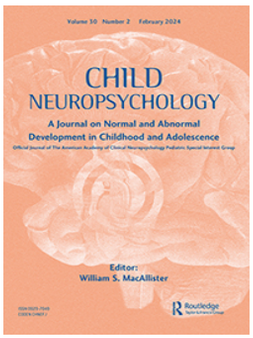

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A follow up investigation of placental pathology, responsive parenting, and preschool children's executive functioning and language development

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ABSTRACT

Despite documented effects linking underlying placental diseases and neurological impairments in children, little is known about the long-term effects of placental pathology on children's neurocognitive outcomes. In addition, maternal responsivity, known to positively influence early postnatal cognitive development, may act to protect children from putative adverse effects of placental pathology. The current study is a follow up of medically healthy, term born, preschool age children, born with placental pathology. A sample of 118 children (45 comparison children with normal placental findings, 73 born with placental pathology) were followed when children were 3–4 years old. In comparison to children born to mothers with normal placentas, placental pathology was associated with poorer performance in the executive function involving cognitive flexibility, but not inhibitory control or receptive language. Maternal responsivity was observed to be marginally protective on the impact of placental pathology risk on cognitive flexibility, but this was not seen for either inhibitory control or receptive language.

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Intrauterine influence: placental pathology and children's executive functioning and language development

In recent years, there has been growing interest in studying the neurocognitive outcomes of children who are born with prenatal or perinatal biomedical risk factors, such as preterm birth (Do et al., 2020; Wade & Jenkins, 2016; You et al., 2019). However, the role of the placenta, a crucial organ in fetal development, has received comparatively less attention in the literature. The placenta's multifaceted functions, from nutrient exchange to immunological protection (Burton & Jauniaux, 2015) and its pivotal role in the underlying mechanisms of fetal programming (Beijers et al., 2014) highlight its importance in ensuring the well-being of both mother and fetus. The placenta's role in shaping

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the fetal brain has been termed "neuroplacentology" (Kratimenos & Penn, 2019). Although research in this area is still emerging, there is a growing interest in investigating the potential link between placental diseases and the risk of neurocognitive impairments in children. This has led to discussions suggesting that analyzing the placenta at birth could be a valuable tool in identifying early developmental challenges (O'Connor et al., 2019). Placental gross morphological and histopathological features have been associated with several adverse fetal and neonatal outcomes. A systematic review of 18 studies found that placental histopathology was linked to a range of poor neurological outcomes, including acute early neurological diseases mostly affecting pre-term, low birth weight infants (Redline, 2008). Subtle neurological impairments were found to emerge later in development in term-born infants with cerebral palsy (Redline, 2005; Redline & O'Riordan, 2000; Roescher et al., 2014).

Follow-up examinations of neurocognitive outcomes in children born with placental complications are limited due to cost implications and challenges in isolating the effects of placental pathology from other risk factors like preterm birth and cerebral palsy (Ananth et al., 2017; Redline, 2005; Redline & O'Riordan, 2000; van Vliet et al., 2012). As a result, there is a significant knowledge gap regarding the long-term influence of placental pathology on apparently healthy infants born at term (Nelson & Blair, 2011). This study aims to address this gap by investigating the association between placental pathology and specific neurocognitive aspects, namely executive function (EF) and language, in healthy, term-born children to understand how placental pathology may influence these cognitive domains.

EF and language abilities are complex cognitive processes that involve higher-order thinking, the integration of multiple skills, and the coordination of various cognitive functions (Diamond, 2013; Price, 2000) which have long-term consequences for children's cognitive and socioemotional development (Cortés Pascual et al., 2019; Hentges et al., 2021; Jacob & Parkinson, 2015). EF includes inhibitory control, working memory, cognitive flexibility, and goal-directed behavior (Miyake et al., 2000), while language abilities encompass phonological processing, vocabulary acquisition, syntax, semantic comprehension, and pragmatic language use (Vigneau et al., 2006). These processes rely on the coordinated functioning of multiple brain regions, such as the prefrontal cortex (PFC) for EF (Moriguchi & Hiraki, 2013) and large-scale architecture networks in left hemisphere regions like Broca's and Wernicke's areas for language processing (Vigneau et al., 2006).

