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Psychological implications of preterm birth

Edited by
Livio Provenzi, Evalotte Mörelius, Mia McLean
and Minesh Khashu

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Psychological implications of preterm birth

Topic editors
Livio Provenzi — University of Pavia, Italy
Evalotte Mörelius — Linköping University, Sweden
Mia McLean — Auckland University of Technology, New Zealand
Minesh Khashu — University Hospitals Dorset NHS Foundation Trust, United Kingdom

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Leonardo De Pascalis,
University of Liverpool, United Kingdom

*CORRESPONDENCE
Livio Provenzi
livio.provenzi@unipv.it

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Editorial: Psychological implications of preterm birth

Livio Provenzi[1,2]*, Minesh Khashu[3], Mia McLean[4] and Evalotte Morelius[5,6,7]

[1]Department of Brain and Behavioral Neuroscience, University of Pavia, Pavia, Italy, [2]Developmental Psychobiology Lab, IRCCS Mondino Foundation, Pavia, Italy, [3]Neonatal Service, University Hospitals Dorset, Poole, United Kingdom, [4]Department of Psychology and Neuroscience, Auckland University of Technology, Auckland, New Zealand, [5]Department of Health, Medicine and Caring Sciences, Linköping University, Linköping, Sweden, [6]School of Nursing and Midwifery, Edith Cowan University, Joondalup, WA, Australia, [7]School of Nursing, University of Jordan, Amman, Jordan

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Editorial on the Research Topic
Psychological implications of preterm birth

Too early. And then?

Preterm birth, which occurs in approximately 10% of births worldwide (Ohuma et al., 2023), has far-reaching implications for the child, parents, and extended family members. While the physical health challenges associated with preterm birth are extensively documented (Camerota et al., 2023; Crump, 2020), the psychological repercussions—both short- and long-term—remain partially underexplored. This gap in knowledge is concerning, as preterm birth not only presents significant physical and mental health burdens but also imposes substantial economic costs on society (Frey and Klebanoff, 2016). Understanding the psychological implications of preterm birth is essential for developing effective interventions and support systems for affected individuals and families.

The experience of preterm birth and the subsequent hospitalization in the Neonatal Intensive Care Unit (NICU) can be extraordinarily distressing for both infants (Cong et al., 2017) and parents (Caporali et al., 2020). In the NICU, the infant is often exposed to an environment filled with overwhelming sensory stimuli, such as bright lights (Aita et al., 2013), loud noises (Casavant et al., 2017), and frequent medical procedures (Carbajal et al., 2008). These stressors, compounded by the painful separation from their parents, may have a profound impact on the infant's socio-emotional and cognitive development (McLean et al., 2022a), partly through epigenetic modifications of genes critical for stress regulation (Provenzi et al., 2015, 2020). Additionally, the psychological strain on parents during this critical period cannot be understated. The uncertainty surrounding their infant's health, coupled with the stress of navigating the NICU environment, can lead to significant mental health challenges for parents, including anxiety, depression, and post-traumatic stress disorder (PTSD) (Axelin et al., 2022; McLean et al., 2022b; Persson et al., 2023).

Moreover, the psychological effects of early interventions, both during and after the NICU stay, are a critical area of concern. Since medical advancements have improved the survival rates of preterm infants, the focus of NICU professionals needs to shift beyond survival, to quality of life and optimizing long term health outcomes through family-centered care programs (Aita and Snider, 2003; Alberts et al., 2024). Yet, the potential long-term psychological consequences of early medical care and hospitalizations are not fully understood. As infants transition from the NICU to home and beyond, the quality of the parent-child relationship emerges as one of the most important protective factors in supporting healthy developmental trajectories (Provenzi et al., 2015; Toole et al., 2024). Research suggests that early parent-infant interactions, from the NICU to the early years of life, play a crucial role in promoting emotional and cognitive resilience in preterm infants (Arwehed et al., 2024; Spence et al., 2023). However, the influence of these interactions on long-term psychological outcomes warrants further investigation.

This Research Topic seeks to address these important gaps in knowledge, bringing together interdisciplinary perspectives on the psychological implications of preterm birth for both infants and parents. We aim to explore the complex interplay between early medical experiences, parental wellbeing, and child development, with a focus on the psychological mechanisms at play. By advancing our understanding in this area, we hope to contribute to the development of targeted interventions that can mitigate the psychological challenges faced by preterm infants and their families, ultimately improving their quality of life and long-term outcomes.

What can you find in this article collection?

The present Research Topic features contribution from interdisciplinary groups coming from many different countries: from New Zealand to Ukraine, from Spain to China, from France to US, from Italy to Germany, from Switzerland to Finland. The contributions can be clustered into three main areas: psychological outcomes of preterm birth and NICU stay in preterm-born individuals and their parents; promoting early interventions for preterm infants and their parents matters; innovative approaches to study the psychological implications of preterm birth.

Psychological outcomes of preterm birth and NICU stay in preterm-born individuals and their parents

Lee et al. assessed executive functioning (EF) in adolescents born very preterm (VPT, <32 weeks) at age 17. The results showed that VPT adolescents performed worse than full-term (FT) peers in areas such as working memory, planning, and cognitive flexibility, with the most significant deficits seen in those born before 28 weeks. The relationship between gestational age and EF was mediated by neonatal medical complexity and white matter abnormalities. These findings emphasize the need for continued cognitive support, especially for those with higher medical and neurological risks.

Another contribution (Pavlyshyn et al.) explored the connection between stress markers in preterm infants during their NICU stay and developmental outcomes at 24–30 months. The study found positive correlations between melatonin levels and communication and problem-solving skills, while cortisol levels were negatively correlated with these abilities. Longer NICU stays and mechanical ventilation were also predictive of developmental delays. This highlights the critical impact of neonatal stress on later development and the importance of addressing medical factors during early life.

In the study by Martinez-Shaw et al., the health-related quality of life (HRQoL) of 8-year-old children born preterm with very low birth weight (VLBW) was examined. The study revealed that VLBW children reported better HRQoL than the general population, with maternal stress and social support acting as key mediators between perinatal factors and child HRQoL. This underscores the importance of considering maternal wellbeing in interventions aimed at improving the quality of life for families with VLBW children.

Jean-Dit-Pannel et al. focused on the emotional and psychological challenges fathers face when navigating the complexities of having a preterm infant in the NICU during the COVID-19 pandemic. COVID-19 restrictions led to separations, affecting fathers' perceived paternal identity. Additionally, concerns about the infant's development and COVID-19 health risks heightened fathers' vulnerability to postpartum depression. This highlights the compounded psychological stress fathers experience during this period, underlining the need for targeted mental health support.

Huang et al. conducted a study on the needs of grandparents of preterm infants in the NICU and how demographic factors influence these needs. The study identified that grandparents primarily sought reassurance regarding the quality of care, followed by information and proximity to the infant. Addressing these needs is crucial for alleviating the emotional burden on families, particularly grandparents, of preterm infants.

Promoting early interventions for preterm infants and their parents matters

Filippa et al. studied the effects of maternal singing and speaking on the general movements (GMs) of preterm infants in the NICU. The intervention group engaged in maternal vocalizations three times per week for 2 weeks, and GMs were assessed at term-equivalent and 3 months corrected age. Results showed significant improvements in GMs for the intervention group. Maternal vocal interaction could enhance neurobehavioral development in preterm infants and should be integrated into NICU care routines.

Ludwig et al. present the results from two randomized controlled trials compared standard care (SC) with SC plus Family Nurture Intervention (FNI) in level-4 NICUs. The FNI program focused on mother-infant interactions to foster autonomic emotional connection. The trials demonstrated significant long-term benefits for infant neurobehavior, development, and the autonomic health of both mother and child. These findings support the integration of FNI into preterm care and provide a new perspective on emotional co-regulation between mother and infant.

Trautmann-Villalba et al. explored the impact of skin-to-skin contact (SSC) on emotional and behavioral outcomes in children born preterm. The study, part of the Deisy Study, assessed 33 children aged 6–8 years and found that parental stress 6 months post-discharge was the main predictor of emotional and behavioral issues. However, SSC immediately after birth did not significantly influence these outcomes. This highlights the importance of addressing parental stress in the care of preterm infants.

In another review of the literature, Leppänen et al. revised psychosocial parent-infant interventions for preterm infants, analyzing 22 studies published from 2000 to 2024. Most interventions focused on counseling and emotional support, and the majority showed positive effects on the parent-child relationship. The findings emphasize the need for more standardized, long-term research to better support families with preterm infants, particularly those at higher risk.

Innovative approaches to study the psychological implications of preterm birth

In the paper by Billeci et al. a study protocol investigating the impact of early video-feedback (VF) intervention on brain-to-brain co-regulation between very preterm (VPT) infants and their mothers is anticipated. The study uses EEG hyperscanning to assess brain synchronization during mother-infant interactions, comparing VPT and full-term (FT) dyads. VPT dyads will receive the VF intervention post-discharge, and outcomes such as mother-infant interaction and maternal mental state will be measured at 3, 6, and 9 months. The study aims to enhance understanding of VF interventions and their impact on infant development and maternal wellbeing.

Sadjadpour et al. compared the performance of logistic regression with machine learning (ML) models in identifying parents at risk for depression after their infant's NICU admission. Data from 300 parents of NICU infants was analyzed using eight ML algorithms to predict depression risk. Results showed that all models, including logistic regression, had high performance in identifying at-risk parents. Logistic regression provided a reliable tool for targeted depression screening in NICU parents.

Conclusion

In summary, this Research Topic highlights the importance of considering both the medical and psychological aspects of preterm birth and not just for the infant but for the whole family and larger society and healthcare policy makers and providers. To improve the quality of life and long-term outcomes for preterm-born children and their families, it is crucial to integrate emotional support with medical care. By advancing our understanding of these complex dynamics, we can develop more effective and comprehensive care strategies for this vulnerable population.

Author contributions

LP: Conceptualization, Writing – original draft, Writing – review & editing. MK: Writing – original draft, Writing – review & editing. MM: Writing – original draft, Writing – review & editing. EM: Writing – original draft, Writing – review & editing.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Livio Provenzi,
University of Pavia, Italy

REVIEWED BY
Flora Koliouli,
Aristotle University of Thessaloniki, Greece
Christine Tuden Neugebauer,
Texas Tech University Health Sciences Center, United States

*CORRESPONDENCE
Halyna Pavlyshyn
✉ halynapavlishin@gmail.com

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The relationship between neonatal stress in preterm infants and developmental outcomes at the corrected age of 24–30 months

Halyna Pavlyshyn*, Iryna Sarapuk and Kateryna Kozak

Department of Pediatrics, I. Horbachevsky Ternopil National Medical University, Ternopil, Ukraine

Aim: The aim of research was to study the relationship between the stress experienced by preterm infants in the neonatal intensive care unit (NICU) and developmental status in the follow up, and to establish factors, associated with their neurodevelopment.

Methods: The first stage of research involved measuring stress markers (cortisol, melatonin) in infants ($n = 56$) during their NICU stay; the second phase assessed the developmental status at the corrected age of 24–30 months.

Results: The total ASQ-3 score, communication, problem solving, and personal-social skills scores at the corrected age of 24–30 months were positively correlated with melatonin level determined in the neonatal period ($r = 0.31$, $p = 0.026$; $r = 0.36$, $p = 0.009$; $r = 0.30$, $p = 0.033$, and $r = 0.32$; $p = 0.022$ respectively). In the same time, ASQ-3 communication and personal-social scores were negatively correlated with cortisol level ($r = -0.31$, $p = 0.043$; $r = -0.35$, $p = 0.022$). The ROC-curve analysis revealed that a decrease of melatonin below 3.44 ng/mL and 3.71 ng/mL during the neonatal period could predict communication and problem-solving delay, respectively. An increase in cortisol above 0.64 mcg/dl is predictive in personal-social delay. Negative correlation was identified between the NICU and total hospital stay duration and ASQ-3 communication scores in the follow-up ($r = -0.27$; $p = 0.049$ and $r = -0.41$; $p = 0.002$, respectively). The duration of mechanical ventilation was negatively correlated with gross motor scores ($r = -0.46$; $p = 0.043$). Apgar score was positively correlated with ASQ-3 communication ($r = 0.29$; $p = 0.032$) and personal-social scores ($r = 0.28$; $p = 0.034$); maternal age—with ASQ-3 total ($r = 0.29$; $p = 0.034$), communication ($r = 0.37$; $p = 0.006$), and personal-social scores ($r = 0.29$; $p = 0.041$). Positive correlations were observed between gestational age and communication scores ($r = 0.28$; $p = 0.033$). Infants who suffered neonatal sepsis had significantly often delay of communication ($p = 0.014$) and gross motor skills ($p = 0.016$). Children who required mechanical ventilation were more likely to have communication delay ($p = 0.034$).

Conclusion: Developmental outcomes in preterm infants at the corrected age of 24–30 months were associated with neonatal stress. Correlations between the communication, problem-solving and personal-social development in the follow up and cortisol and melatonin levels determined in the neonatal period supported this evidence. Factors as low gestational age, duration of hospital and NICU stay, mechanical ventilation, and sepsis were associated with more frequent delays in communication, gross motor and problems-solving skills.

