low average or impaired range. The low average scores were classified as clinically concerning given the young age and high-risk nature of the sample. When considering neurodevelopment longitudinally, the proportion of scores that were classified as clinically concerning on the cognitive measures was reported at each assessment time point. Proportions above 25% were designated as clinically concerning.

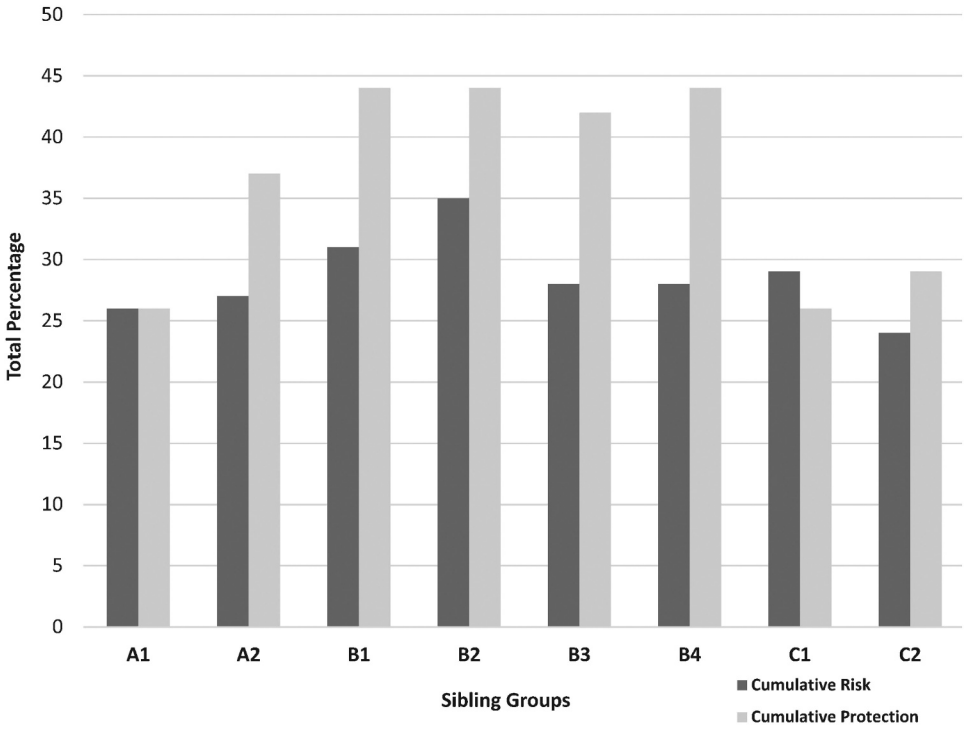

Figure 2. Total cumulative risk and protection percentages across all domains. Reprinted from *Child Abuse & Neglect, 108*(Bondi et al., 2020c), Bondi, B. C., Pepler, D. J., Motz, M., Andrews, N. C. Z., Establishing clinically and theoretically grounded cross-domain cumulative risk and protection scores in sibling groups exposed prenatally to substances, 104631, Copyright (2020), with permission from Elsevier.

Early intervention service usage

Age at entry into BTC programming was calculated for each child by subtracting the date of birth from the date of BTC intake. Length of time in BTC programming was calculated for each child by subtracting the age at entry into programming from the age at discharge. The proportion of lifetime in BTC programming was calculated for each child by dividing the length of time in BTC programming by the age at discharge.

Results

Cross-domain cumulative risk and protection

An overview of the total cumulative risk and protection percentages for each child across all domains is shown in (Figure 2), indicating variability in cumulative risk and protection both within and between the sibling groups. The number of clinically notable domains of risk and protection are shown in (Figure 3(a); illustrated with shaded boxes), with the quantified balance of cross-domain