Although the mechanisms that underpin the relationship between placental pathology and children's neurodevelopmental outcomes are not fully understood, the adaptive mechanisms that the fetus evokes in response to reduced placental function may in turn mediate subtle effects upon fetal brain development. For example, impaired placental function will lower the pre-determined genetic growth potential of the fetus, but if the birth weight remains > 10th percentile, this type of subtle fetal growth restriction may go undetected (Lees et al., 2022). Similarly, in the face of reduced transplacental oxygen transfer, the vulnerable fetus is capable of redirecting preferential oxygen delivery to the fetal brain via the phenomenon of "fetal brain sparing" (Zhu et al., 2016). Thus, placental pathology may have broad effects on brain structure and function, including reduced total brain volume, altered cortical volume and structure, decreased cell count, myelination deficits, impaired brain connectivity, and less efficient neural networks (Miller et al.,

2016; O'Connor et al., 2019). These broad effects may potentially compromise higher-order cognitive demands such as EF and language abilities since these processes rely on the integration of multiple brain regions and the coordination of various skills (Diamond, 2013; Moriguchi & Hiraki, 2013; Price, 2000; Vigneau et al., 2006). Indeed, systemic biological risk factors, such as fetal growth restriction have been shown to have greater influence on complex cognitive processes, such as language compared to relatively basic processes like motor development (van Vliet et al., 2012) which primarily rely on localized cortical regions, such as the primary motor cortex (Teka et al., 2017).

From vulnerability to resilience: the potential moderating effects of maternal responsivity

During the first two years of life, the infant brain experiences rapid growth and plasticity, reaching 90% of its final size (Pfefferbaum et al., 1994). This period is characterized by significant increases in myelination and synaptic pruning, which contribute to the emergence of fundamental cognitive abilities (Gao et al., 2009; Huttenlocher & Dabholkar, 1997). The quality of experiential input during this phase plays a vital role in shaping neural systems, making parenting a crucial factor in normative early brain development (Gunnar, 2007; Gunnar et al., 2000). This is especially significant as it coincides with a period of rapid development in EF and language (Garon et al., 2008; Hart & Risley, 1995; Reilly et al., 2007).

The current study aims to investigate the potential moderating influence of maternal responsivity, a specific aspect of parenting, on the association between placental risk and children's EF and language development. Maternal responsivity refers to a caregiver's attunement to a child's emotional and cognitive states and has been shown to predict children's cognitive outcomes (Ainsworth et al., 1978; Landry & Smith, 2011; Vygotsky, 1978). Observational studies have found that maternal responsivity can have a protective effect on children who have experienced pregnancy complications (Wade et al., 2015), with positive associations found between responsiveness and children's EF (Rodrigues et al., 2021; Valcan et al., 2018) and language outcomes (Madigan et al., 2019; Rodrigues et al., 2021). Neuroimaging studies have also shown that responsive parenting strengthens neural connections in brain regions responsible for language (Romeo et al., 2018) and EF (Rifkin-Graboi et al., 2015), as well as children's global neural structure, such as increased brain volume and cortical thickness (Kok et al., 2015; Milgrom et al., 2010).

While adverse prenatal risks can compromise cognitive functioning and mental health (Madigan et al., 2015; Wade et al., 2015), maternal responsivity has been found to protect children's neurodevelopmental outcomes against prenatal risk, such as low birth weight (Landry et al., 2006; Madigan et al., 2015). Additionally, children with low birth weight have been found to be more susceptible to the adverse effects of low responsive parenting compared to those with normal birth weight (Jaekel et al., 2015). Early intervention during this period may be particularly effective in promoting healthy brain development and mitigating the negative effects of placental pathology. Randomized controlled trials have shown that programs to foster parental responsivity improve neurodevelopmental outcomes. For instance, Lewis-Morrarty et al. (2012) randomized foster parents who were caring for children exposed to prenatal risks (preterm, low birth weight, prenatal drug exposure) to an intervention or control, where the intervention was a responsive

parenting intervention. Children in the intervention group showed stronger cognitive flexibility scores relative to children who had received a control intervention. Similarly, Landry et al. (2006) randomized children with low birth weight to a responsive caregiving intervention and reported better cognitive and socioemotional outcomes for children in the intervention versus the control group.