KEYWORDS

developmental status, preterm infants, neonatal NICU-related stress, cortisol, melatonin

Introduction

Survival of extremely preterm infants has increased significantly over the past two decades (Younge et al., 2017) and is 74% in Norway (Stensvold et al., 2017) and 78.3% in the USA (Bell et al., 2022). In Ukraine, the survival of newborns with extremely and very low birth weight in the early neonatal period was 70.2% in 2020 (Znamenska et al., 2022). Despite the increase in the survival rate of very and extremely preterm newborns, the frequency of neonatal morbidity with long-term outcomes and complications associated with premature birth does not decrease (National Guideline Alliance (UK), 2017). The NICE guideline summarizes that infants born prematurely can be at risk of developing a range of motor problems, including cerebral palsy, executive functioning, learning, speech, language, sensorineural hearing loss, blindness, mental retardation, autism spectrum disorders, feeding and eating difficulties (National Guideline Alliance (UK), 2017; Chung et al., 2020; Morgan et al., 2022). Regular follow-up assessment allowed identifying more and more disorders of neuropsychological and social–emotional development in this cohort of children. These disorders include learning disabilities, low average IQ scores, attention deficit hyperactivity disorder, neuropsychological deficits, impairments in visual-motor integration and executive functions, various temperamental difficulties, emotional problems, and regulatory disorders (Hollanders et al., 2019; Jois, 2019). These problems are related to gestational birth age as well as neonatal, biological and maternal factors. Among them are: gender, birth weight, neonatal sepsis, retinopathy of prematurity, bronchopulmonary dysplasia, neonatal surgery, antenatal and postnatal steroids, access to breastmilk in the neonatal/infant period, socioeconomic status, and exposure to neonatal stress and pain (Synnes et al., 2017; Cheong and Preterm Follow Up Guideline Development Group, 2023).

Problem of neonatal pain, discomfort, and stress remains relevant in neonatal intensive care units (NICUs), especially for preterm infants (Kothari et al., 2016). Their first days and sometimes months of life are full of painful and harmful procedures in an overstimulating environment where they are physically separated from their mothers. It is quite difficult to differentiate between stress and pain in the neonatal period (Abdallah and Geha, 2017). Every painful event is believed to be stressful, but not all stress is painful. At the same time stress is an important factor influencing how infants perceive and respond to pain (Jones et al., 2018). Some authors concluded that early and frequent pain perception in the youngest infants was associated with the development of a persistent stress state (Grunau, 2013).

Neonates experience numerous painful manipulations in the intensive care unit, undergoing 10 to 18 painful procedures per day (Cruz et al., 2016; Victoria and Murphy, 2016). At the same time, in 42–100% of cases, infants are exposed to painful manipulations without any form of anesthesia (Cruz et al., 2016). The neurobiological vulnerability to pain in preterm infants is well established due to their lower pain threshold, sensitization to repeated pain, and immature homeostatic systems (Grunau et al., 2009). Uncontrolled and long-lasting pain and pain-related stress can lead to a sensitization phenomenon in extremely and very preterm infants, resulting in persistent dysregulation of stress response systems (Provenzi et al., 2015), and significant short-term and long-term adverse outcomes. The early consequences of painful procedures cause the disturbances of vital parameters (heart rate variability, desaturation, apnea, arterial hypertension, intracranial pressure fluctuations) (Lavanga et al., 2021), which together deplete insufficient energy reserves of a preterm child, increasing the risk of morbidity and mortality (Hatfield, 2014; Walker, 2019).

The experience of pain and stress in the neonatal period forms a somatosensory basis for further perceptual, cognitive and social development. Excessive and prolonged exposure to stress during NICU stay may exceed the infant's natural regulatory capacity, and may permanently alter neuroendocrine, autonomic, cardiovascular, and neuronal functions (Lammertink et al., 2021). The mismatch between the brain development needs of preterm infants and the realities of NICU period treatment causes severe neurophysiological, psycho-emotional, and psychosocial developmental problems, resulting in persistent neurological and psychiatric morbidities throughout life. A range of long-term consequences such as visual impairment/blindness, hearing impairment/deafness, cerebral palsy, developmental delay and intellectual impairment in childhood and adulthood are attributed to painful medical procedures received early in life, during a critical period of neurological development (Valeri et al., 2015; Burnett et al., 2018; Chau et al., 2019). In general, the NICU stay of a preterm infant is a potentially toxic stressor with negative outcomes for brain architecture and neuroendocrine function throughout the life, even in the absence of serious clinical complications (Montirosso et al., 2016).

A long-term response to chronic stress leads to prolonged activation of the hypothalamic-pituitary-adrenal and sympathetic nervous systems, increasing levels of glucocorticoids and catecholamines (Liang and Booker, 2024). Glucocorticoids bind to receptors in the hippocampus, are able to change its structure and function and, at elevated levels, impair neurogenesis, increase vulnerability to strokes, and reduce dendritic branching (Chetty et al., 2014; Finegood et al., 2017). Corticosteroids might decrease the activity of N-acetyl-transferase during stress events, and hence, raised levels of cortisol may negatively influence synthesis of melatonin (Sertaridou et al., 2018). This neuro-hormone protects the developing brain of newborn infants being able to prevent abnormal myelination and inflammatory glial reaction, which are the main causes of white matter damage (Garofoli et al., 2021). The neuroprotective effect of melatonin also manifests due to its antioxidant properties. Melatonin provides not only a direct neuro-protective effect, but also protects the body from excessive stress, especially pain-induced stress with all its negative long-term consequences, showing analgesic properties (Perrone et al., 2023). It is shown that peak melatonin levels occur when cortisol levels are at their lowest (Sertaridou et al., 2018).

The aim of this research

The aim of this research was to study the relationship between the stress experienced by the preterm infants in the NICU and developmental status at the corrected age of 24–30 months. The secondary objective was to establish factors that were associated with developmental delay of those patients.

Methods

Study design

The study design included two stages. At the first stage, the stress markers (cortisol, melatonin) were investigated in preterm infants during their NICU (level III NICU of Ternopil Regional Perinatal Center, Ukraine) stay at the early neonatal period (the first week of life).

At the next stage, development assessment was carried out at the corrected age of 24–30 weeks in the follow-up center of Ternopil Regional Children's hospital by the ASQ-3 questionnaire.

Recruitment and randomization

There were 84 eligible infants during the first study period, with 72 recruited (2 infants did not meet the inclusion criteria, 4 neonates were excluded because of insufficient investigated sample (saliva), and 6—parents declined to participate). Prematurity (GA ≤ 34 weeks) was the criteria for inclusion in this study. Exclusion criteria were the following: chromosomal disorders, congenital malformations.

At the second stage of the study of 72 recruited infants at the neonatal period, developmental assessment was carried out for 58 children according to the follow-up program. Two extremely preterm infants of recruited 72 children died in the late neonatal period, 9 children did not visit the follow up examination due to transfer to other countries (because of the war in Ukraine), 3 mothers refused to pass developmental status screening tests. Two of 58 examined children at the corrected age 24–30 months were diagnosed with cerebral palsy, and thus were excluded from the study.

Thus, infants who withdrew from the study ($n = 16$), or did not survive to the corrected age 24–30 months ($n = 2$), or whose parents refused to participate at the first or second stage of the research ($n = 10$) were not included in the analysis as no outcomes could be obtained. The characteristics of the 56 infants included in the study are presented in the results chapter of the manuscript.

Sample collection and stress markers assay

We examined the level of salivary cortisol as the main stress marker and the level of urinary melatonin that had anti-stress properties. Saliva samples were collected by using the cotton sponges, after that were extracted from the sponges by centrifugation (2 min at 2000 × g). Saliva samples were collected without the usage of any salivation stimulating agents. After extraction samples were frozen and stored at −20°C. Enzyme Immunoassay for the quantitative determination of free cortisol in human saliva was used to analyze cortisol levels in the samples (IBL International GmbH, Hamburg, Germany).

Urine was collected by using the cotton sponges and after that was extracted from the sponges by centrifugation (2 min at 2000 × g). After extraction, urine samples were centrifuged for 20 min at 1000 × g at 2–8°C and after that were frozen and stored at-80° C. Enzyme Immunoassay for the quantitative determination of melatonin sulfate was used to analyze melatonin levels in the urine samples (Elabscience, Wuhan, China). Samples were analyzed in duplicate, and assays were performed using provided controls according to the manufacturer's instructions.

Developmental status assessment. Neurodevelopmental outcomes of children at the corrected age of 24–30 months were assessed by using the ASQ-3 questionnaires (Ages and Stages Questionnaire-3rd Edition). The ASQ is a screening tool that assesses a child's developmental status in five areas of development: communication, gross motor, fine motor, problem solving, and personal-social development, helping to identify impairments in the early stages. Each questionnaire contains 30 questions addressing five specific developmental domains and one general section that focuses on common concerns for parents. Parents completed the questionnaire after they obtained detailed instructions on how to fill in it. Parents observed their child's skills and answer "Yes" (score: 10), "Sometimes" (score: 5) and "Not yet" (score: zero) to six questions in each of the five domains. At the next stage, the summed scores achieved in each developmental area were compared with threshold values for different age groups. Both the sum of points for each area of development and the frequency of delays in each area were evaluated. The total score for each area of development is the sum of all items in the area, ranging from zero to 60, with higher scores indicating better development (Squires et al., 2009). Cronbach's alpha coefficients for the Ukrainian version of the ASQ-3 indicated it good consistency (0.847).

Ethics statement

The local ethical committee of I. Horbachevsky Ternopil National Medical University approved the study. All the participants who took part in the study signed the informed consent.

Statistics

All computations were performed using StatSoft STATISTICA Version 13 (Tulsa, OK) and IBM SPSS Statistics 21. Quantitative data were presented as the median and interquartile range (IQR; 25th to 75th percentiles). For qualitative parameters, absolute and relative frequencies were presented. Age, anthropometric measures, and scores of ASQ-3 questionnaire results were presented as mean (Mean) and standard deviation (SD). The Mann–Whitney U-test (for two independent groups) was used to compare numerical data. Proportions were compared between the two groups using the two-tailed Fisher exact test. Significance was assumed at $p < 0.05$. To assess the influence of the factor on the result, the Odds Ratio, its 95% confidence interval, and the confidence level were calculated. Spearman correlations were used to assess the associations among measures. ROC-curves were analyzed to define biochemical predictors of neurodevelopmental outcomes. Sensitivity and specificity for diagnostic tests were evaluated.

Results

Fifty-six preterm infants with a gestational age of less than 34 weeks participated in the study. There were 26 (46.4%) males and 30 (53.6%) females. The mean gestational age was (30.91 ± 2.47) 31.0 [29.0; 33.0] weeks. There were 10 (17.9%) extremely, 30 (53.6%) very preterm, and 16 (28.5%) moderate preterm infants. The mean birth weight was (1539.4 ± 443.7) g. There were 8 (14.3%) extremely low birth weight infants, 20 (35.7%)—very low birth weight, and 28 (50.0%)—low birth weight. Five newborns were small for gestational age. The main characteristics of infants (pregnancy and delivery history, early neonatal period) are shown in Table 1.

Assessment of the preterm infants' stress in the NICU was carried out by measuring the level of the stress hormone cortisol and the anti-stress hormone melatonin. The level of cortisol in infants was 0.427 [0.251; 1.236] μg/dL. The level of melatonin in infants was 4.42 [2.15; 6.64] ng/mL. It was established that these markers were reliably negatively correlated with each other ($r = -0.40$; $p = 0.013$).

Developmental status assessment of preterm infants at the corrected age of 24–30 months showed that 18 infants (32.1%) had delayed communication development, 4 (7.1%)—delay in the gross motor development, 10 (17, 9%)—delay in the fine motor skills, 15 (26.8%)—delayed problem solving skills, 7 (12.5%)—delayed personal-social development. Fifteen (26.8%) children had delay in one area of development, 9 (16.1%)—in 2 areas, and 6 (10.7%) infants—in 3 or more areas. Results of developmental status assessment of the studied cohort of children according to the ASQ-3 questionnaire scores are presented in the Table 2.

Reliable correlations between the developmental areas scores of preterm infants at the corrected age of 24–30 months and levels of cortisol and melatonin determined in the neonatal period showed the relationship between the stress experienced by a preterm newborn in the NICU and the developmental status in the follow-up period. It was revealed that the total ASQ-3 score, communication, problem solving, and personal-social skills scores at the corrected age of 24–30 months were positively correlated with melatonin level determined in the neonatal period ($r = 0.31$, $p = 0.026$; $r = 0.36$, $p = 0.009$; $r = 0.30$, $p = 0.033$, and $r = 0.32$; $p = 0.022$ respectively), (Figure 1). At the same time, ASQ-3 communication and personal-social scores were negatively correlated with stress hormone cortisol ($r = -0.31$, $p = 0.043$; $r = -0.35$, $p = 0.022$, Figure 2).

The study identified cut-off points for developmental delays in preterm infants at the corrected age of 24–30 months based on neonatal levels of melatonin and cortisol. The ROC-curve analysis confirmed that decrease of the melatonin level below 3.44 ng/mL with sensitivity 0.72 and specificity 0.76 can predict the delay in communication development (AUC = 0.76). Melatonin level below 3.71 ng/mL can predict problem-solving skills delay (AUC = 0.68; sensitivity 0.67 and specificity 0.64, Table 3 and Figure 3). Increase cortisol above 0.64 mcg/dL in the neonatal period can predict the delay in personal-social skills (AUC = 0.82; sensitivity 0.83 and specificity 0.69, Table 4 and Figure 4).

According to the secondary objective of our research, we studied factors that could be associated with developmental delay of preterm infants. Negative correlation was revealed between the duration of the NICU treatment, total duration of hospital stay and ASQ-3 communication scores at the corrected age of 24–30 months ($r = -0.27$; $p = 0.049$ and $r = -0.41$; $p = 0.002$, respectively, Figure 5). The duration of mechanical ventilation was negatively correlated with ASQ-3 gross motor scores ($r = -0.46$; $p = 0.043$, Figure 6). Apgar scores were positively correlated with ASQ-3 communication ($r = 0.29$; $p = 0.032$) and personal-social development scores ($r = 0.28$; $p = 0.034$, Figure 7). It was found the positive correlation between maternal age and ASQ-3 total ($r = 0.29$; $p = 0.034$), communication ($r = 0.37$; $p = 0.006$), and personal-social development scores of the child ($r = 0.29$; $p = 0.041$).