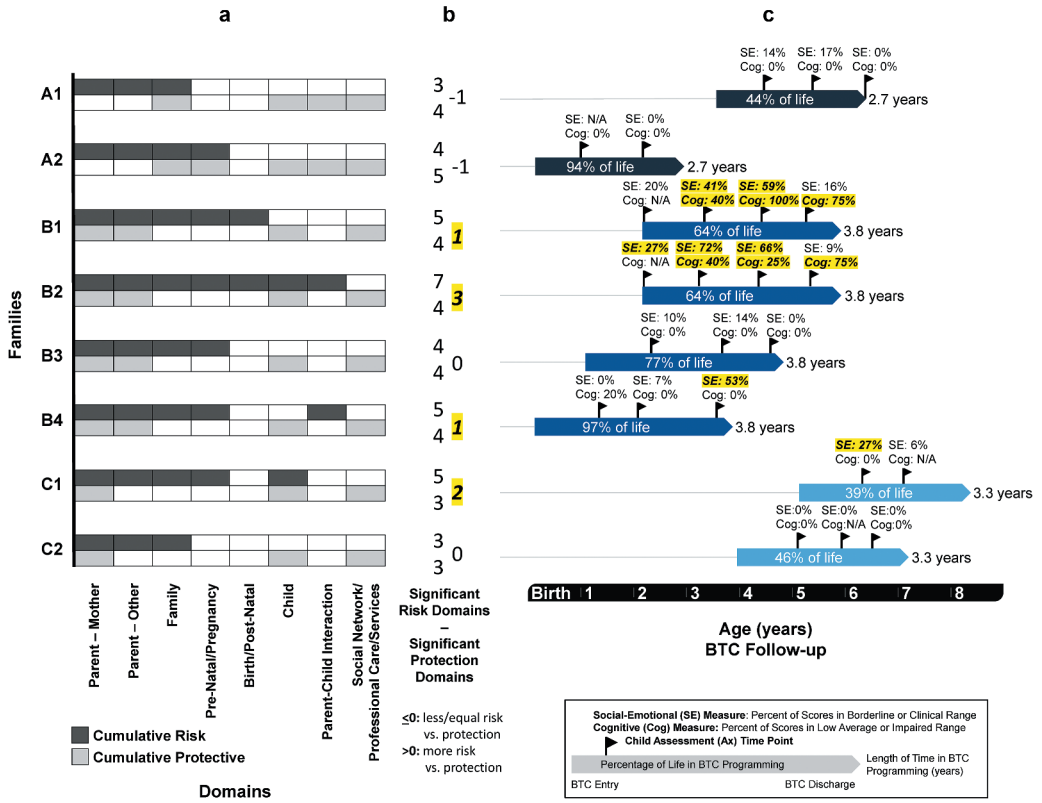

Figure 3. Patterns of cumulative risk and protection and neurodevelopment.Panel a: Clinically notable cumulative risk and protection domains. Clinically notable levels of cumulative risk and protection (percentages > 25%) are shaded within each domain. **Panel b: Net Risk Score**. The number of clinically notable protective domains (shown in Panel a) subtracted from the number of clinically notable risk domains, to quantify the balance of cross-domain cumulative risk and protection. Positive numbers indicate more clinically notable risk domains relative to protection domains and are highlighted, bolded, and italicized. Panels a and b adapted from *Child Abuse & Neglect, 108*(Bondi et al., 2020c), Bondi, B. C., Pepler, D. J., Motz, M., Andrews, N. C. Z., Establishing clinically and theoretically grounded cross-domain cumulative risk and protection scores in sibling groups exposed prenatally to substances, 104631, Copyright (2020), with permission from Elsevier. **Panel c: Longitudinal neurodevelopmental data**. At each assessment, the percentage of social-emotional scores that fell within the borderline clinical or clinical range, and the percentage of cognitive scores that fell within the low average or impaired range. Scores in the clinically concerning range (percentages > 25%) are highlighted, bolded, and italicized. Age at entry and the proportion of lifetime spent in early intervention programming are shown.