Thus, we expect that postnatal maternal responsivity may also protect the early cognitive development for children who experienced placental pathology in utero. Protective effects are typically operationalized using two criteria: a significant statistical interaction between the risk factor (placental pathology) and the putative protective factor (maternal responsivity), and that the pattern of the interaction shows that the effect of the putative protective factor (maternal responsivity) is stronger in the high-risk group (placental pathology) than the low-risk group (comparison). Investigating the moderating role of maternal responsivity in the relationship between placental risk and children's neurocognitive outcomes can provide valuable insights into the complex interplay between prenatal risk and postnatal experiences. Ultimately, this research can contribute to advancing our knowledge of healthy brain development and enhancing our ability to support children's cognitive and language outcomes.

Current study

Children born with ($n = 73$) and without ($n = 45$) placental pathology were followed up when they were 3–4 years old. We made the following hypotheses:

(1) Firstly, we expect to find a negative association between placental pathology and preschool children's EF and language outcomes. That is, we expect that children born with placental pathology may experience deficits in these neurocognitive domains.
(2) Second, we predicted that maternal responsivity would play a protective role for children with placental pathology. Specifically, we predicted that the effects of maternal responsivity would be stronger in the placental pathology group than in the comparison group.

Method

This study was conducted using the Toronto *Placental Health Study*, a longitudinal comprehensive clinical, biomarker and ultrasound study in 745 nulliparous (first pregnancy continuing beyond 20 weeks' gestation) who gave birth at Mount Sinai Hospital, University of Toronto, Canada. The following participation exclusion criteria were applied: multi-fetal pregnancy, recurrent antepartum hemorrhage, major fetal abnormality (detected at 19-week ultrasound), short cervix (<1 cm, detected at 19-week ultrasound), ruptured membranes, or preexisting severe IUGR, pre-term births, and a diagnosis of severe illness at birth (e.g., cerebral palsy). The University of Toronto Research Ethics Board approved all procedures, including informed consent. After delivery, placentas were examined blinded to antenatal data collection, by a perinatal pathologist. Gross morphology was recorded, and samples were collected and processed for histological examination. A second developmental follow-up study occurred at the

University of Toronto when children were 3–4 years of age. As developmental follow-up was not originally anticipated, a lower recruitment rate was expected. From this database of 745 participants, many families were unable to be reached during the follow up period or declined to participate. Children whose primary language was English were eligible to participate. If children were exposed to more than one language at home, their data were included in the study as long as they were exposed to English at least 75% of the time. After contacting eligible participants, a total of 136 individuals were recruited for the study, but 18 families withdrew prior to data collection. Out of the remaining 118 participants, 45 were classified as controls with normal placental pathology findings, while 73 had placental pathology.

The study design involved two lab visits for the participating children. During the first visit, the research assistant obtained informed consent from the mothers. Additionally, functional near-infrared spectroscopy (fNIRS) data was collected from the children. The data utilized for the current report pertains to the second lab visit, which lasted approximately 40 minutes and involved warm-up play with the child, neurocognitive testing, and a 5-minute structured parent-child task to assess maternal responsivity. The parent-child task was filmed and subsequently coded for analysis. At the conclusion of the session, participating families were reimbursed for their travel expenses, and a small toy was provided as a token of appreciation for the child.

Placental pathologies

Placental pathologies consisted of confirmed and suspected chorion regression, uteroplacental vascular insufficiency, chronic maternal inflammation, acute ascending infection or fetal thrombotic vasculopathy. See Supplemental S1 for a detailed description of placental pathologies under study.