ASQ-3 communication scores of preterm infants were positively correlated with their gestational age ($r = 0.28$; $p = 0.033$). Extremely and very preterm infants significantly more often had delay in the area of communication (66.7% vs. 14.3%, $p = 0.043$; OR = 4.67; 95% CI 0.93–23.37; $p = 0.061$) and problem-solving development (60.0% vs. 0%, $p = 0.003$; OR = 20.06; 95% CI 1.12–358.58; $p = 0.041$) compared to moderately preterm infants.

It was shown that infants who suffered sepsis in the neonatal period had significantly more often delay in the communication development (52.4% vs. 20.0%, $p = 0.014$; OR = 4.40; 95% CI 1.34–14.38; $p = 0.015$), gross motor skills (23.5% vs. 0%, $p = 0.016$; OR = 18.25; 95% CI 0.93–358.49; $p = 0.056$) compared to those who did not have neonatal sepsis. The infants who were diagnosed with RDS in early neonatal period had significantly more often delayed fine motor skills (25.0% vs. 0%, $p = 0.024$; OR = 11.36; 95% CI 0.63–206.39;

TABLE 1 Characteristics of preterm infants in the neonatal period.

Parameter	Statistical indicators	Study group
		$n = 56$
Maternal factors during pregnancy		
Maternal age	Mean ± SD	29.3 ± 4.4
Gravida		
1	[n (%)]	27 (48.2%)
≥2	[n (%)]	29 (51.8%)
Preeclampsia, eclampsia, gestational hypertension	[n (%)]	17 (30.4%)
Thyroid gland disorders	[n (%)]	6 (10.7%)
Acute respiratory viral infection	[n (%)]	9 (16.1%)
Polyhydramnios	[n (%)]	10 (17.9%)
Urinary tract infections	[n (%)]	14 (25.0%)
Multiple pregnancies	[n (%)]	17 (39.4%)
Maternal bleeding	[n (%)]	7 (12.5%)
Mode of delivery		
C-section	[n (%)]	44 (78.6%)
Characteristics of infants in the early neonatal period neonatal period		
Apgar score at the 1st min	Me [Lq; Uq]	6.0 [6.0; 7.0]
Apgar score at the 5th min	Me [Lq; Uq]	7.0 [7.0; 7.0]
Apgar score at the 1st min < 7 points	[n (%)]	29 (51.8%)
Apgar score at the 5th min < 7 points	[n (%)]	9 (16.1%)
Primary resuscitation	[n (%)]	31 (55.4%)
Surfactant replacement therapy	[n (%)]	20 (35.7%)
Respiratory distress syndrome (RDS)	[n (%)]	40 (71.4%)
Early-onset infection	[n (%)]	13 (23.2%)
Intraventricular hemorrhage	[n (%)]	19 (26.8%)
Mechanical ventilation	[n (%)]	20 (35.7%)
Continuous positive airway pressure	[n (%)]	46 (82.1%)
Late-onset sepsis	[n (%)]	14 (25.0%)
Necrotizing enterocolitis	[n (%)]	7 (12.5%)
Broncho-pulmonary dysplasia (BPD)	[n (%)]	7 (12.5%)
Retinopathy of prematurity ≥ III grade	[n (%)]	5 (8.9%)
Neonatal seizures	[n (%)]	13 (23.2%)
Duration of NICU treatment, days	Me [Lq; Uq]	9.0 [6.0; 15.0]
Duration of total hospital stay, days	Me [Lq; Uq]	31.5 [25.0; 41.0]
Duration of mechanical ventilation, days	Me [Lq; Uq]	8.5 [5.5; 19.5]

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$p = 0.101$) compared to those who did not have RDS. Children who required mechanical ventilation in the neonatal period were significantly more likely to have delayed communication skills at the corrected age of 24–30 months (37.5% vs. 0%, $p = 0.034$; OR = 3.50; 95% CI 1.08–11.36; $p = 0.037$). The frequency of delay in each area of development in preterm infants depending on neonatal factors and morbidity are presented in Table 5.

We found neonatal factors (Apgar score and mechanical ventilation) that were associated both with the developmental status outcomes in the follow-up period and stress hormones in the neonatal period. Apgar score at the 1st and 5th minutes negatively correlated with cortisol level ($r = -0.41$; $p = 0.007$ and $r = -0.48$; $p = 0.001$ respectively). Cortisol was higher in children who had an Apgar score below 7 at the 1st minute (0.619 [0.353; 2.004] µg/dL vs. 0.344 [0.161; 0.738] µg/dL, $p = 0.057$) and at the 5th minute (1.521 [0.637; 2.872] µg/dL vs. 0.371 [0.195; 0.809] µg/dL, $p = 0.012$). In the same time, Apgar score at the 1st and 5th minutes positively correlated with melatonin level ($r = 0.33$; $p = 0.017$ and $r = 0.36$; $p = 0.009$ respectively). Melatonin was lower in children with Apgar scores below 7 at the 1st minute (5.34 [3.60; 7.46] vs. 2.49 [1.75; 6.08] ng/mL, $p = 0.029$) and at the 5th minute (4.73 [2.44; 6.84] vs. 2.48 [1.69; 3.68] ng/mL, $p = 0.077$). The duration of mechanical ventilation positively correlated with cortisol level ($r = 0.76$; $p = 0.002$) and a negatively—with melatonin level ($r = -0.51$; $p = 0.027$) in preterm newborns in the neonatal period.

TABLE 2 Indicators of the developmental status of preterm infants at the corrected age of 24–30 months according to the results of the ASQ-3 questionnaire.

Developmental area	Mean ± SD
Communication score	43.84 ± 18.49
Gross motor score	56.34 ± 6.14
Fine motor score	51.25 ± 8.75
Problem solving score	43.12 ± 12.23
Personal-social score	48.48 ± 10.44
Total ASQ-3 score	243.03 ± 37.69

Discussion

Currently, the connection between neonatal stress, its physiological mechanisms and its association with clinical, laboratory and instrumental signs of health and development of preterm infants is being actively studied (van Dokkum et al., 2021). This is due to concerns that early exposure to stress may have a negative impact on neurocognitive development (Finegood et al., 2017), and better understanding of these problems can contribute to the improvement of newborn care (van Dokkum et al., 2021).

Although there are strong arguments for the association of neonatal stress with the nervous system development (Walker, 2019;

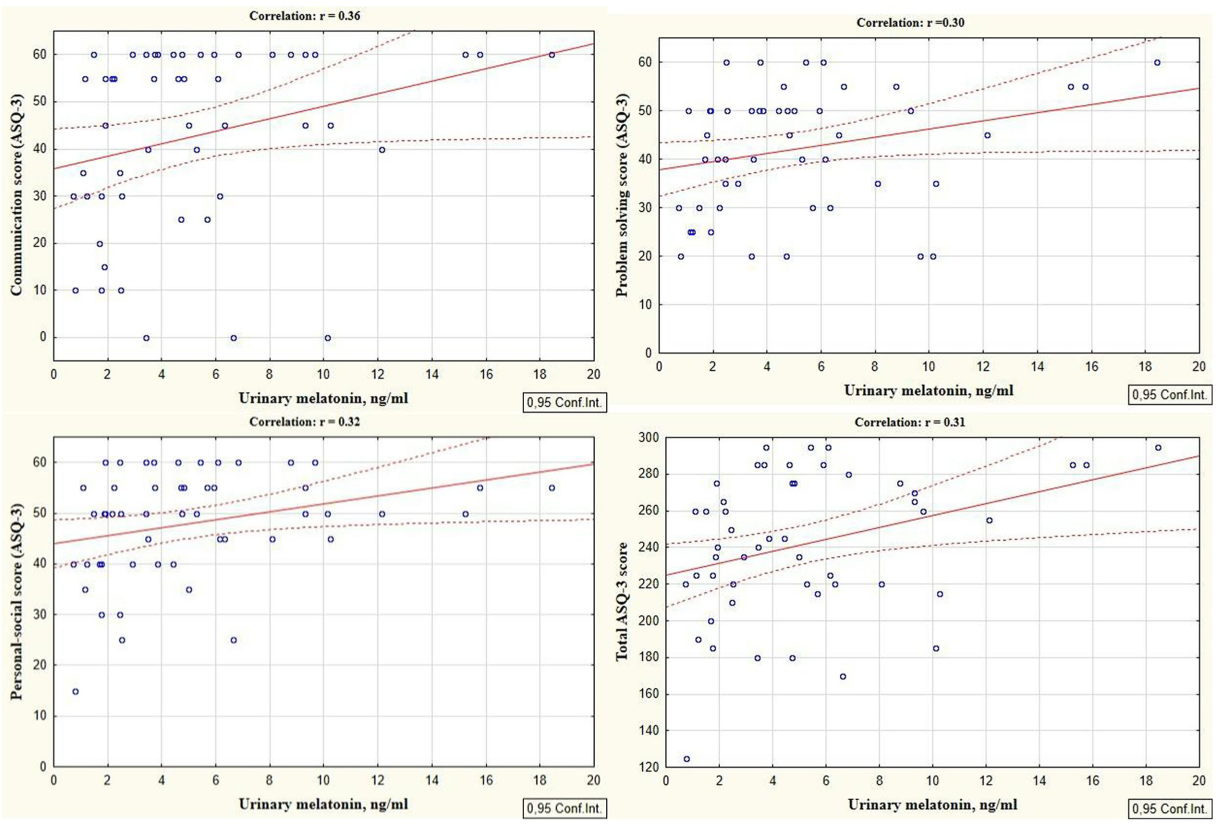

FIGURE 1
Correlations between ASQ-3 communication, problem solving, personal-social, and total scores of preterm infants at the corrected age of 24–30 months and melatonin level determined in the neonatal period.

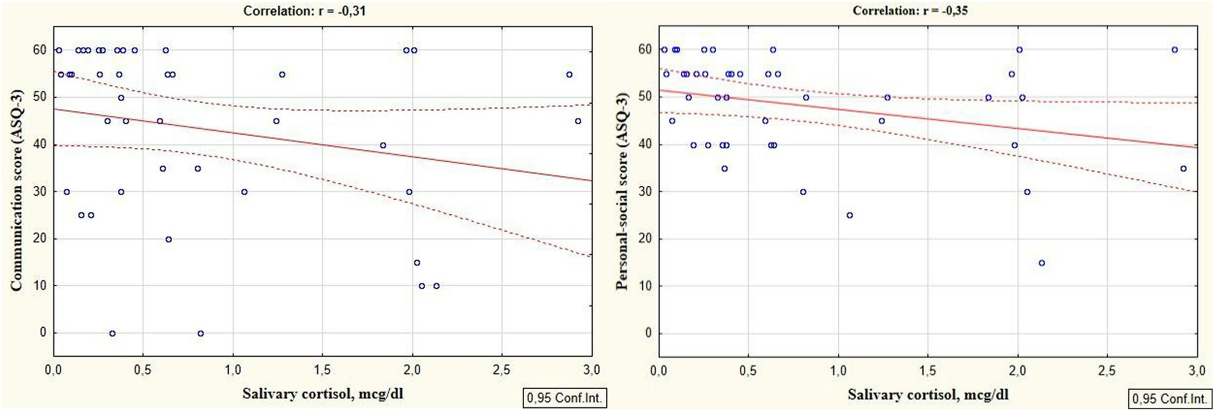

FIGURE 2
Correlations between ASQ-3 communication and personal-social scores of preterm infants at the corrected age of 24–30 months and cortisol level determined in the neonatal period.

TABLE 3 Melatonin level and developmental status outcomes in preterm infants at the corrected age of 24–30 months.

Groups	Communication delay	Gross motor skills delay	Fine motor skills delay	Problem solving skills delay	Personal-social development delay
AUC	0.76	0.72	0.52	0.68	0.71
95% CI AUC	0.61–0.99	0.46–0.97	0.33–0.72	0.51–0.85	0.50–0.91
p	0.003*	0.215	0.834	0.041*	0.082
Cut-off point	3.44	2.71	3.41	3.71	3.44
Sensitivity	0.72	0.67	0.44	0.67	0.71
Specificity	0.76	0.67	0.62	0.64	0.64

*statistically significant result.

Lavanga et al., 2021; van Dokkum et al., 2021), our research is the first known study that showed the association of laboratory confirmed NICU-related stress with developmental status outcomes in preterm infants at the follow-up period. In addition, we identified the factors associated with developmental status delays in the study group.

Our research showed that delay in the area of communication (32.1%) and problem solving skills (26.8%) were present most often in preterm infants at the corrected age of 24–30 months. They were followed by delayed fine motor (17.9%), personal-social (12.5%), and gross motor skills development (7.1%), which is consistent with numerous studies that indicate a language and cognitive development disorders in prematurely born children (Do et al., 2019; Wolke et al., 2019; You et al., 2019). Delay in one area of development occurred in 26.8% of children of the study group, in two areas of development—in 16.1%, and in 3 or more areas—in 10.7%. Our data are consistent with the results of the Mansson et al. research who found that 20% of preterm infants at the corrected age of 2.5 years had delay in only one area of development (cognition, expressive or impressive language, fine or gross motor skills) according to the Bayley-III scale assessment. Fourteen percent of children had developmental delay in two areas, 13 and 12.5%—in three and five areas, respectively (Mansson and Stjernqvist, 2014).

Our study showed the significant correlations between the ASQ-3 scores of developmental status of preterm infants at the corrected age of 24–30 months and the cortisol and melatonin levels measured during the neonatal period. It indicates that developmental delays in premature children were associated with the experienced stress in the NICU, characterized by elevated stress hormones and reduced anti-stress hormones. Thus, it was proven that ASQ-3 communication and personal-social scores were negatively correlated with the cortisol level ($r = -0.31$; $p = 0.043$ and $r = -0.35$; $p = 0.022$ respectively). At the same time, the total ASQ-3 score, communication, problem solving, and personal-social skills scores were positively correlated with melatonin level ($r = 0.31$, $p = 0.026$; $r = 0.36$, $p = 0.009$; $r = 0.30$, $p = 0.033$, and $r = 0.32$; $p = 0.022$ respectively).