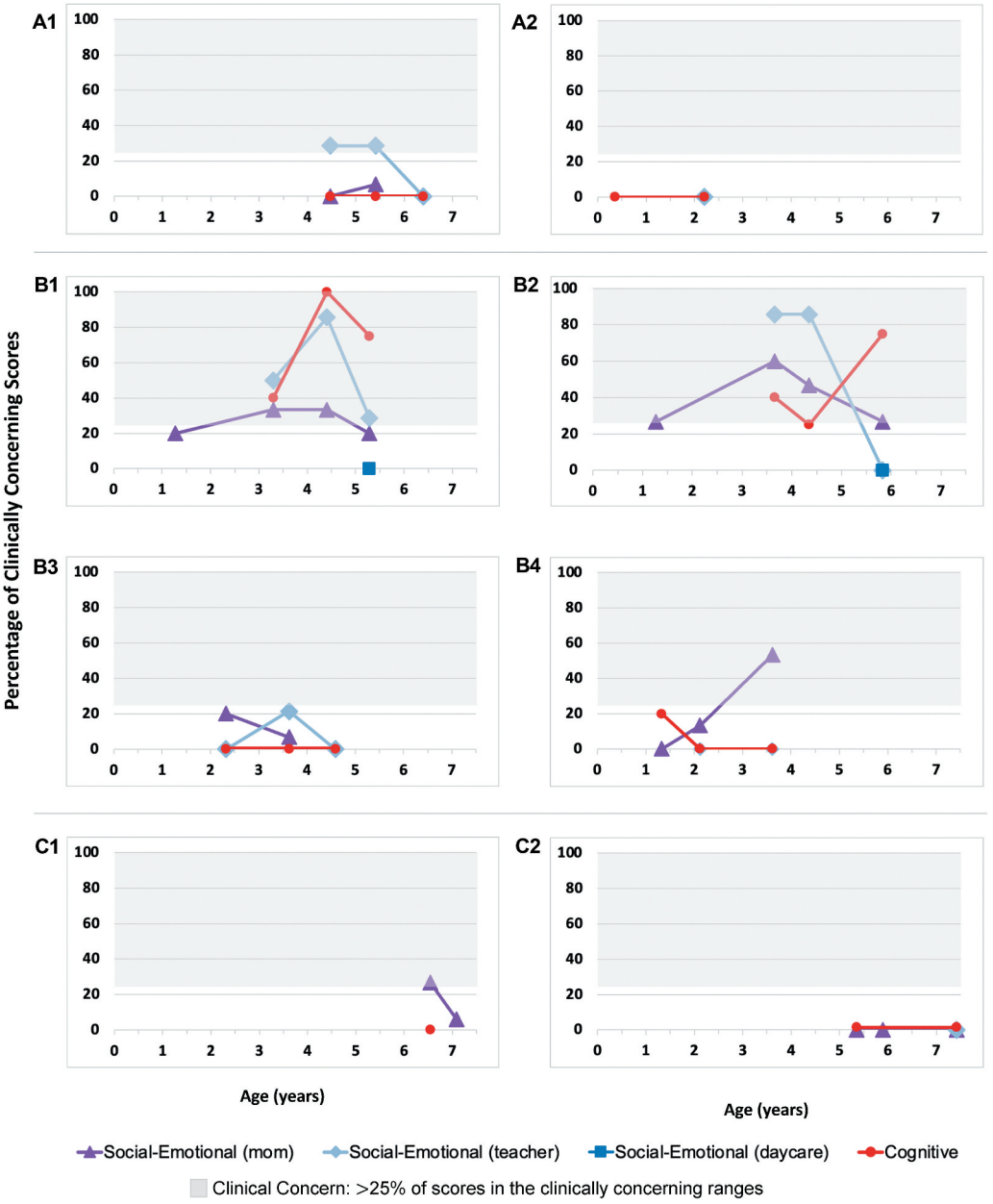

Figure 4. Multi-informant longitudinal neurodevelopmental trajectories. The percentage of clinically concerning scores is indicated in the shaded area for social-emotional outcomes (maternal, teacher, and/or daycare worker report) and cognitive outcomes. Neurodevelopmental trajectories are depicted by age in years across the various developmental assessments undergone for each child.

cumulative risk and protection (i.e., Net Risk Score) shown in (Figure 3(b)). Positive numbers indicate more clinically notable risk domains relative to protection domains (highlighted, bolded, and italicized in Figure 3(b)). For example, child B2 had notable risk in seven of eight domains and notable protection in four of eight domains, with a Net Risk Score of three. For a quantitative cross-family and child-specific description of cumulative risk and protection, as well as an overview of the balance

of domains of cumulative risk and protection, see PAPER 2 (Bondi et al., 2020c). For a qualitative case study description of each sibling group's cross-domain context of risk and protection, see PAPER 3 (Bondi et al., 2020a).

Longitudinal neurodevelopmental trajectories

The multi-informant longitudinal neurodevelopmental trajectories which are unique to this final study are shown for each child in (Figure 4). This depicts the percentage of clinically concerning scores for social-emotional outcomes across maternal, teacher, and/or daycare worker report, as well as cognitive outcomes. The trajectories are depicted by age (years) across the various developmental assessments undergone for each child (range of one to four assessments) across follow-up. A more nuanced depiction of longitudinal social-emotional (T-scores) and cognitive (percentiles) outcomes across various areas of functioning is shown for each child in the Supplementary Materials. For a qualitative case study description of each child's longitudinal neurodevelopmental profileand relevant contextual factors (e.g., home environment, mother's substance use and relationships, parent-child relationships), see PAPER 3 (Bondi et al., 2021). The quantitative multi-informant reports of social-emotional functioning presented in this study aligned with the prior qualitative case study descriptions of A1-A2 and B1-B4's neurodevelopmental profiles. Although there were minimal concerns noted by C2's mother and teacher in the present study (quantitatively), C2's prior qualitative case study indicated that C2 demonstrated neurodevelopmental concerns around deprivation, lack of safety, loss and separation, and a high attunement to the needs of others according to clinician reporting (PAPER 3; Bondi et al., 2021). Clinicians' notes also indicated high risk of future mental health challenges for both C1 and C2 (PAPER 3; Bondi et al., 2021). This indicates some discrepancy between prior qualitative and current quantitative reporting and emphasizes the importance of building upon our prior qualitative findings to enable a mixed-method approach which yields more comprehensive understanding.