Neurocognitive outcomes

Neurocognitive outcomes examined in this study were EF and receptive language. *Executive Functioning (EF)*: *Cognitive Flexibility and Inhibitory Control.* To assess EF, two computerized measures from National Institutes of Health (NIH) Toolbox for Neurological and Behavioral Function-Cognition Battery were used (Zelazo et al., 2013). The Dimensional Change Card Sort (DCCS) task (a measure of *cognitive flexibility)* and Flanker task (a measure of *inhibitory control)* were used to assess EF. Both tasks have been normed for early childhood through late adulthood and have been shown to have good reliability and validity (Zelazo et al., 2013). *Receptive Language*. The Picture Vocabulary Test (PVT) from the NIH Toolbox was used to measure receptive vocabulary skills for children aged ≥2 years. For all neurocognitive outcomes, we used standardized scores, which are based on age-normed data. All neurocognitive testing was conducted in the laboratory.

Maternal responsivity

Maternal responsivity was assessed during a cooperative building task. Mothers and their children were asked to copy a developmentally challenging design (with four colors of bricks) from a picture using Duplo building blocks for 5 min. Each person was only

allowed to touch two colors, necessitating turn-taking and cooperation in the dyad. Responsivity during interactions was assessed using the Responsive Interactions for Learning (RIFL) scale. Numerous studies using this measure have demonstrated RIFL as a well-validated measure for the assessment of responsivity in parents, teachers, and siblings, and RIFL scores have shown to be significantly associated with children's cognitive and language skills (Prime et al., 2014, 2015; Schneider et al., 2021; Sokolovic et al., 2021a, 2021b). Coders watched the video of the 5-min interaction and rated mothers on their responsive behaviors based on the 11 items that make up the scale (5-point Likert scale, 1, not at all true to 5 very true). All tapes were double coded, and reliability was high ($\alpha = .96$). The mean responsivity reported in this sample was high 4.13 (.78).

Statistical analyses were conducted with the statistical software SPSS Version 27 (IBM Corp, 2020). Missing data were handled using Full Information Maximum Likelihood (FIML) estimation in Mplus 8.0 (Muthén & Muthén, 1998–2017), as this has been found to result in least bias for estimates (Enders, 2001).

Results

Sample demographics are given in Table 1. It can be seen that the sample shows low socioeconomic and racial diversity. We compared the placental risk group with the comparison group on various factors such as child age, sex, birth weight, ethnicity, household income, and maternal education, and found no significant differences. Next correlations were run, and this matrix can be found in Supplemental S2. Demographic factors were not found to be significantly correlated with EF and language outcomes. The lack of association between income and education is likely related to low sociodemographic diversity in the sample. Since demographic factors such as income and education did not significantly correlate with study measures, they were not included in the final regression model.

EF: cognitive flexibility

Table 2 displays the results of the regression analyses. The Supplemental S3 provides bootstrapped bias-corrected estimates, which consistently align with the results presented in Table 2 across outcome measures. It was found that children in the placental pathology group had significantly lower scores on cognitive flexibility ($b = -5.171$, $p < .05$). Maternal responsivity did not significantly predict cognitive flexibility as a main effect ($b = 1.370$, $p = .467$). However, it did marginally moderate the relationship between placental pathology and cognitive flexibility ($b = 5.985$, $p = .057$). This interaction conformed to the protective effect hypothesized (stronger effects of maternal responsivity seen in the placental pathology group). Testing of simple slopes revealed that the association between placental risk and cognitive flexibility was significant at low levels responsivity but not at high levels of responsivity. For children who had placental risk, lower responsivity predicted lower cognitive flexibility scores ($b = -8.786$, $p = .023$). For children whose mothers were highly responsive, placental risk status was not significantly related to cognitive flexibility ($b = -1.566$, $p = .689$). This interaction is illustrated in Figure 1.

Table 1. Sample characteristics.