Our study also identified cut-off points for developmental delays in preterm infants at the corrected age of 24–30 months based on the levels of melatonin and cortisol. The ROC-curve analysis confirmed that these values are associated with communication (urinary melatonin level <3.44 ng/mL), problem solving (urinary melatonin level <3.71 ng/mL), and personal-social development delays (salivary cortisol >0.64 mcg/dL). Our results indicate the need for both clinical and laboratory monitoring of stress and pain indicators in the NICU, which are very difficult to distinguish in the neonatal period, and their adequate management can prevent neurodevelopmental delays in preterm children.

Our findings align with Grunau et al. research, which revealed a relationship between a greater number of skin-breaking procedures during the neonatal period and reduced cognitive and motor scores as assessed by the Bayley scale at the age of 8 and 18 months (Grunau et al., 2009). Other authors also revealed by the association of neonatal

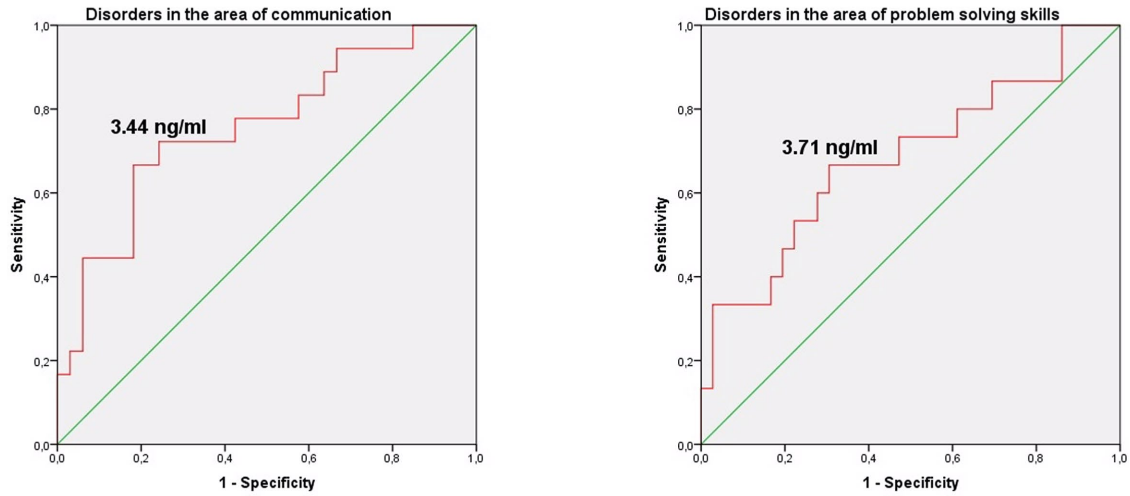

FIGURE 3
Melatonin level in the prediction of disorders in the area of communication and problem solving skills in preterm infants at the corrected age of 24–30 months.

TABLE 4 Cortisol level and developmental status disorders in preterm infants at the corrected age of 24–30 months.

Groups	Communication delay	Gross motor skills delay	Fine motor skills delay	Problem solving skills delay	Personal-social development delay
AUC	0.62	0.36	0.56	0.56	0.82
95% CI AUC	0.44–0.80	0.01–0.84	0.34–0.78	0.39–0.74	0.65–0.99
p	0.215	0.420	0.597	0.531	0.013*
Cut-off point	0.52	2.04	1.55	0.63	0.64
Sensitivity	0.64	0.33	0.38	0.46	0.83
Specificity	0.61	0.92	0.82	0.62	0.69

*statistically significant result.

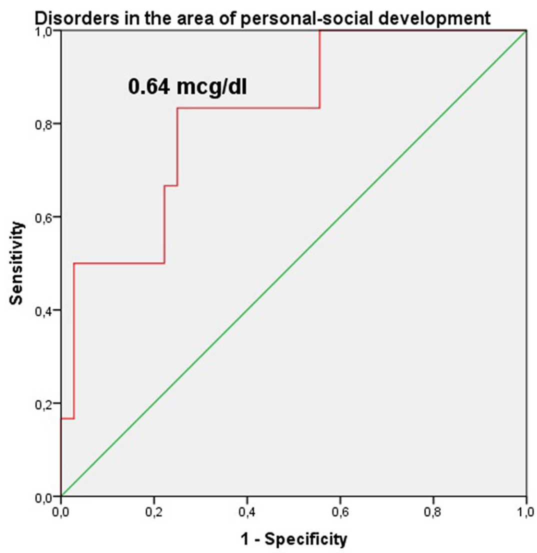

FIGURE 4
Cortisol level in the prediction of disorders in the area of personal-social development in preterm infants at the corrected age of 24–30 months.

stress with the emotional, behavioral, and attention deficit disorders in early childhood (18–36 months) (Montirosso et al., 2016; Gaspardo et al., 2018), and at school age (7 to 11 years) (Chau et al., 2019). Valeri et al. showed that early-life stress experienced during critical periods of nervous system development in preterm infants affects brain development by altering its structure, as well as the infant's behavior, motor skills, and reactivity to stress (Valeri et al., 2015).

Smith et al. revealed that increased exposure to stressors in the NICU was associated with a decrease of brain size in the frontal and parietal regions and altered brain microstructure and functional connectivity in the temporal lobes, which was clinically manifested by the neurobehavioral changes of preterm neonates at the postconceptual age of 40 weeks (Smith et al., 2011). These changes in the structure of the frontal lobe are important for social, concentration and executive development and information processing. Functions related to emotion and attention have been described to originate in the frontal lobe, cerebellum, and cortical areas of the brain that have been reported to be affected by neonatal stress (van Dokkum et al., 2021).

The impact of neonatal stress on the developmental status can be explained through the direct influence of stress hormones, particularly cortisol, on the nervous system formation and maturation in the preterm infants. Premature children in NICU are exposed to the stress, which is accompanied by an increase in cortisol during a

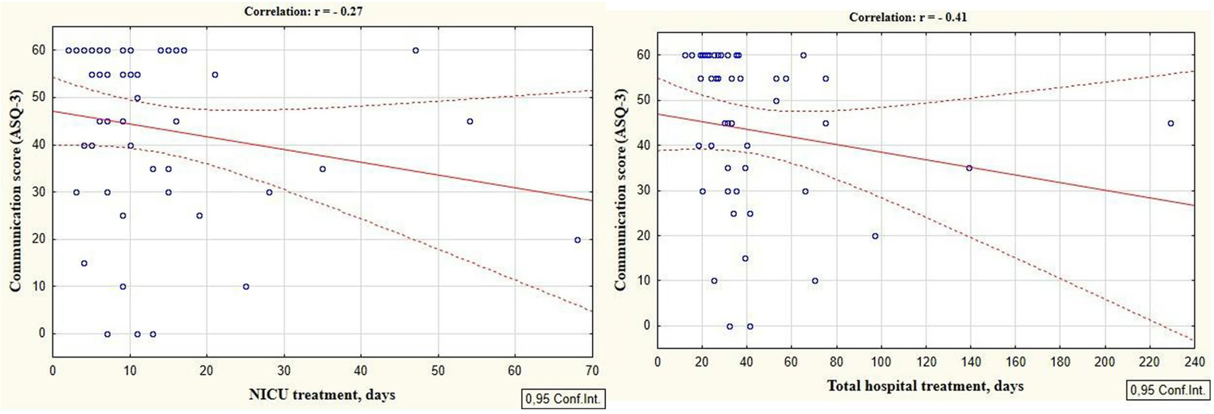

FIGURE 5
Correlations between ASQ-3 communication scores of preterm infants at the corrected age of 24–30 months and the duration of hospital treatment in the neonatal period (NICU and total hospital stay).

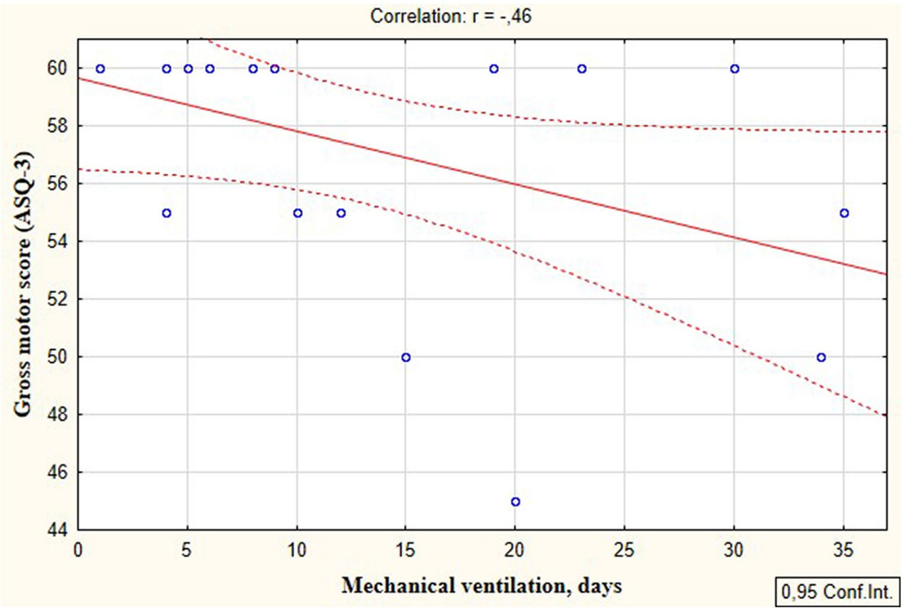

FIGURE 6
Correlations between ASQ-3 gross motor development scores of preterm infants at the corrected age of 24–30 months and the duration of mechanical ventilation in the neonatal period.

critical period of brain development when synaptic connections are being formed and cortical networks are being established (van Dokkum et al., 2021; Pavlyshyn and Sarapuk, 2023). At the same time, positive correlations of the ASQ-3 total scores, communication, problem solving, personal-social development scores of the children with melatonin level confirm its neuroprotective properties (Garofoli et al., 2021; Perrone et al., 2023).

The secondary objectives of our research aimed to identify the factors that were additionally associated with developmental status outcomes in the study group. Our study showed an association between the developmental status of preterm children at the corrected age of 24–30 months and their gestational age. Extremely and very preterm neonates were significantly more likely to have delayed communication and problem-solving skills development compared to moderately preterm children. Other authors also indicate that children born extremely premature have the highest risk of adverse developmental outcomes, with the risk of developmental adversities decreasing with each additional week of gestation through to full-term period (Poulsen et al., 2013; Hanly et al., 2018; Dhamrait et al., 2021). Recent literature data describes that preterm birth is associated with poor outcomes in infants (especially extremely and very preterm, and those who weigh <1,500 g) in various developmental domains, including motor, cognitive, behavioral, and sensory (de Jong et al., 2015; Ionio et al., 2016). There is a dose-dependent relationship between gestational age and poorer school readiness (Dhamrait et al., 2021). Such associations between the gestational age and the developmental status of preterm infants can be explained by the

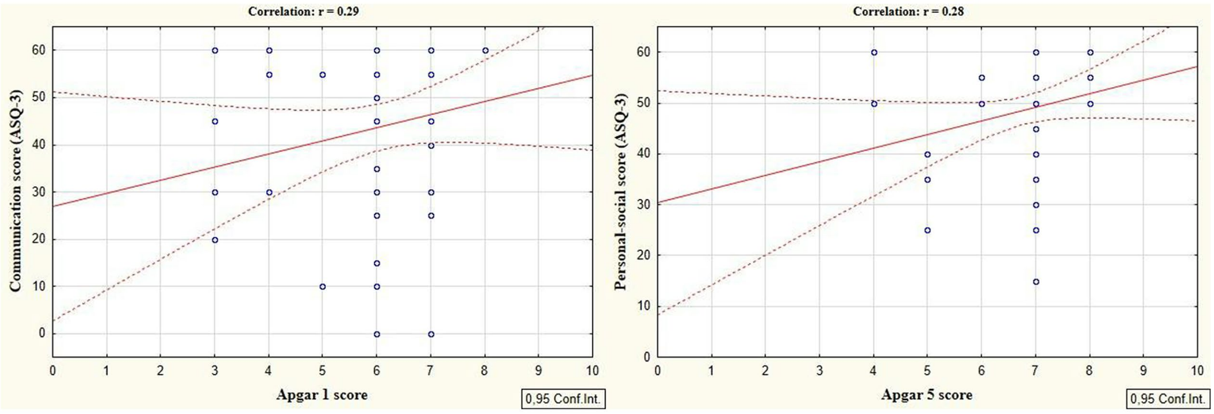

FIGURE 7
Correlations between ASQ-3 communication and personal-social scores of preterm infants at the corrected age of 24–30 months and the Apgar scores.

immaturity of the brain in extremely and very premature newborns in combination with the stress experienced in the neonatal period. Preterm birth can affect the process of proliferation, differentiation, migration, and cerebral, cerebellar growth, leading to structural and functional neurodevelopmental disorders (Wallois et al., 2020). At the same time, extremely and very preterm infants are exposed to a greater number of repeated painful treatment and care procedures during a period of rapid brain development and programming and formation of stress systems (D'Agata et al., 2017), and have been shown to experience more pronounced stress in the NICU (van Dokkum et al., 2021).

Our findings also revealed that infants with lower Apgar scores exhibited lower ASQ-3 communication and personal-social development scores at the corrected age of 24–30 months, as evidenced by negative correlations. Additionally, these infants displayed significantly higher levels of cortisol and lower levels of melatonin in the NICU. These data suggest that children with low Apgar scores experience greater stress in the neonatal period, which negatively affects their development. Premature infants with low Apgar scores undergo resuscitation in the delivery room and intensive neonatal care during the first hours of life (D'Agata et al., 2017; Pados, 2019), which can serve as an additional trigger for an excessive long-lasting stress response. It was shown that the rate of mortality, morbidity, and therefore the frequency of neonatal interventions and complications is significantly higher in preterm infants with low Apgar scores (American Academy of Pediatrics, 2015).