Patterns linking cumulative risk and protection with neurodevelopmental profiles

The patterns of cumulative risk and protection, and the neurodevelopmental outcomes of children exposed prenatally to substances both between and within the sibling groups are shown in (Figure 3 (a-c)). (Figure 3(c)) depicts a summary of the novel longitudinal neurodevelopmental data, showing the proportion of social-emotional scores that fell within the borderline clinical or clinical range (across respondents), and the proportion of cognitive scores that fell within the low average or impaired range. When the proportion of scores in the clinically concerning ranges surpassed 25%, they were highlighted, bolded, and italicized to indicate clinical concern. Additionally, (Figure 3(c)) shows each child's age at entry and the proportion of their lifetime in early intervention programming. Within each family, siblings were in BTC programming for the same length of time. It is vital to note, however, that the younger children entered the program at a younger age and, at the time of BTC exit, had spent a larger proportion of their life in BTC programming. (Figure 3) incorporates these novel longitudinal neurodevelopmental and early intervention data from this study (Figure 3(c)) with the previously described (see PAPER 2; Bondi et al., 2020c) number of clinically notable domains of risk and protection (total domain percentages above 25% shaded; Figure 3(a)) and quantified balance of cross-domain cumulative risk and protection (Net Risk Score; more clinically notable risk domains relative to protection domains highlighted, bolded, and italicized; Figure 3(b)).

Family A

A1 entered BTC programming at 3.5 years of age and spent 44% of life in BTC services. A2 entered BTC programming immediately after birth and spent 94% of life in BTC services. A1 had a higher proportion of clinically concerning social-emotional scores compared to A2 (who had no clinically concerning scores). Although A1 had no concerning cognitive scores, A1's social-emotional concerns

increased slightly from 14% to 17% between time one and two, then decreased down to 0% by time three, thus demonstrating improvements across A1's time at BTC (see Figure 3(c)). It is important to consider these findings in light of contexts of risk and protection. A1 experienced clinically notable levels of risk in three domains: maternal, other parental figure, family, and clinically notable levels of protection in four domains: family, child, parent-child interaction, social network/ professional services (PAPER 2; Bondi et al., 2020c; see also Figure 3(a)). A2 experienced clinically notable risk and protection in the same domains as A1, as well as both risk and protection in the prenatal /pregnancy domain (PAPER 2; Bondi et al., 2020c). Based on these scores, A2 appeared to have fewer neurodevelopmental concerns compared to A1, despite a heightened level of risk.

Family B

B1 and B2 (twins) entered BTC programming at 2 years of age and spent 64% of their lives in BTC services. B3 and B4 entered the program at a younger age relative to B1 and B2, with B3 entering at 1 year of age (77% of life) and B4 entering at birth (97% of life). B1 and B2 had a substantially higher proportion of social-emotional and cognitive scores that were of clinical concern compared to B3 and B4. B1's proportion of clinically concerning social-emotional scores increased across time points one, two, and three, peaking at 59% and decreasing to 16% at time point four (see Figure 3(c)). B1 also showed a clinically concerning proportion of cognitive scores across follow-up, increasing from time points two to three to peak at 100%, then decreasing to 75% at time point four. B2 had a higher proportion of clinically concerning social-emotional scores relative to B1, which increased across time points one to two, peaking at 72% and then dropping at time points three and four to a low of 9% at the end of follow-up. B2 also showed cognitive concerns, with the proportion of scores of clinical concern decreasing from time points two to three, only to increase to a peak of 75% at time point four. These scores demonstrated more neurodevelopmental concerns for B2 relative to B1.

B3 demonstrated minimal concerns across time in the program; however, showed an increase in the proportion of clinically concerning social-emotional scores from time points one to two, peaking at 14% then dropping to 0% by time point three. B3 also had no cognitive scores in the clinically concerning range. B4 showed a slow increase in the proportion of clinically concerning social-emotional scores, initially increasing to 7% from time points one to two, then increasing to a peak of 53% at time point three. These scores demonstrated behaviors that were of growing concern with age. B4 initially had 20% of cognitive scores at the clinically concerning level, which dropped to 0% at the two subsequent time points.