Study Variable	Comparison Group $n = 45$	Placental Pathology Group $n = 73$
Child Age (months) mean (SD)	39.4 (4.3)	39.01 (3.93)
Gestational Age (weeks) mean (SD)	38.9 (1.7)	39.3 (1.1)
Birth Weight (grams) mean (SD)	3329 (446.2)	3275(416.6)
Child Gender (% female)	40	54.8
DCCS Scores: Cognitive Flexibility		
n	39	59
mean (SD)	101.30 (1.71)	97.88 (1.41)
range	85.07–119.89	74.48–124.00
Flanker Scores: Inhibitory Control		
n	37	60
mean (SD)	1.37 (11.96)	98.95 (12.94)
range	75.26–12.88	7.52–13.95
PVT Scores: Receptive Language		
n	44	71
mean (SD)	105.19(14.60)	101.89(13.38)
range	77.06–137.71	68.39–146.37
Maternal Responsivity		
n	36	63
mean (SD)	4.03(.82)	4.32(.58)
range	2–5	2–5
Household Income (%)		
$25–40,000	6.8	0
$50–74,000	4.5	5.6
$75–99,000	11.4	16.9
$100–124 000	13.6	21.1
$124–149,000	4.5	5.6
$150,000+	59.1	5.7
Maternal Education (%)		
Highschool	6.7	4.1
Post-Secondary	37.8	6.3
Master's Degree	42.2	21.9
PhD/MD/JD	12.3	13.7
Ethnicity (%)		
Black	2.2	0
East Asian	11.1	1.8
South Asian	2.2	9.2
Hispanic	2.2	6.2
White	71.1	66.2
Bi-racial/Mixed	6.6	7.7

Table 2. Regression results.

	EF: Cognitive Flexibility			EF: Inhibitory Control			Receptive Language		
	B	SE B	*p* value	B	SE B	*p*	B	SE B	*p*
Placental Pathology	−5.171	2.232	.020	−2.683	2.670	.315	−3.812	2.643	.149
Maternal Responsivity	1.370	1.884	.467	6.876	2.282	.003	2.418	2.586	.350
Pathology * Responsivity	5.985	3.141	.057	−6.616	3.594	.066	−2.351	3.802	.536
R^2	0.128			0.095			0.023		
p-value	0.067			0.113			0.437		

EF: inhibitory control

Placental pathology status did not significantly predict inhibitory control ($b = -2.683$ $p = .315$). Maternal responsivity did significantly predict inhibitory control ($b = 6.876$, $p < .05$) showing that at higher levels of maternal responsivity, children showed better

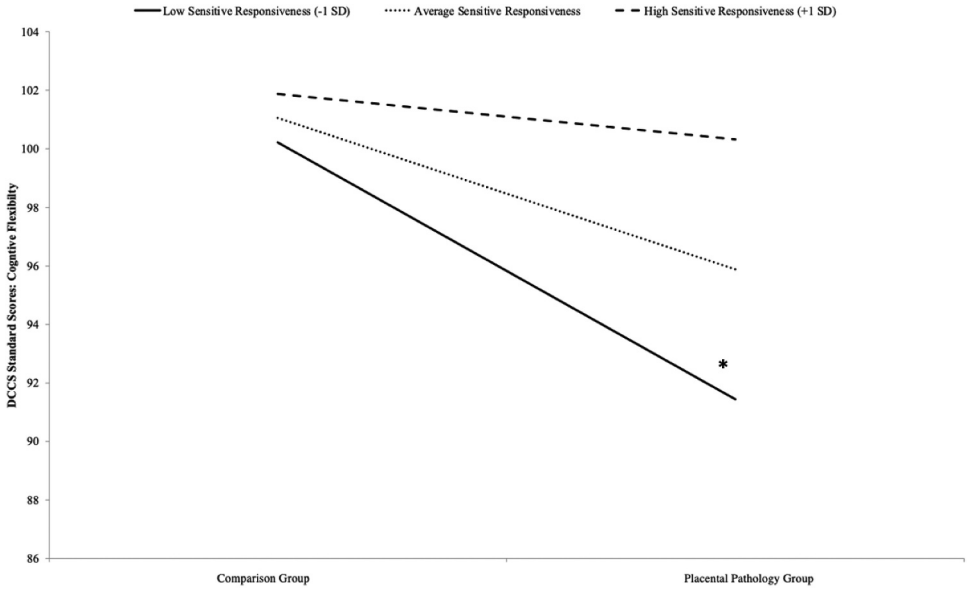

Figure 1. Cognitive flexibility plotted as a function of placental pathology, maternal responsivity, and their interaction. Results of simple slopes analysis to probe interaction of placental pathology and maternal responsivity (±1 SD of the mean). Simple slopes which are significant at $p < .05$ are denoted with an *