Our study revealed an association between the mechanical ventilation in the neonatal period and further development of infants. In particular, children who required mechanical ventilation had significantly more delayed communication, as well as a negative correlation was established between the duration of mechanical ventilation and ASQ-3 gross motor development scores. At the same time, neonatal stress markers were also associated with the duration of mechanical ventilation. The positive correlation of cortisol and negative correlation of melatonin with the duration of mechanical ventilation confirms that this intervention is stressful for preterm infants.

These findings align with those from another study, where the authors reported that invasive ventilation represented a stressful experience for newborns and leads to changes in neuroendocrine system, pain indicators and physiological responses (Bellù et al., 2021). Assisted lung ventilation in newborns is believed to lead to long-lasting persistent pain, which is associated with adverse long-term outcomes (Bellù et al., 2021). This association is confirmed by the results of delayed developmental status of preterm infants in our study. Voss et al. also showed that mechanical ventilation for more than 2 weeks significantly increased the risk of developmental disorders in extremely premature neonates (Voss et al., 2016).

Our study also revealed that longer durations NICU stay and total hospitalization dare associated with the lower ASQ-3 communication scores at the corrected age of 24–30 months, confirming the significant consequences of long-term NICU-related stress for the development and functioning of the preterm infants' brain (Aita et al., 2017).

Delayed communication and gross motor skills development occurred more often in children who experienced sepsis during the neonatal period compared to those who did not have this condition. Our results are consistent with the data of a meta-analysis by Cai, which indicated that very preterm infants with neonatal sepsis are at the higher risk of cerebral palsy and neurosensory deficits (Cai et al., 2019). Studies show that the developing brain is vulnerable to a systemic inflammatory response including cytokine and free radical activation, as well as to ischemic damage from hypotension and reduced cerebral blood flow. These factors together lead to white matter damage and diffuse lesions of premyelinated oligodendrocytes, which, as was shown to be closely associated with an increased risk of impaired cognitive and motor functions (Hemels et al., 2012; Hentges et al., 2014; Cai et al., 2019).

Maternal age emerged as the factor associated with the developmental status of preterm infants. It was established that an older maternal age was associated with the higher total ASQ-3 scores, as well as improved ASQ-3 communication, and personal-social development scores. The link between maternal age and neonatal outcomes, however, remains controversial in the literature. Tseng et al. reported that maternal age was not associated with major morbidity and long-term neurodevelopmental impairment among very low birth weight infants. The exception was an observed association between older maternal age and delay in language skills, a finding the authors noted requires further investigation (Tseng et al., 2019). In contrast, other recent population-based cohort studies have shown that older maternal age may be beneficial for early child development (Barclay and Myrskylä, 2016; Kato et al., 2017). Today's older mothers often have a higher socioeconomic status, which is frequently linked with higher education, higher family income, and

TABLE 5 Developmental status outcomes in preterm infants at the corrected age of 24–30 months depending on neonatal factors and neonatal morbidities.

Neonatal factors and neonatal morbidities	Communication delay	Gross motor skills delay	Fine motor skills delay	Problem solving skills delay	Personal-social development delay
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Gestation age					
<32 weeks (*n* = 40)	16 (40.0%)	3 (7.5%)	8 (20.0%)	15 (37.5%)	7 (17.5%)
33–34 weeks (*n* = 16)	2 (12.5%)	1 (6.25%)	2 (12.5%)	0	0
p	0.043*	0.679	0.406	0.003*	0.08
Gender					
Male (*n* = 26)	8 (30.8%)	2 (37.8%)	4 (15.4%)	8 (30.8%)	5 (19.2%)
Female (*n* = 30)	10 (33.3%)	2 (6.7%)	6 (20.0%)	7 (23.3%)	2 (6.7%)
p	0.533	0.638	0.463	0.372	0.156
Singleton (*n* = 39)	13 (33.3%)	3 (7.8%)	5 (12.8%)	11 (28.2%)	5 (12.8%)
Twins (*n* = 17)	5 (29.4%)	1 (5.9%)	5 (29.4%)	4 (23.5%)	2 (11.8%)
p	0.515	0.647	0.134	0.494	0.643
Mode of delivery					
Vaginal (*n* = 12)	5 (41.7%)	2 (16.7%)	2 (16.7%)	3 (25.0%)	1 (8.3%)
Cesarean section (*n* = 44)	13 (29.5%)	2 (4.5%)	8 (18.2%)	12 (27.3%)	6 (13.6%)
p	0.321	0.198	0.637	0.595	0.531
Apgar score 5 min					
<7 points	5 (55.6%)	1 (11.1%)	1 (11.1%)	2 (22.2%)	2 (22.2%)
≥7 points	13 (27.7%)	3 (6.4%)	9 (19.1%)	13 (27.7%)	5 (10.6%)
p	0.107	0.514	0.49	0.547	0.312
Mechanical ventilation					
Yes (*n* = 20)	10 (50.0%)	1 (5.0%)	2 (10.0%)	6 (30.0%)	3 (15.0%)
No (*n* = 36)	8 (22.2%)	3 (8.3%)	8 (22.2%)	9 (25.0%)	4 (11.1%)
p	0.034*	0.549	0.222	0.459	0.487
Neonatal sepsis					
Yes (*n* = 21)	11 (52.4%)	4 (19.0%)	5 (23.8%)	7 (33.3%)	5 (23.8%)
No (*n* = 35)	7 (20.0%)	0	5 (14.3%)	8 (22.9%)	2 (5.7%)
p	0.014*	0.016*	0.29	0.29	0.061
RDS					
Yes (*n* = 40)	14 (35.0%)	3 (7.5%)	10 (25.0%)	11 (27.5%)	7 (17.5%)
No (*n* = 16)	4 (25.0%)	1 (6.3%)	0	4 (25.0%)	0
p	0.349	0.679	0.024*	0.566	0.08
BPD					
Yes (*n* = 7)	4 (57.1%)	1 (14.3%)	1 (14.3%)	2 (28.6%)	2 (28.6%)
No (*n* = 49)	14 (28.6%)	3 (6.1%)	9 (18.4%)	13 (26.5%)	5 (10.2%)
p	0.141	0.423	0.635	0.612	0.163
Intraventricular hemorrhage					
Yes (*n* = 19)	8 (42.1%)	3 (15.8%)	2 (10.5%)	2 (10.5%)	2 (10.5%)
No (*n* = 37)	10 (27.0%)	1 (2.7%)	8 (21.6%)	13 (35.1%)	5 (13.5%)
p	0.199	0.108	0.261	0.045*	0.556
Neonatal seizures					
Yes (*n* = 13)	7 (53.8%)	1 (7.7%)	2 (15.4%)	5 (38.5%)	2 (15.4%)
No (*n* = 43)	11 (25.6%)	3 (7.0%)	8 (18.6%)	10 (23.3%)	5 (11.6%)
p	0.06	0.664	0.222	0.23	0.519

*statistically significant result.

private health insurance. These factors together create a more optimal environment and contribute to more favorable developmental outcomes for children (Carolan and Frankowska, 2011).

Practical implications

The health care providers to prevent developmental delays in preterm children should systematically monitor the exposure of preterm infants to stress in the NICU. Minimizing the impact of NICU-related stress on newborns is extremely important. Implementing such developmental care practices as pain management, creation of a healing NICU environment, and family-integrated approach to care can significantly reduce the impact of neonatal stress and therefore improve developmental status in the follow-up period (van Dokkum et al., 2021). Developmental care includes a variety of early intervention strategies that help protect the infant from adverse environmental factors, create a neonatal environment that minimizes stress for the infant, reduces pain, and provides sensory experiences appropriate to the infant's development (Pierrat et al., 2016). Parental participation in care is one of the most important components of developmental care, which improves the neurological and behavioral development of a child up to 24 months of corrected age (Vanderveen et al., 2009). Neuro-developmental care approaches also help to improve the processes of myelination, neurobehavioral and neurophysiological functioning of the child, promoting cognitive, motor and language development in the follow up period (Soleimani et al., 2020). Montirosso suggest that high quality developmental care in newborns may mitigate behavioral problems in preterm infants at 18 months of age potentially leading to a behavioral profile that is similar to that of full-term peers (Montirosso et al., 2016).

Kangaroo mother care with skin-to-skin contacts is also an important strategy for the care of preterm infants, which minimizes stress and improves the developmental status outcomes. It was found in our previous study that regular and repeated skin-to-skin contacts can lead to a stress-buffering anxiolytic effect for preterm infants in the NICU (Pavlyshyn et al., 2022), while deprivation of pleasant maternal touch in newborns can lead to toxic stress, which is associated with a number of developmental disorders in infants (Bergman, 2019). Skin-to-skin contact helps improve the neurological development of children, their motor, cognitive and behavioral functions, and sleep organization in the follow-up period (Feldman et al., 2014).

Strengths and limitations

This is the first known study to show the association between the laboratory confirmed NICU-related stress and developmental status disorders in preterm infants during the follow-up period. However, the study has some limitations. Firstly, it was conducted as a single-center descriptive study and was constrained by a small sample size, since not all children who underwent laboratory stress tests in the neonatal period had reached the correct age of 24–30 months at the time of follow-up assessment. With this reason, this study was with single time point for developmental follow-up. Secondly, we did not analyze the cumulative NICU-related stress. There are numerous factors influencing the developmental trajectories of preterm infants, and these factors were considered and analyzed in our study. In addition, there was a lack of control for stress-buffering factors.

Conclusion

Neonatal stress was associated with long-term developmental disorders in preterm infants at the corrected age of 24–30 months. This association was highlighted by correlations between the neonatal cortisol and melatonin levels with communication, problem-solving skills and personal-social development at the follow up. Levels of melatonin below and cortisol above the certain cut-off values in the neonatal period may serve as one of the predictors of developmental status disorders in preterm neonates. Additionally, factors such as low gestational age, long duration of hospital stay, in particular in the NICU, mechanical ventilation, neonatal sepsis were associated with more frequent developmental delays in the areas of communication, gross motor, and problems solving skills.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by The Local ethical committee of the I. Horbachevsky Ternopil National Medical University (protocol no 74 issued 28.09.2023). The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

HP: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. IS: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Writing – original draft, Writing – review & editing. KK: Writing – original draft, Writing – review & editing, Conceptualization, Formal analysis, Investigation, Methodology, Software.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Suresh Munuswamy,
Public Health Foundation of India, India
Enamul Kabir,
University of Southern Queensland, Australia

*CORRESPONDENCE
Fatima Sadjadpour
fsadjadpour@vt.edu

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Comparative analysis of machine learning versus traditional method for early detection of parental depression symptoms in the NICU

Fatima Sadjadpour[1]*, Niyousha Hosseinichimeh[1], Vida Abedi[2] and Lamia M. Soghier[3,4,5]

[1]Department of Industrial and Systems Engineering, Virginia Polytechnic Institute and State University, Blacksburg, VA, United States, [2]Department of Public Health Sciences, Penn State University, College of Medicine, Hershey, PA, United States, [3]Department of Neonatology, Children's National Hospital, Washington, DC, United States, [4]The George Washington University School of Medicine and Health Sciences, Washington, DC, United States, [5]Children's Research Institute, Children's National Hospital, Washington, DC, United States

Introduction: Neonatal intensive care unit (NICU) admission is a stressful experience for parents. NICU parents are twice at risk of depression symptoms compared to the general birthing population. Parental mental health problems have harmful long-term effects on both parents and infants. Timely screening and treatment can reduce these negative consequences.

Objective: Our objective is to compare the performance of the traditional logistic regression with other machine learning (ML) models in identifying parents who are more likely to have depression symptoms to prioritize screening of at-risk parents. We used data obtained from parents of infants discharged from the NICU at Children's National Hospital ($n = 300$) from 2016 to 2017. This dataset includes a comprehensive list of demographic characteristics, depression and stress symptoms, social support, and parent/infant factors.

Study design: Our study design optimized eight ML algorithms – Logistic Regression, Support Vector Machine, Decision Tree, Random Forest, XGBoost, Naïve Bayes, K-Nearest Neighbor, and Artificial Neural Network – to identify the main risk factors associated with parental depression. We compared models based on the area under the receiver operating characteristic curve (AUC), positive predicted value (PPV), sensitivity, and F-score.

Results: The results showed that all eight models achieved an AUC above 0.8, suggesting that the logistic regression-based model's performance is comparable to other common ML models.

Conclusion: Logistic regression is effective in identifying parents at risk of depression for targeted screening with a performance comparable to common ML-based models.

KEYWORDS

parental depression, neonatal intensive care unit, NICU, screening system, machine learning, logistic regression

Introduction

Postpartum depression (PPD) can occur in women after childbirth for up to one year, affecting around 15% of mothers, and is the most common complication of childbirth (1). Neonatal intensive care unit (NICU) admission is a stressful experience for parents and together with prematurity are well known risk factors for PPD. Multiple studies have determined that the incidence of PPD in parents whose infants are admitted to the NICU is approximately 40–45%, which is considerably higher than the 15% risk among general birthing population (2, 3). Therefore, early detection of PPD at critical times during admission and discharge through screening programs can play a significant role in preventing the negative consequences for the family and child (4). Given the importance of early diagnosis of depression symptoms, multiple NICUs have developed and implemented screening programs for PPD in the NICU (4–6). Early identification of depression symptoms in parents is crucial to mitigate adverse effects such as infant neurodevelopmental delays (7). However, the current screening process is both expensive and time-consuming, requiring a tracking system that could span multiple healthcare settings.