Despite being identical twins, B2 experienced clinically notable levels of risk in seven of the eight risk domains, whereas B1 experienced clinically notable levels of risk in only five of the eight domains (B2 had clinically notable risk in the child and parent-child interaction domains, whereas B1 did not; PAPER 2; Bondi et al., 2020c; see also Figure 3(a)). In contrast, B1 and B2 experienced clinically notable levels of protection in the same domains: mother, other parental figure, child, social network/ professional services (PAPER 2; Bondi et al., 2020c). B3 and B4 had fewer domains of clinically notable risk relative to B1 and B2 (PAPER 2; Bondi et al., 2020c). While B3 had notable risk in 4 domains: mother, other parental figure, family, prenatal/pregnancy, B4 experienced notable risk in these domains as well as in the parent-child interaction domain (PAPER 2; Bondi et al., 2020c). B3 and B4 experienced clinically notable levels of protection in the same domains as B1 and B2 (PAPER 2; Bondi et al., 2020c). Overall, B3 and B4 appeared to have fewer neurodevelopmental concerns relative to B1 and B2 given their lower levels of risk alongside consistent levels of protection. Another notable difference within these siblings is that B3 and B4 received intervention at an earlier age relative to B1 and B2.

Family C

C1 spent 39% of life in BTC programming and C2 spent 46% of life in BTC programming. Notably, both C1 and C2 entered BTC at older ages relative to the children in the other sibling groups, entering at ages 5 and 4 years old, respectively. Although C1 had no clinically concerning cognitive scores, C1 had an initially high proportion of clinically concerning social-emotional scores, with 27% at time point one which decreased to 6% at the second time point (Figure 3(c)). These scores demonstrated an improvement across C1's time at BTC. On the basis of C2's performance on the selected neurodevelopmental assessment measures, C2 was reported to have no clinically concerning cognitive or social-emotional scores across C2's time at BTC. As previously noted, however, these results differ from the qualitative report by clinicians of C2's functioning across C2's time at BTC (that is, C2 demonstrated concerns around deprivation, lack of safety, and loss and separation; PAPER 3; Bondi et al., 2021). Clinicians' qualitative notes also indicated concern for high risk of mental health challenges for both C1 and C2 (PAPER 3; Bondi et al., 2021). C1 experienced clinically notable levels of risk in five domains: mother, other parental figure, family, prenatal /pregnancy, child (PAPER 2; Bondi et al., 2021; see also Figure 3(a)). C2 experienced clinically notable levels of risk in only three of these five domains: mother, other parental figure, family (PAPER 2; Bondi et al., 2020c). Both C1 and C2 experienced clinically notable levels of protection in three domains: mother, child, social network/professional services (PAPER 2; Bondi et al., 2020c).

Discussion

This study is the final paper in a four-part paper set. We build upon our prior studies at BTC wherein quantitative measures (PAPER 1; Bondi et al., 2020b) and profiles (PAPER 2; Bondi et al., 2020c) of cumulative risk and protection were established alongside qualitative case study descriptions of cumulative risk, protection, and neurodevelopment (PAPER 3; Bondi et al., 2021) in substance-exposed sibling groups. The novel goal of this study was to outline each child's quantitative neurodevelopmental trajectory longitudinally across infancy and early development. Integrating current results with those from the prior studies enabled us to explore the balance of cross-domain cumulative risk and protection as they relate to novel quantitative neurodevelopmental outcomes. Throughout the discussion we endeavor to interpret the integration of these results and generate hypotheses surrounding how profiles of cumulative risk and protection, and early intervention, may impact the neurodevelopment of young substance-exposed children, thus filling a crucial gap in knowledge in the literature on this topic.

Broadly, the children in this study demonstrated child-specific improvements in neurodevelopment across their time receiving services at BTC. Only two of eight children (B1 and B2) reached our assigned threshold of > 25% of scores in the clinically concerning range regarding cognitive functioning across their time at BTC. Contrastingly, four of eight children (B1, B2, B4, C1) reached the threshold for concerning social-emotional functioning across their time at BTC. Most children (i.e., six of eight; A1, A2, B3, B4, C1, C2) showed stable or improved cognitive functioning across their time at BTC. B1 and B2 showed ongoing cognitive challenges, with B1 showing an initial decline then improvement in cognitive functioning, whereas B2 showed an initial improvement then decline in cognitive functioning. Half the children (i.e., four of eight; A1, A2, C1, C2) showed stable or improved social-emotional functioning across their time at BTC. B1, B2, and B3 showed an initial decline then improvement in social-emotional functioning, and B4 showed a decline in social-emotional functioning across time at BTC. Throughout the remainder of the discussion, neurodevelopment will be discussed more broadly as encompassing both cognitive and social-emotional development given that the overarching patterns observed differentiate children with clinically concerning neurodevelopment across cognitive and/or social-emotional domains relative to children without any clinically concerning neurodevelopment (i.e., children with highlighted, bolded, and italicized scores in (Figure 3(c) relative to children without).