inhibitory control. Maternal responsivity marginally moderated the relationship between placental pathology and inhibitory control $b = -6.616$, $p = .066$), but the pattern was opposite to the protective effect hypothesized (stronger effects of maternal responsivity were seen in the comparison group). Testing of simple slopes revealed that the association between placental risk status and inhibitory control was significant at high levels of responsivity but not at low levels of responsivity. For comparison children, higher responsivity predicted higher inhibitory control scores ($b = -7.294$, $p = .049$). For children whose mothers were less responsive, placental risk status was not significantly related to inhibitory control ($b = 1.928$, $p = .599$). Since this pattern was opposite to our prediction, we included a figure of the interaction in the Supplemental section (Figure S3) rather than the main text.

Receptive language

Placenta pathology was not found to predict children's receptive language skills ($b = -3.812$, $p = .149$). In addition, maternal responsivity did not show a significant association with child language and did not moderate the relationship between pathology risk and receptive language outcomes.

Discussion

Summary of study findings

The present study examined the association between placental pathology at birth and the development of EF and language skills in preschool-aged children. The findings revealed

that children with placental pathology demonstrated poorer performance in cognitive flexibility tasks at 3–4 years of age. However, no significant differences were observed between the placental pathology group and comparison children in terms of language skills and inhibitory control.

Although the significance level was borderline, maternal responsivity provided some level of protection in the development of cognitive flexibility for children in the placental pathology group. Specifically, children in the placental pathology group with responsive mothers tended to perform well on cognitive flexibility tasks (similar to children in the comparison group). However, within the placental pathology group, children whose mothers showed low levels of responsivity exhibited poor outcomes in cognitive flexibility. No protective effects were seen for inhibitory control or receptive language.

Placental pathology

The study findings on the role of the placenta in cognitive flexibility are consistent with prior research linking prenatal risk factors to adverse outcomes in EF (Sandoval et al., 2022; Zimmerman, 2018). Moreover, these results align with meta-analytic research that compares children born preterm and/or with low birth weight, which also supports the notion of a stronger influence of prenatal risks on cognitive flexibility compared to inhibitory control (van Houdt et al., 2019). These differential effects may be attributed to the distinct functions of cognitive flexibility and inhibitory control during early childhood (Memisevic & Biscevic, 2018; Miyake et al., 2000) and their activation in specific brain regions. Cognitive flexibility activates a distributed frontoparietal network involving cortical association areas (Kim et al., 2012; Niendam et al., 2012), while inhibitory control tasks elicit activation in the right inferior frontal gyrus and dorsal anterior cingulate cortex (Aron et al., 2014; Hampshire et al., 2010). Consequently, the specific neural networks associated with each executive function may render cognitive flexibility more susceptible to the effects of placental pathology, while inhibitory control may be less affected by these prenatal factors.

Second, cognitive flexibility encompasses a diverse array of cognitive processes, including task switching, mental strategy shifting, and the integration of multiple cognitive functions that allows individuals to adapt their thinking and behavior in response to changing circumstances, facilitating effective problem-solving and decision-making (Diamond, 2013). This integration of various cognitive processes, within cognitive flexibility, may make it more susceptible to the influence of prenatal insults, such as placental pathology, which can disrupt the coordinated functioning of these interconnected processes (O'Connor et al., 2019). In contrast, although inhibitory control represents a higher-order cognitive domain, it has a comparatively narrower focus on cognitive restraint and inhibitory mechanisms, and thus may be less affected than cognitive flexibility due to its relatively simpler cognitive demands.