Having a predictive model to identify parents at risk of developing postpartum depression can assist in prioritizing those in need of screening. Prior research has focused on training machine learning (ML) models to predict postpartum depression (8–19). A review of these studies revealed several significant predictors, including age, education, marital status, income, ethnicity, lifetime depression, depression during pregnancy, anxiety, smoking, mode of delivery, gestational age, APGAR score (appearance, pulse, grimace, activity, and respiration), BMI (body mass index), and history of antidepressant use (10). Although ML models have been used to predict postpartum depression, no study has applied ML to predict postpartum depression of NICU parents. There is only one study that has utilized logistic regression to investigate the risk factors associated with parental depression symptoms at NICU (20) and found that higher levels of parental stress, older gestational age, and lower levels of social support contribute to parental depression symptoms at NICU (20). However, it is worth noting that this study has yet to present performance metrics for the model, which are essential for facilitating a comprehensive comparison with other predictive models. Notably, the study also did not employ segmentation of the data into training and testing sets, a practice pivotal for evaluating the model's performance using unseen testing data. The absence of such data partitioning is a common feature of preliminary investigations which may raise concerns about the model's ability to generalize beyond its training data.

This study contributes to the existing literature in three distinct ways. Firstly, it pioneers the application of machine learning (ML) approaches to NICU data to comprehensively investigate factors predicting postpartum depression among NICU parents. A central objective is to discern whether ML methodologies surpass the predictive capabilities of the traditional Logistic Regression (LR) model. Secondly, the study employs rigorous methodology by dividing the dataset into distinct training and testing sets. Multiple performance measures are reported to systematically compare and assess the efficacy of eight ML models on previously unseen data (testing dataset). The study also undertakes data imputation and parameter optimization, ensuring robustness and reliability of the findings. Thirdly, this research enhances the existing logistic regression model by incorporating two pivotal variables, namely anxiety level and self-efficacy. Moreover, improvements in data preprocessing steps contribute to a more nuanced understanding of the intricate relationship between these variables and parental depression in the NICU context.

Methodology

Study population

This study is based on the clinical data collected from three hundred parent-infant dyads who were anticipating discharge from the level IV NICU at Children's National Hospital in Washington, DC, between January 2016 and February 2017 as part of the giving parents support (GPS) trial (20). This level IV NICU provides care to complex term and preterm infants and offers parental support services such as parental education, support groups, social work, and mental health services. Inclusion criteria were one parent (either mother or father) aged ≥18 years who were self-identified as the primary caregiver for the next year. Questionnaires were used to collect data about parent and infant characteristics, and validated screening tools [Center for Epidemiological Studies-Depression scale 10 (CES-D-10)] were given prior to discharge to determine incidence of depression symptoms. The study was reviewed and approved by the CN Institutional Review Board, and it was registered with https://clinicaltrials.gov (NCT02643472) (20).

Data elements

A total of eighteen independent variables, including demographics of the parents, health profile of the infants, hospital stay, and various stress levels and social support network of the family, were used in this study. More specifically, parents' demographic characteristics included race, age, gender, education, relationship status, having other children at home, working status prior to having the NICU infant, and current working status. Stress and anxiety were assessed using the following scales: Perceived Stress Scale (PSS-10), which assesses general stress. Parental Stress Scale (PSS) which measures parental stress regarding their new parenting role. Parental Stress Scale at NICU (PSS NICU) which evaluates NICU-specific stress after admission to the NICU and is based on infant appearance, NICU sights and sounds, parental role alterations, and parent relationships with staff. Multidimensional Scale of Perceived Social Support MSPSS was used to assess the parents' perception of social support given to them by significant others, family, and friends. Perceived Maternal Parenting Self-efficacy PMPSE measured the parent's belief in their ability to provide sufficient care for the infant. STAI Y-1 (state anxiety scale) and STAI Y-2 (trait anxiety scale) assessed the current anxiety state of parents and parents' baseline anxiety characteristics. Infant characteristics were included as the independent variables such as infant gender in NICU, birth weight, birth weight < 1,500 grams, gestational age (weeks), and length of stay (LOS) in NICU (days) (20). The primary outcome measure was depression symptoms of each parent which was collected by the 10-item questionnaire of Center for Epidemiological Studies

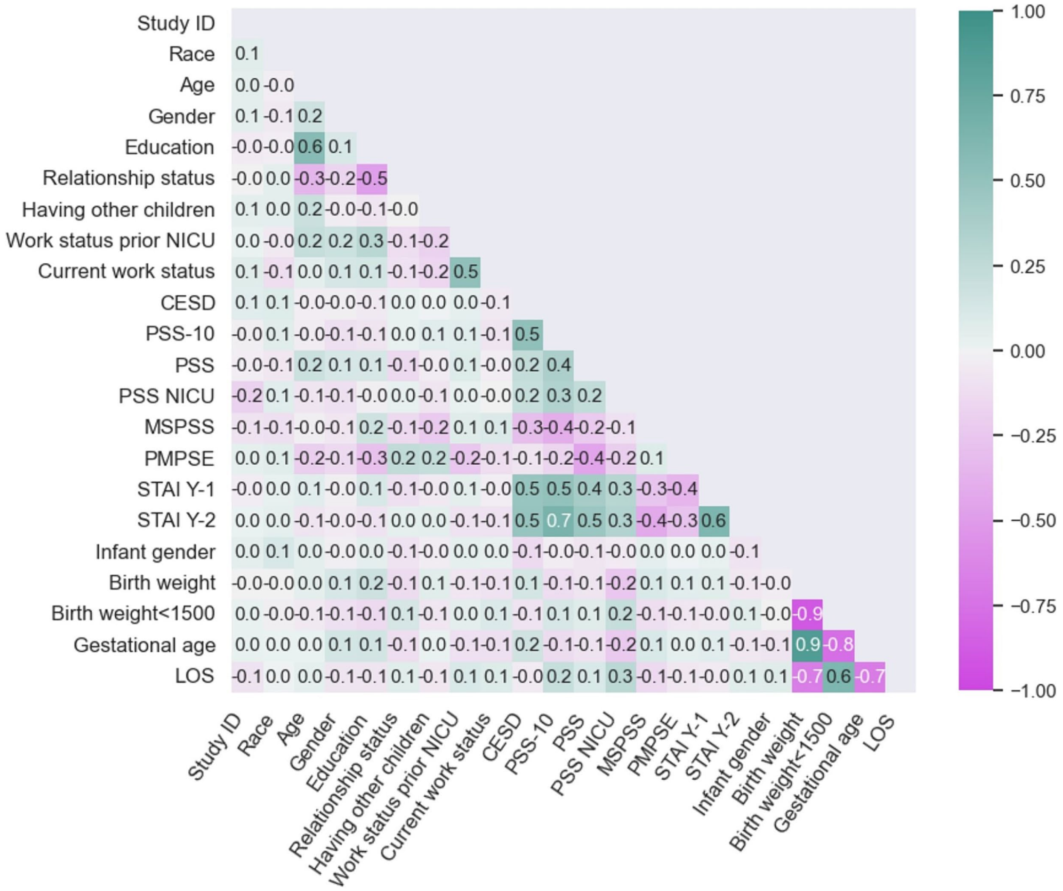


FIGURE 1
Correlation plot.

Depression Scale (CESD-10) and a total score of ≥10 indicated an elevated depression symptom.

Data preprocessing and imputation

Data preprocessing

Multicollinearity was addressed by examining the correlation matrix presented in Figure 1, which enabled the identification of predictors exhibiting high correlation. Variables with a correlation exceeding 0.8 or falling below −0.8 were deemed highly correlated. To mitigate the impact of multicollinearity on the results, the variables representing birth weight and birth weight less than 1,500 grams were excluded from further analysis, given their significant correlation with gestational age.

Missing data and imputation

Some independent variables exhibited missing values that required addressing before analysis commenced. The number of missing values per variable was as follows: PSS NICU: 9 (3%), PMPSE: 9 (3%), MSPSS: 6 (2%), PSS: 5 (1%), STAI Y-2: 5 (1%), STAI Y-1: 4 (1%), PSS-10: 4 (1%). To address this, we implemented an imputation criteria approach. The highest number of missing values per participant was seven, which indicated a lack of response to all seven surveys. The three participants with seven missing values were excluded ($n = 3$, 1%). Imputation was applied for participants with less than two missing values ($n = 18$), encompassing 15 participants with only one missing value, and 3 participants with two missing values. After evaluating the distribution of variables with low missing rates and determining their non-normal distribution, we chose median imputation as the preferred technique. Median imputation is often favored for handling skewed data distributions due to its reduced sensitivity to outliers in comparison to mean imputation techniques. This decision was specifically made to address the conditions of low missing rates (6%) and non-normal distributions, ensuring a robust imputation approach for the dataset (21). Less than two missing values per patient for a total of eighteen patients (6%) were imputed using this strategy. The entire process of data cleaning, analysis, and the development of machine learning models was conducted in Python 3 using the Jupyter Notebook interface.

Statistical analysis

A descriptive statistical analysis was performed to analyze the characteristics of the study population and identify the prevalence of depression symptoms among various groups. The cohort for this study included three hundred parent-infant pairs; after excluding three participants due to high missingness, a total of 297 parent-infant pairs were analyzed and included in the study. To ensure consistency with the past similar studies (20), a same stratifying strategy for birth weight categories, gestational age, and length of stay was employed during the analysis. Table 1 shows the demographic and clinical characteristics of the parents and their infant. Importantly, the variables presented in the following table did not have any missing values, reinforcing the robustness of our dataset and analysis. The unadjusted statistics presented in Table 1 reveal significant distinctions between the high-risk and low-risk groups in terms of infant gender (p-value = 0.02) and gestational age (p-value = 0.03), without accounting for the influence of other variables.

Model development

The refinement process of the 297 participants included in this study involved a random split into training (80%) and testing (20%) sets. Given the small sample size and complexities of predicting parental depression symptoms, this split ratio was considered appropriate to strike a balance between model performance and the robustness of the findings. The stratified sampling technique (22) was employed during this split to ensure a balanced distribution of samples between the training and testing subsets. For the final evaluation, 20% of the data was reserved for testing, while the remaining 80% was utilized in the cross-validation process. This involved dividing the 80% dataset into 10 folds, with the model undergoing training 10 times. Each iteration used a different fold as the test set (24 data points) and the remaining as the training data (213 data points), ensuring a robust learning experience. The assessed accuracy of the models is reported as the mean score across these 10 repetitions.

Eight diverse algorithms, namely Logistic Regression (LR), Support Vector Machine (SVM), Decision Trees, Random Forest (RF), Extreme Gradient Boosting (XGBoost), Naive Bayes (NB), and K-Nearest Neighbor (KNN), were implemented using the scikit-learn package in Python (23). Additionally, Artificial Neural Networks (ANN) were utilized through the Keras library in Python (24). Hyperparameter tuning using a combination of grid search, parallel processing and dropout regularization was conducted for ANN to identify optimal parameter combinations while monitoring corresponding learning curve to prevent overfitting issues.

Moreover, it is important to note that cross-validation was employed solely to obtain the mean accuracy of each ML algorithm. The actual performance metrics such as area under the receiver operating characteristic curve (AUC), precision (positive predicted value – PPV), sensitivity (recall), F-score, and in-depth analysis were implemented using the initial 20% of the test data, ensuring a comprehensive evaluation based on a separate, independent subset. A process chart of model development is provided in Figure 2.

Results

Logistic regression

In our study, we enhanced the performance of the existing logistic regression (LR) model, originally constructed on this dataset (20), by incorporating additional variables capturing perceived self-efficacy (PMPSE), STAI Y-1 (state anxiety scale) and STAI Y-2 (trait anxiety scale). Furthermore, we implemented a meticulous preprocessing procedure to address missing values. The summarized results in Table 2 displays the LR model's outcomes, revealing PSS-10 (perceived stress scale), MSPSS (multidimensional scale of perceived social support), STAI Y-1 (state anxiety scale), infant female gender, and older gestational age (GA) as significant variables in predicting parental depression symptoms. Notably, our findings align with the outcomes of the previous study that employed logistic regression on this same dataset (20). This consistency underscores the robustness and reliability of our extended LR model.

Training machine learning models

Models were trained on 80% of the dataset and then evaluated on the remaining 20% of the data. The actual value of performance metrics including area under the curve (AUC), precision, or positive predicted value (PPV), sensitivity or recall, and F-score are presented in Figure 3. Also, the 95% confidence interval of the performance metrics are shown as the error bars in Figure 3 and in more detail presented in Table 3.

In analyzing the performance metrics of the various models, several key observations emerge. The mean accuracy on the training set, as assessed through cross-validation, reveals that Logistic Regression and Support Vector Machine achieved relatively high accuracies at 0.77. However, it is crucial to consider additional metrics for a comprehensive evaluation. The AUC on the test set serves as a vital indicator of a model's ability to discriminate between two classes of low and high depression risks, with values closer to 1 indicating better performance. Notably, Logistic Regression, Support Vector Machine, Naïve Bayes, Artificial Neural Network, Random Forest and XGBoost demonstrated competitive AUC values ranging from 0.83 to 0.85. Precision represents the accuracy of the model in identifying parents at risk of depression among those predicted as high-risk. A high precision indicates a low rate of false positives, meaning that when the model predicts a parent as high-risk, there is a high probability that they indeed have an elevated risk of depression. Decision Tree stands out with a high precision value of 0.89. Sensitivity, also called recall, measures the ability of the model to correctly identify parents who are truly at high risk of depression among all the parents who are at high risk. High sensitivity implies that the model is effective in capturing a significant portion of parents with a high risk of depression, minimizing the number of cases being missed. Naïve Bayes excels in sensitivity at 0.77, emphasizing its' effectiveness in identifying positive cases despite a relatively lower mean accuracy. F-score is a metric that combines precision and sensitivity into a single score, providing a balanced assessment of a model's performance in making accurate positive predictions while minimizing both false positives and false negatives. Naïve Bayes, XGBoost, and Artificial Neural Network demonstrate high F-score values ranging from 0.75 to 0.77, indicating a good model performance in terms of both precision and sensitivity. The choice of the optimal model should consider trade-offs between precision and sensitivity based on specific application goals —for instance, whether avoiding false alarms (high precision) or capturing as many true cases as possible (high sensitivity) or both is more critical in the context of predicting depression risk in parents of NICU infants.