Children who entered the program at a younger age spent a larger proportion of their life in BTC programming, potentially contributing to the better neurodevelopment found relative to those who entered the program at an older age. Similarly, children with lower levels of clinically notable cumulative risk, alongside higher levels of clinically notable cumulative protection, were found to have fewer neurodevelopmental concerns. Taken together, the neurodevelopment of young children exposed prenatally to substances appears to be dependent on 1) the balance of cumulative risk and protection, 2) salient perinatal domains of risk (i.e., birth/postnatal, child, and parent-child interaction; postnatal environment) and protection (i.e., family, parent-child interaction), and 3) the timing and duration of early intervention. Three hypotheses based on the interpretation of these results are outlined below:

(1) Neurodevelopment is shaped by the balance of cumulative risk and protection.

Within the present study, Family B had the highest level of cumulative risk, with B1 and B2 showing higher levels of risk relative to B3 and B4. Although family B had the highest level of risk overall, the risk was balanced by high levels of cumulative protection. Despite the notable differences in risk between B1 and B2 relative to B3 and B4, all four children had clinically notable protection in the same four domains. Clinicians classified family B as having made "fair" clinical progress during their time at BTC, likely due to the overall balance of high levels of protection alongside high levels of risk. B1 and B2 showed notable deficits in their neurodevelopment (cognitive and social-emotional) relative to B3 and B4, which is consistent with B1 and B2's higher levels of risk (alongside consistent levels of protection). B1 and B2 also entered intervention services at an older age (i.e., age ~ 2 years) relative to B3 (i.e., age ~ 1 year) and B4 (i.e., birth), suggesting that B3 and B4's more positive neurodevelopment may have been due to receiving early intervention, in addition to experiencing less cumulative risk compared to B1 and B2. Further, the heightened level of risk in the absence of heightened protective factors may explain why B2 experienced more neurodevelopmental concerns relative to B1 (i.e., clinically concerning scores at four versus three time points), despite being identical twins.

Although families A and C experienced comparably lower levels of both risk and protection relative to family B, they differed substantially in their clinical progress, classified by clinicians as "good" and "poor," respectively. A1 had fewer clinically notable cumulative risk domains and more clinically notable protection domains relative to A2. These differences might lead to an expectation of heightened neurodevelopment for A1 compared to A2, rather than the observed neurodevelopmental concerns in A1 (although still below clinically concerning threshold). It is important to note, however, that A1 entered intervention services at an older age (~3.5 years) relative to A2 (birth), suggesting that A2's lack of neurodevelopmental concerns, despite higher levels of risk and less protection compared to A1, may have been due to A2 accessing early intervention earlier and for a longer proportion of life.

C1 had more clinically notable cumulative risk domains relative to C2, and C1 and C2 had the same clinically notable domains of protection. C1 showed deficits in neurodevelopment, namely social-emotional concerns exclusively, aligning with C1's higher level of risk relative to C2 alongside comparable levels of protection. Nonetheless, clinicians qualitatively reported that C2 demonstrated neurodevelopmental concerns around deprivation, lack of safety, loss and separation, and a high attunement to the needs of others, despite the quantitative data failing to portray these concerns. C1 also entered intervention services at an older age (i.e., age ~5) relative to C2 (i.e., age ~4); however, C2 still entered services at an older age relative to the children in families A and B, who ranged in age from birth to 3.5 years at entry to BTC. Therefore, although C2 demonstrated fewer neurodevelopmental concerns relative to C1, this may have been due to C2 accessing intervention at an earlier age than C1. Both C1 and C2's neurodevelopmental concerns (quantitatively or qualitatively reported) may have been due, in part, to their late entry into BTC programming. Additionally, C1 and C2's older age at entry into intervention may explain the discrepancy between the clinical progress of family A (i.e., good), relative to family C (i.e., poor), despite comparable levels of cumulative risk and protection.

(2) Postnatal risk domains (i.e., birth/postnatal, child, and parent-child interaction domains) and relational protective domains (i.e., family, parent-child interaction domains) have the most salient impact on neurodevelopment.