The absence of a statistically significant relationship between placental pathology and language outcomes in this study should be interpreted cautiously. Participating families came predominantly from educated and economically advantaged backgrounds. Higher SES has been consistently linked to favorable language outcomes, as individuals from such backgrounds have access to resources, quality education, language-rich environments, and increased social interactions (Hackman & Farah, 2009; Hart & Risley, 1995;

Hoff, 2006; Pace et al., 2017). The consequence of low variance in the sample, is the inability to detect true predictor-outcome relationships that may exist. Evidence in children born preterm suggests that the response to early-life brain injuries is modified by the socioeconomic circumstances of children and families (Benavente-Fernández, 2020), and socioeconomically advantaged environments have been found to support better language development compared to pharmacological interventions (Luu et al., 2009). Thus, replication in a more diverse sample is important before concluding that placental function does not influence language development.

Maternal responsivity

The current study suggests the possibility that the postnatal caregiving environment may protect children's neural development even when children have experienced placental pathology. Parents who are sensitive and responsive scaffold children's neurocognitive development by building on the moment-to-moment shifts in children's attention providing a finely tuned enhancement to the child's cognitive experience which provide the optimal relational environment where children can adequately learn and explore with support from their caregiver (Landry & Smith, 2011; Vygotsky, 1978). Neural development is thought to occur through the internalization of finely tuned, reciprocal interactions with responsive caregivers (Kok et al., 2015; Milgrom et al., 2010; Rifkin-Graboi et al., 2015; Romeo et al., 2018). In the current study even when children experienced placental pathology, this did not result in impaired cognitive flexibility, in the presence of maternal responsivity. This beneficial role of maternal responsivity in cognitive flexibility was also seen in a randomized controlled trial of children with prenatal risks whose parents were given responsivity training (Lewis-Morrarty et al., 2012). In the current study, we must interpret this protective effect cautiously as it was only of borderline significance, and it was only seen for one out of three outcomes (i.e., cognitive flexibility).

Results for inhibitory control are more complex to interpret. The main effect for responsivity agrees with the literature (Rodrigues et al., 2021), but the direction of the interaction effect was not expected. The pattern of the interaction showed that the effect of the putative protective factor (maternal responsivity) was stronger in the low-risk group (comparison) than the high-risk group (placental pathology). Two explanations are relevant to consider. First, the main effect of placental pathology, although non-significant, does not imply that it is completely absent or nonexistent. This might suggest that placental function may be playing a weak role in the development of inhibitory control, and that our sample size was too small to detect this. Even though a vulnerability consequent to placental pathology may be weak, it may be enough to suppress, or disallow, a role for maternal responsivity. Second, the similarity of children's scores in the placental pathology group irrespective of levels of maternal responsivity suggests that other factors may be more important in understanding within group heterogeneity. Harshness, poverty, genetic influences, and their interactions have been found to explain variation in inhibitory control (Moilanen et al., 2010). It is clear from the present study that the caregiving environment may have some effect on how placental function influence neurocognitive development. These effects are not strong or consistent, but because interactions between placental pathology risk status and responsivity were present in 2/3 of

the analyses reported, future work needs to attend to the contingencies that may operate between the uterine and postnatal environments. A very large and economically diverse sample that allows for variation on placental pathology, maternal responsivity, and other aspects of postnatal caregiving will be key to identifying the subtle but potentially far-reaching influence of the uterine environment on brain development. Inexpensive measurement tools will be key to this undertaking (Agrawal et al., 2022; Prime et al., 2015). Likewise, the unsupervised learning algorithms of machine learning, that enhance prediction of outcomes through the specification of non-linearity and multiway interactions across variables may also be helpful in identifying children at developmental risk from prenatal risks.

Strengths and limitations

This study has several notable strengths. First, it is the only follow-up study of medically healthy, term-born preschool-age children born with placental pathology. Most studies of placenta and neurodevelopmental outcomes are confounded by biological risks such as pre-term birth, low birth weight, and cerebral palsy. By including a comparison group of full-term infants (non-identified for disease and neurological injury) we were able to isolate placental pathology as a distinct biomarker of risk for an important component of EF, cognitive flexibility. Second, this is the first study to examine maternal responsivity as a potential protective factor between placental risk and neurocognitive outcome. Results from this study highlight the potential importance of responsive parenting in children born with placental pathology.