Building on the discussion of trade-offs between performance metrics, the SHAP value analysis of variable importance in Figure 4

TABLE 1 Demographic and clinical characteristics of the parents and their infant.

		Total (*n* = 297)	High depression score (*n* = 135)	Low depression score (*n* = 162)	*p*-value
Parental demographic characteristics		Variables, *n* (%)			
Race	White/Caucasian	116 (39)	54 (40)	62 (38)	0.2517
	Black/African American	132 (44)	53 (39)	79 (48)	
	Asian	17 (6)	8 (6)	9 (6)	
	American Indian	8 (3)	5 (4)	3 (2)	
	Mixed race	24 (8)	15 (11)	9 (6)	
Age (years)	Mean ± SD	30 ± 6	30 ± 6	30 ± 7	0.6268
Gender	Female	264 (89)	121 (90)	143 (88)	0.8532
	Male	33 (11)	14 (10)	19 (12)	
Education	High school diploma or less	77 (26)	36 (27)	41 (25)	0.4018
	Trade/vocational training/some college	85 (29)	43 (32)	42 (26)	
	College/university degree or higher	135 (45)	56 (41)	79 (49)	
Relationship status	Married partner/spouse	159 (54)	70 (52)	89 (55)	0.9103
	Unmarried partner/spouse	87 (29)	42 (31)	45 (28)	
	Single	49 (16)	22 (16)	27 (16)	
	Divorced	2 (1)	1 (1)	1 (1)	
Having other children	Yes	169 (57)	77 (57)	92 (57)	1
	No	128 (43)	58 (43)	70 (43)	
Work status prior NICU infant	Yes	210 (71)	98 (73)	112 (69)	0.5252
	No	87 (29)	37 (27)	50 (31)	
Current work status	Yes, full time	114 (38)	50 (37)	64 (39)	0.6665
	Yes, part time	37 (12)	15 (11)	22 (14)	
	No	146 (49)	70 (52)	76 (47)	
Infants' clinical characteristics					
Infant gender in NICU	Female	126 (42)	67 (50)	59 (36)	0.0252 *
	Male	171 (58)	68 (50)	103 (64)	
Birth weight < 1,500 gr	Yes	63 (21)	23 (17)	40 (25)	0.1185
	No	234 (79)	112 (83)	122 (75)	
Birth weight category (grams)	< 1,000	31 (10)	10 (7)	21 (13)	0.0974
	1,000–1,499	31 (10)	12 (9)	19 (12)	
	1,500–2,499	62 (21)	24 (18)	38 (23)	
	> 2,500	173 (58)	89 (66)	84 (52)	
Gestational age (weeks)	< 28	29 (10)	7 (5)	22 (13)	0.0353 *
	28–33	61 (21)	24 (18)	37 (23)	
	34–36	39 (13)	18 (13)	21 (13)	
	> 37	168 (57)	86 (64)	82 (51)	
Length of stay (days)	1–7	78 (26)	38 (28)	40 (25)	0.2321
	8–17	71 (24)	29 (21)	42 (26)	
	18–47	75 (25)	40 (30)	35 (21)	
	48–181	73 (25)	28 (21)	45 (28)	

*Statistically significant *p*-value.

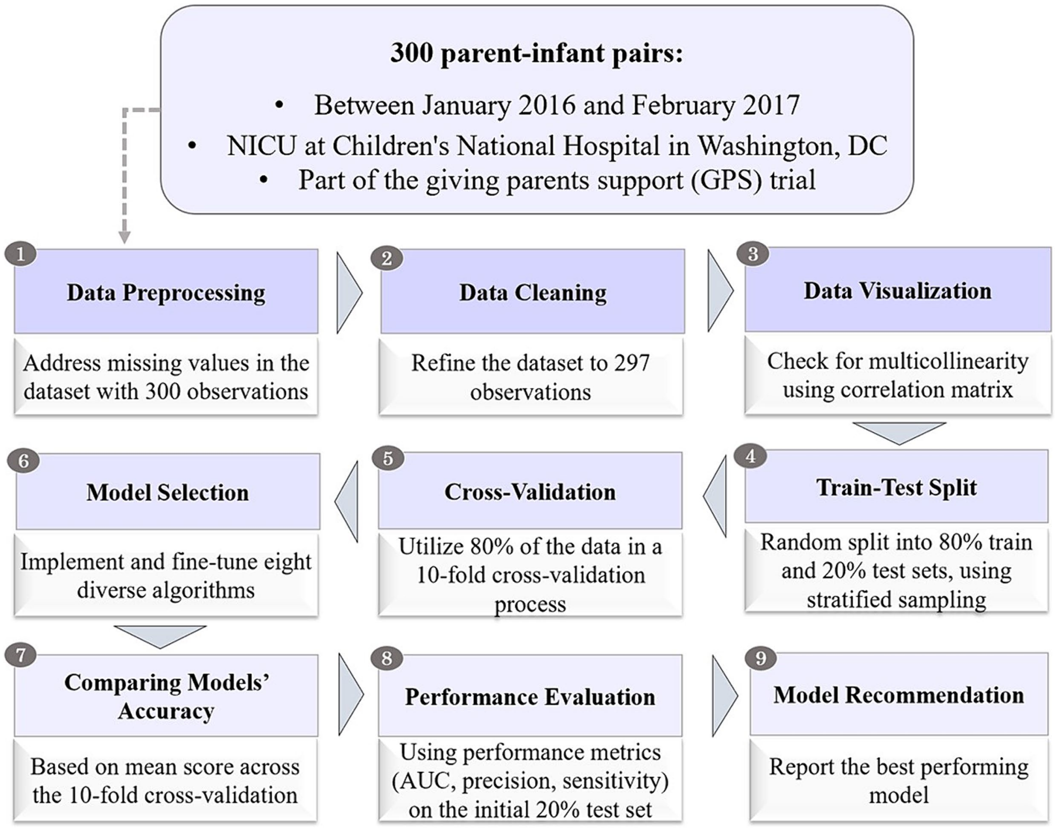


FIGURE 2
Process chart for model development.

sheds light on the key contributors to predicting parental depression symptoms at NICU discharge. According to the Figure 4, the top five variables impacting the risk of depression are STAI-Y2 (trait anxiety scale), PSS-10 (perceived stress scale), STAI-Y1 (state anxiety scale), PSS-NICU (parental stress scale NICU), and MSPSS (multidimensional scale of perceived social support). These findings provide valuable insights into the specific variables driving the model's predictions, reinforcing the significance of specific variables in predicting parental depression symptoms at NICU discharge. The SHAP analysis approach is specifically useful as it allows us to assess the extent of the impact of these variables on the prediction of our outcome (25). For example, Figure 4 pinpoints STAI-Y2 (trait anxiety scale), as the most important variable for parental depression estimation. When STAI-Y2 is "low" (blue), the log-odds of model predicting "high risk class" decreases by up to 0.15 units. Conversely when STAI-Y2 is "high" (pink), the log-odds of model predicting "high risk class" increases by up to 0.10 units.

Comparison of logistic regression with other ML models

Building upon the observation of overlapping confidence intervals in Figure 3, signifying comparable performance across models, it becomes evident that distinctions in sensitivity, precision, F-score, and area under the curve are not statistically significant. For instance, the sensitivity of the Naïve Bayes (0.77) surpasses that of logistic regression (0.74), yet falls within the confidence interval of logistic regression's sensitivity (0.56–0.9), a trend echoed in other performance metrics (detailed confidence interval information is available in Table 3). Given these findings, it is clear that all models exhibit comparable performance statistics, with logistic regression standing out in Figure 5 by achieving the highest area under the curve (AUC). This consistency in performance, coupled with the superior interpretability of logistic regression, positions it as a preferable choice for predicting parental depression symptoms at NICU discharge.

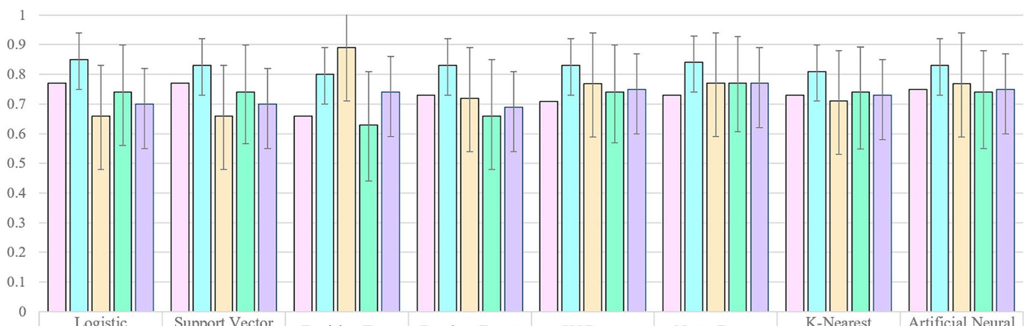
Discussion

In tackling the complexities inherent in forecasting the risk of parental depression upon NICU discharge, our study takes a comprehensive approach, aiming to identify and prioritize factors associated with this crucial outcome. We sought to establish the most effective predictive model by systematically comparing results obtained from various machine learning (ML) techniques and logistic regression (LR). While previous research in the domain of predicting parental mental health outcomes has delved into the application of ML models (8–19), the specific context of parental depression in the NICU remains underexplored, with only logistic regression studies to date (20). In the absence of conclusive evidence supporting ML's superiority in predicting parental depression within the NICU, our study fills a

TABLE 2 Logistic regression results for predictors of parental depression symptoms at NICU.

Variables	Coef.	Std. err.	z	p > |z|	[0.025]	[0.975]
Race	0.0993	0.1550	0.6408	0.5217	−0.2045	0.4032
Age	−0.0038	0.0328	−0.1153	0.9082	−0.0681	0.0605
Parent gender	−0.2878	0.5992	−0.4802	0.6311	−1.4622	0.8867
Education	−0.3261	0.2840	−1.1482	0.2509	−0.8828	0.2306
Relationship status	−0.2359	0.2636	−0.8950	0.3708	−0.7525	0.2807
Having other children	−0.5163	0.4043	−1.2770	0.2016	−1.3088	0.2762
Working prior NICU infant	0.3531	0.4980	0.7090	0.4783	−0.6230	1.3291
Currently working	−0.1749	0.3021	−0.5791	0.5626	−0.7670	0.4171
PSS-10[a]	0.1090	0.0354	3.0797	0.0021*	0.0396	0.1783
PSS[b]	−0.0457	0.0284	−1.6090	0.1076	−0.1015	0.0100
PSS NICU[c]	0.0032	0.0046	0.6948	0.4872	−0.0058	0.0122
MSPSS[d]	−0.0464	0.0168	−2.7590	0.0058*	−0.0794	−0.0135
PMPSE[e]	−0.0153	0.0194	−0.7869	0.4313	−0.0533	0.0228
STAI Y-1[f]	0.0610	0.0192	3.1783	0.0015*	0.0234	0.0986
STAI Y-2[g]	0.0339	0.0282	1.2034	0.2288	−0.0213	0.0892
Infant gender (female)	−0.9698	0.3598	−2.6952	0.0070*	−1.6750	−0.2645
Older gestational age	0.6299	0.2388	2.6382	0.0083*	0.1619	1.0978
LOS[h]	0.0353	0.2165	0.1632	0.8703	−0.3889	0.4596

*Statistically significant *p*-value.
[a]PSS-10: perceived stress scale.
[b]PSS: parental stress scale.
[c]PSS NICU: parental stress scale NICU.
[d]MSPSS: multidimensional scale of perceived social support.
[e]PMPSE: perceived maternal parenting self-efficacy.
[f]STAI Y-1: state anxiety scale.
[g]STAI Y-2: trait anxiety scale.
[h]LOS: length of stay.



	Logistic Regression	Support Vector Machine	Decision Tree	Random Forest	XGBoost	Naïve Bayes	K-Nearest Neighbor	Artificial Neural Network
Mean Accuracy (Train Set-CV)	0.77	0.77	0.66	0.73	0.71	0.73	0.73	0.75
AUC (Test Set)	0.85	0.83	0.8	0.83	0.83	0.84	0.81	0.83
Precision (Test Set)	0.66	0.66	0.89	0.72	0.77	0.77	0.71	0.77
Sensitivity (Test Set)	0.74	0.74	0.63	0.66	0.74	0.77	0.74	0.74
F-Score (Test Set)	0.7	0.7	0.74	0.69	0.75	0.77	0.73	0.75

Mean Accuracy (Train Set-CV)　AUC (Test Set)　Precision (Test Set)　Sensitivity (Test Set)　F-Score (Test Set)

FIGURE 3
Performance metrics for machine learning models.

critical gap by offering a rigorous comparison between ML techniques and logistic regression. This investigation emerges from a motivation to challenge the assumption that ML universally outperforms traditional methods, especially in the nuanced domain of parental mental health within the NICU. By providing empirical evidence and insights into the predictive efficacy of different methodologies, our research contributes to advancing the understanding of optimal prediction strategies in this unique healthcare context.

Building upon this motivation, our study endeavors to elevate the field by advancing beyond the limitations of the existing logistic regression study on parental depression in the NICU. We explore this uncharted territory by employing eight distinct machine learning (ML) models, each meticulously assessed and compared through comprehensive performance evaluations on previously unseen test data. This departure from conventional methodologies is facilitated by the implementation of a cross-validation technique, dividing the data into two subsets for model evaluation, ensuring robustness and applicability to real-world scenarios. Figure 3 presents a visual representation of our findings, encapsulating crucial performance measures such as accuracy, AUC, precision, sensitivity, and F-score. This not only facilitates an in-depth comparison of the models but also ensures the reproducibility of our results across different frameworks. Furthermore, our study enhances the existing paradigm by fine-tuning a previous model (20), incorporating additional independent variables such as state anxiety scale (STAI-Y1), trait anxiety scale (STAI-Y2), and perceived maternal parenting self-efficacy. This augmentation, coupled with refined preprocessing procedures, contributes to the evolution of predictive models in the NICU setting.