The four children that had clinically concerning neurodevelopmental deficits (cognitive and/or social-emotional) at one point during their time at BTC, namely B1, B2, B4, and C1 (see highlighted, bolded, italicized scores in Figure 3(c)), also experienced more clinically notable risk domains relative to notable protection domains (i.e., Net Risk Score, see highlighted, bolded, italicized scores in Figure 3 (b)). These quantitative results align with previous qualitative case study descriptions of these children (PAPER 3; Bondi et al., 2020a), suggesting that more clinically notable domains of risk relative to protection relate to neurodevelopmental deficits. Although these results suggest that the balance of levels of cumulative risk and protection relates to neurodevelopment, a domain-specific perspective suggests that some domains of risk and protection may be more salient than others in their influence on neurodevelopment. B1, B2, B4, and C1 had clinically concerning neurodevelopmental deficits (cognitive and/or social-emotional) and experienced more clinically notable risk domains relative to notable protection domains. They were also the only children who experienced notable levels of *risk* in the birth/postnatal, child, and parent-child interaction domains. These results suggest that ongoing risks in the postnatal environment may be more indicative of neurodevelopmental deficits (cognitive and/or social-emotional; at least in this sample) compared to maternal or family history risks, or risks within the prenatal period. Notably, the levels of risk within the parent-child interaction domain, across all children in this study, are likely an underestimation. That is because many of the factors within this domain were dependent on maternal self-report at entry into BTC programming, rather than clinical reporting across each child's time at BTC. Therefore, the children we identified as experiencing clinically notable levels of risk in the parent-child interaction domain likely experienced extreme levels of risk in this domain. The children in family A were the only children who had clinically notable levels of *protection* within the family and parent-child interaction domains. It may be that these two domains are particularly important and contributed to family A's superior clinical progress and neurodevelopment amongst the three families. Overall, a mixed-method and cross-domain examination of cumulative risk and protection alongside neurodevelopment enabled consideration of unique domains of risk and protection in the neurodevelopment of children exposed prenatally to substances.

(3) Early intervention is important as soon as possible postnatally and before age 3 years.

Results highlight the importance of early intervention for this high-risk population of children exposed prenatally to substances. The potential effect of early intervention might be specific to BTC's early intervention program, which focuses on child development, maternal mental health and addiction, as well as the mother-child relationship. The results support the notion that early intervention within the first three years of life is most crucial to neurodevelopment. More specifically, however, there appeared to be additional benefits to the neurodevelopment of children within this sample with earlier timing and longer duration of early intervention. The results indicated neurodevelopmental differences between children who entered programming with as little as a one-year age difference at entry (e.g., age 1 versus 2 years; Family B). Therefore, the results highlight the potential importance of early intervention commencing as early as possible postnatally. As such, the typical conceptualization of the sensitive period of early intervention (i.e., ~age 0–6) may warrant additional consideration.

Early intervention is essential as it capitalizes on brain plasticity, and thus is capable of altering a child's developmental trajectory; however, there are few studies on the effects of early intervention with young children exposed prenatally to substances (Lester, Boukydis, & Twomey, 2000). Related literature on early intervention with young, disadvantaged children during the first six years of life has revealed improvements in language and cognitive abilities with decreased behavioral concerns

(Martin, Ramey, & Ramey, 1990; Warr-Leeper, 2001). Although there is minimal research on the long-term efficacy of early intervention programs with at-risk children who have not yet received formal diagnoses, some studies demonstrate improvements in language, social skills, and intellectual abilities in multidisciplinary, individualized, and contextually embedded programs (Ramey, Campbell, & Ramey, 1999). Additionally, other studies indicate a moderating role of the parent-child relationship on the efficacy of early intervention on development in at-risk children (Mahoney, Boyce, Fewell, Spiker, & Wheeden, 1998). Furthermore, early intervention prevents cognitive and language delays, as well as behavioral problems, in young children exposed prenatally to cocaine, with sustainable improvements over time (Bono et al., 2005). Overall, the present study catalyzes consideration of the potential influence of early intervention (and particularly, *very early* intervention), alongside contexts of risk and protection, for the neurodevelopment of young substance-exposed children.