While this study has several strengths, there are also limitations to consider when interpreting its results. First, the small sample size means that the findings should be considered preliminary and interpreted with caution until replicated with larger and more diverse samples. Both the main effect of placental pathology and its interaction with maternal responsivity may vary across socioeconomic levels. Second, due to budget constraints and limitations in data collection with preschool-aged children, we were unable to examine all potentially relevant aspects of cognitive functioning already known to be linked to prenatal experience such as working memory, episodic memory, and expressive language (du Plooy et al., 2016; Fuemmeler et al., 2023). It is recommended that future research continues to explore the full range of neurocognitive domains that may be impacted by placental pathology. Lastly, we examined inhibitory control, cognitive flexibility, and receptive language using single assessments from the NIH toolbox. However, it's widely acknowledged that young children's performance varies considerably across tasks and within short periods (Deák & Wiseheart, 2015). Various tasks, even those targeting the same fundamental construct, can produce different results due to minor differences in task demands, presentation methods, or response formats. Considering this intrinsic variability and the noticeable floor effects seen in preschoolers' performance (Becker et al., 2023), obtaining a robust understanding of cognitive development might be more effectively done using a range of measurement tools. Employing multiple instruments allows for the extraction of common variance among tasks through a latent variable approach may lead to a more precise and reliable representation of children's capacity.

Clinical implications

Pathological examination of the placenta is an underutilized aspect of perinatal medicine, despite being readily available and moderately cost-effective (Nelissen et al., 2011; Turowski et al., 2018). While placental screening post-birth has been proposed as a viable option (O'Connor et al., 2019), identifying placental biomarkers, either alone or in combination with other known risk factors would significantly enhance the prediction of future neurodevelopmental outcomes. This could result in streamlined early care pathways, improved resource allocation, and interventions to help children achieve their full neurodevelopmental potential.

A primary objective of neonatal interventions is to reduce neonatal morbidity and neurodevelopmental impairment rates. For instance, low-dose indomethacin has been extensively studied in preterm infants and has been associated with a reduction in white matter injury on cerebral magnetic resonance imaging (MRI) in preterm boys, decreased cerebral blood flow, and vascular reactivity, as well as the suppression of mediators of CNS inflammation (Hammerman, 1995; Miller et al., 2006; Volpe, 1994). However, longitudinal studies provide mixed evidence regarding the ability of indomethacin to attenuate long-term sequelae, such as language development, in preterm children (Ment et al., 2006; Miller et al., 2006). It may be beneficial for future studies to explore similar interventions for other prenatal risk factors, such as placental pathology.

In consideration of brain development and critical periods, it is important to examine whether maternal responsivity remains a potential protective factor across contexts (e.g., low SES) and age. Development extends throughout the lifespan with middle and late childhood being a critical period of change, particularly in EF due to the changes associated with the development of neural networks involving the PFC during this stage (Anderson, 2002; Zelazo & Carlson, 2012). However, further research is needed to fully understand the influence of maternal responsivity during these important developmental periods.

Overall, early identification of placental biomarkers, coupled with routine pathological examination, could improve the prediction of future neurodevelopmental outcomes, allowing for early interventions and resource allocation to support healthy brain development in children with placental pathology. While placental pathology was found to be associated with adverse neurodevelopmental outcomes in this study, it accounted for only one out of the three outcomes examined. However, the finding that placental pathology predicts poorer cognitive flexibility in preschoolers is significant, considering its established connection to academic achievement, various psychological disorders (Dickstein et al., 2007; Magalhães et al., 2020; Maramis et al., 2021; Ornstein, 2010), and long-term influences such as resilience and response to stress in adulthood (Genet & Siemer, 2011). Further research, with larger and more diverse samples, is warranted to explore the potential impact of placental pathology on a broader range of developmental outcomes.

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