Limitations

Despite the strengths of this study, it is limited by a lack of generalizability. This exploratory, mixed-method, hypotheses generative study involved a small sample of high-risk children embedded within early intervention programing at BTC. The small sample size limited the use of statistical analyses. Child sex and other identifiable participant characteristics were omitted due to the high-risk nature of the small sample, but that may hinder consideration of these factors which may pose contextual perinatal risks. Neurodevelopmental data were only available for these children until the age of 6 years, when services at BTC end (extended data until the age of 8 years were presented for family C given continued maternal involvement and her children's neurodevelopmental needs); therefore, limited information was available on children's outcomes at later stages of development. Although yearly assessment measures were selected as clinically appropriate for each child and for different age ranges, the measures were not completely comparable across the sample. Social-emotional development was assessed using parent/caregiver and/or teacher/daycare provider reports, which have been found to be biased by the informant's mood (Ringoot et al., 2015) and emotional impairment (Najman et al., 2001). Further, inconsistent informant concordance has also been noted as a limitation of these questionnaires (Sollie, Larsson, & Mørch, 2013), which may be compounded by variable understanding of young children's development and age-appropriate expectations. It is possible that the mothers in this study rated their children's development favorably as they tried to represent themselves and their children in a positive light, given that they were in the context of treatment. Cognitive development was assessed using pre-school aged testing measures, which have been criticized for being less predictive of future cognitive functioning relative to school-aged testing measures (Aylward, 2004; Colombo, 1993; Hack et al., 2005). Testing pre-school aged children may have also been limited by the children's lack of sustained attention, task maintenance, or comprehension.

Implications and conclusions

This study is novel in that we explored neurodevelopmental trajectories longitudinally across infancy and early childhood, which is essential to enhance understanding of how early intervention can be maximized during this dynamic period of neurodevelopment. The present study also uniquely considered neurodevelopment within the context of perinatal domains of cumulative risk and protection (with integrated qualitative and quantitative findings from prior studies within this four-part paper set), within early intervention programming at BTC. We have identified some potential domains of risk, specifically in the postnatal environment, that may pose the greatest harm to neurodevelopment (i.e., birth/postnatal, child, and parent-child interaction domains). Additionally, we have begun to identify domains of protection that may pose the greatest benefit to neurodevelopment (i.e., family, parent-child interaction domains). Most notably, the results of this study have highlighted the potential impact of contexts of risk and protection, and the balance of risk and protection, on the neurodevelopment of children exposed prenatally to substances; however, there

also appears to be an important effect of early intervention. It is thus likely that there are multiple interacting perinatal influences (e.g., cumulative risk, cumulative protection, early intervention, etc.) on neurodevelopmental outcomes in this population which warrant further empirical testing within larger samples.

The present study has research implications, highlighting the value in exploring contexts of risk and protection in clinical populations within community settings wherein rich qualitative and quantitative information can be integrated. Given the limited research on measures of cumulative risk and protection for children exposed prenatally to substances, this research contributes novel understanding around the balance of cross-domain cumulative risk and protection and the potential influence on neurodevelopment. Further, our cross-domain consideration was essential in contributing understanding of salient domains of risk and protection that potentially impact neurodevelopment. This study thus highlights the value in exploring neurodevelopmental trajectories within the contexts of risk and protection, and early intervention, in which development unfolds. Future researchers should continue merging the fields of cumulative risk and protection with child neurodevelopment in order to understand neurodevelopment holistically and contextually. This study takes the first step toward this goal.

Results highlight the potential importance of early intervention in young substance-exposed children, suggesting a potential shift in the conceptualization of early intervention, which should occur as early in life as possible, rather than before the age of 6 years more broadly. Future research is needed to further explore the hypotheses generated in this study surrounding the potentially interconnected influence of cumulative risk and protection and early intervention on neurodevelopment within larger samples. This involves more complex statistical analyses within larger samples pertaining to neurodevelopmental trajectories and potential group differences. This work can potentially contribute to enhanced neurodevelopmental outcomes for this highly vulnerable population of children and reduced social and economic costs for society.

The present research has preliminary practice implications for early intervention support for young children exposed prenatally to substances. In better understanding profiles of risk and protection, alongside the impact of early intervention, future empirical work can begin to inform targeted evidence-based early interventions that: 1) commence as soon as possible in the perinatal period, 2) identify vulnerable children at high risk for poor neurodevelopmental outcomes, 3) address salient risk factors, 4) incorporate the most effective protective factors, and 5) target vulnerable domains of neurodevelopment. Providing individualized and relationship-based early interventions can also be an important step to improve these children's neurodevelopmental trajectories.

Authorship statement

Bianca C. Bondi: Conceptualization, Methodology, Formal analysis, Investigation, Writing - Original Draft, Writing - Review & Editing. **Debra J. Pepler, Mary Motz, Naomi N.C. Andrews**: Conceptualization, Methodology, Writing - Review & Editing, Supervision.

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Ethical approval

This retrospective study was conducted at Mothercraft's Breaking the Cycle in Toronto, Canada with approval by York University's Ethics Review Board.

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