Our findings reveal that a higher level of perceived stress (PSS-10), lower perceived social support (MSPSS), and older gestational age

TABLE 3 Confidence intervals of performance metrics for machine learning models.

Method	AUC (95% CI)	Precision (95% CI)	Sensitivity (95% CI)	*F*-score (95% CI)
Logistic regression	(0.75, 0.94)	(0.48, 0.83)	(0.56, 0.90)	(0.55, 0.82)
Support vector machine	(0.72, 0.93)	(0.50, 0.82)	(0.57, 0.90)	(0.55, 0.81)
Decision tree	(0.67, 0.92)	(0.73, 1.00)	(0.44, 0.81)	(0.59, 0.86)
Random forest	(0.73, 0.93)	(0.54, 0.88)	(0.48, 0.85)	(0.53, 0.82)
XGBoost	(0.71, 0.93)	(0.60, 0.92)	(0.57, 0.90)	(0.61, 0.87)
Naïve Bayes	(0.74, 0.93)	(0.60, 0.92)	(0.61, 0.93)	(0.64, 0.89)
K-nearest neighbor	(0.71, 0.91)	(0.54, 0.88)	(0.55, 0.89)	(0.58, 0.84)
Artificial neural network	(0.72, 0.92)	(0.60, 0.92)	(0.55, 0.88)	(0.61, 0.87)

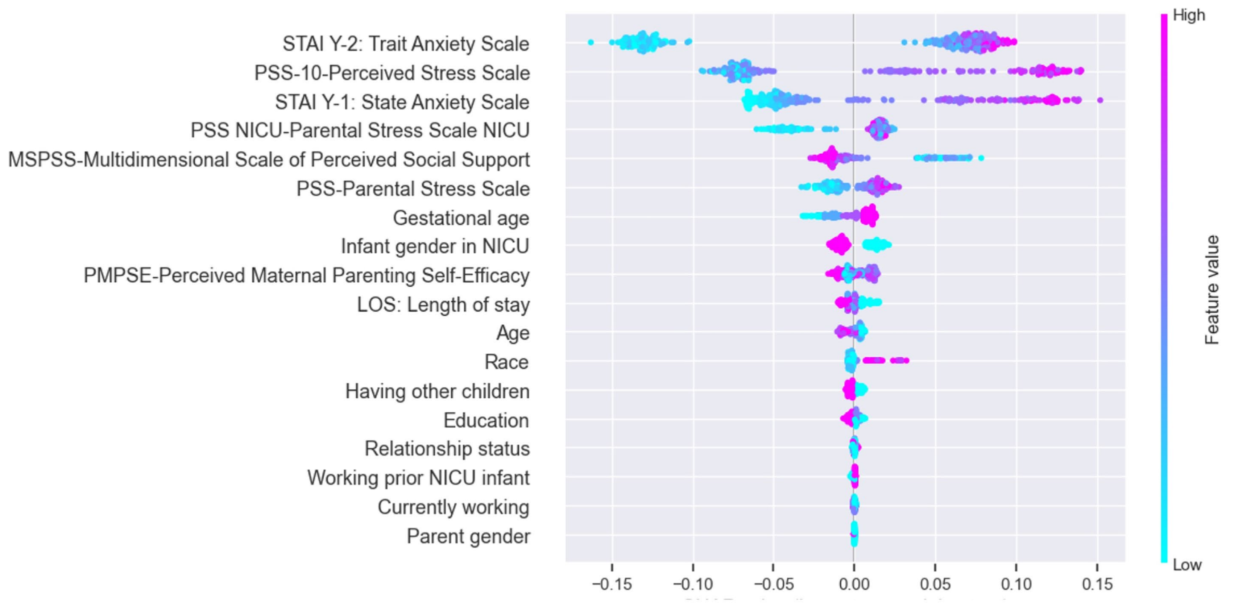


FIGURE 4
SHAP value presenting impact on model output (for output label "1": high risk class).

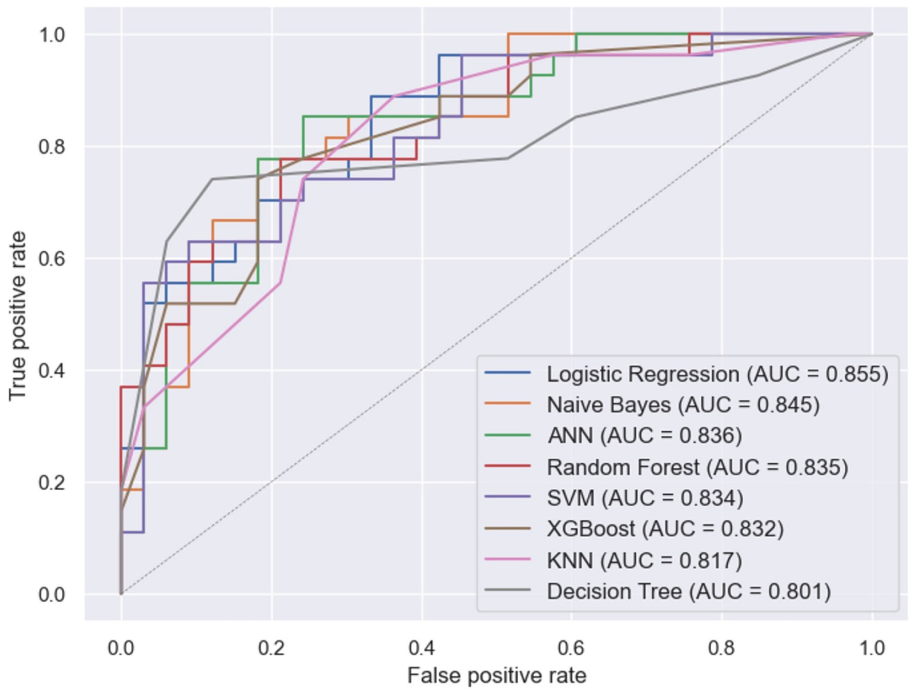


FIGURE 5
ROC curves for machine learning models.

(GA) significantly contribute to depression symptoms among parents of NICU infants. Importantly, our results align statistically with those reported in Soghier et al. (20). Additionally, we observed that parents with a female infant in the NICU face a higher risk of depression symptoms compared to parents of male infants. While the precise reasons for this gender difference remain elusive, analogous results have been noted in other studies, where the reported odds of depression are higher among mothers of female infants (26–28). These studies attribute this outcome to a potential preference for a male infant, suggesting societal influences. Limited evidence also suggests biological differences; mothers carrying a female fetus exhibit elevated levels of β-human chorionic gonadotropin. This indicates that hormonal changes, along with similar alterations, may provide a biological explanation for the impact of the child's gender on postnatal depression (29, 30).

Building on these significant findings, our study introduces an additional layer of insight by delving into feature importance through SHAP analysis. By not exclusively relying on black box ML-based models, we were able to extract nuanced information about the contributors to parental depression symptoms in the NICU. Particularly noteworthy are the state anxiety scale (STAI-Y1) and trait anxiety scale (STAI-Y2), identified as crucial predictors. This finding emphasizes the importance of not only screening for depression but also for anxiety and social support as both naturally predict the onset of depression. While the connection between anxiety, social support, and depression is well-established, it's crucial to highlight that many NICUs primarily screen for postpartum depression (PPD), often assuming that certain questions indirectly address anxiety. Our study challenges this assumption, emphasizing the distinct and significant impact of both anxiety and depression on parental mental health.

Having uncovered nuanced insights into the contributors of parental depression symptoms through SHAP analysis, we turn our attention to the performance aspect. Remarkably, the logistic regression model, a key focus of our study, exhibits comparable effectiveness when benchmarked against commonly used ML models. This finding aligns with broader research on depression, where logistic regression has consistently demonstrated either superior or comparable performance compared to alternative ML models (31–33). Our observation prompts consideration of two pivotal factors that contribute to this alignment. First, the richness of our dataset, encompassing a broad spectrum of variables and free from biases, ensures that optimized models consistently exhibit stable performance across diverse algorithms. All eight models achieved an area under the curve (AUC) above 0.8, suggesting that the logistic regression-based model's performance is comparable to other common ML models. Second, the common ML models typically outperform logistic models in larger datasets. However, the comparable performance observed in our study, possibly attributed to the dataset's size (three hundred observations), underscores the value of an easily interpretable logit model for predicting postpartum depression among NICU parents, boasting a high accuracy of 0.77.

Based on our findings, while Logistic Regression offers its own advantages and remains one of the top-performing models, it is essential to consider the broader performance metrics displayed in Figure 3. Notably, algorithms such as Naïve Bayes, XGBoost, and Artificial Neural Network demonstrate a remarkable balance between precision and sensitivity as evidenced by their notably high F-score values. This underscores their ability in effectively identifying positive cases while simultaneously minimizing both false positives and false negatives. Naïve Bayes stands out as a rapid algorithm with minimal training time, making it ideal for clinical decision support systems where speed is a crucial constraint (12). XGBoost exhibits the robust ability to mitigate overfitting issues commonly encountered in datasets (34). On the other hand, Neural Network emerges as an excellent choice when dealing with substantial amounts of data sourced from diverse healthcare organizations (35). By highlighting the strengths and distinct qualities of each ML technique in relation to predicting PPD in the NICU, our study expands the potential for accurate predictions, enhances the understanding of PPD risk factors, and provides valuable insights for developing targeted interventions in NICU settings.

It is essential to acknowledge the limitations inherent in this study. Notably, the dataset under consideration exhibited a relatively small number of patients. While the size of our sample is limited, it is imperative to underscore the high quality of the data therein. This dataset originates from a meticulously conducted clinical trial, ensuring a high standard of data integrity. It is crucial to emphasize that the sample is devoid of biases, and further enhances its reliability by maintaining a balanced representation across various racial groups which instill confidence in the validity of our study outcomes. To address potential challenges associated with small sample sizes, rigorous monitoring of learning curves for all prediction models was undertaken throughout the training process. Employing a strategic combination of techniques, including cross-validation, regularization, and hyperparameter tuning, we actively mitigated the risk of overfitting, thereby reinforcing the integrity of our study's analytical approach. Another limitation of this study is that the dataset utilized was exclusively sourced from the Children's National Hospital in Washington, DC. Therefore, the generalizability of our study's results to other healthcare systems monitoring parental depression symptoms in the NICU may be limited. Future studies should aim to include larger and more diverse datasets from multiple institutions to enhance the external validity and generalizability of the predictive models developed in this research.

Conclusion

In conclusion, the findings of this study contribute to the ongoing efforts of improving parental depression screening in the NICU context. The implementation of more accurate and targeted screening systems can ease the burden on both patients and healthcare systems by reducing unnecessary interventions and optimizing resource allocation. Our findings emphasize the importance of evaluating perceived stress, perceived social support, and state anxiety scale as essential factors to be screened in NICU parents. Moreover, our results show that the performance of the logistic regression as an interpretable and easy to use model is comparable with other commonly used ML-based models. This finding facilitates informed decision-making for healthcare providers, empowering them to select the most appropriate model for their specific contexts. These advancements aim to enhance the overall well-being of parents and their infants in the NICU by effectively identifying and addressing parental depression.

Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: this is the analysis of an existing dataset. We obtained the de-identified data from authors of this paper. Requests to access these datasets should be directed to LS, LSoghier@childrensnational.org.

Ethics statement

This study was approved by the Children's National Institutional Review Board and it was registered with https://clinicaltrials.gov (NCT02643472). The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

FS: Conceptualization, Formal analysis, Methodology, Visualization, Writing – original draft, Writing – review & editing. NH: Conceptualization, Funding acquisition, Supervision, Writing – review & editing. VA: Methodology, Writing – review & editing. LS: Data curation, Funding acquisition, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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EDITED BY
Grazyna Kmita,
University of Warsaw, Poland

REVIEWED BY
Erica Neri,
University of Bologna, Italy
Magdalena Chrzan-Detkos,
University of Gdansk, Poland

*CORRESPONDENCE
Romuald Jean-Dit-Pannel
✉ romuald.jean-dit-pannel@univ-fcomte.fr

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Becoming first time father of premature newborn during the first wave of the pandemic: a case study approach

Romuald Jean-Dit-Pannel[1]*, Chloé Dubroca[1] and Flora Koliouli[2]

[1]Laboratory of Psychology, UR 3188, University of Franche-Comté, Besançon, France, [2]Laboratory Psyche, School of Early Childhood Education, Faculty of Education, Aristotle University of Thessaloniki, Thessaloniki, Greece

Introduction: The aim of this paper is to delve into the emotional and psychological challenges that fathers face as they navigate the complexities of having a preterm infant in the NICU and in an unprecedented sanitary context.

Methods: We used three data collection methods such as interviews (narrative and the Clinical Interview for Parents of High-risk Infants- CLIP) and the Edinburgh Postnatal Depression Scale (EPDS) to gain a comprehensive understanding of the cases.

Results: The following analysis explores two individuals' personal experiences of becoming a first-time father during the first wave of the COVID-19 pandemic through a close examination of two superordinate themes: "A series of separations through the experienced COVID- 19 restrictions" and "Moments of connection." The transition to fatherhood is essentially with a medicalized form of connection with their newborn and the perceived paternal identity. In terms of temporality, these fathers experienced a combination of concerns about their infants' long-term development and COVID-19 health concerns. Furthermore, they showed indications of phobic or hypochondriac tendencies using a psychoanalytic framework, along with an increased risk of postpartum depression.

KEYWORDS

first-time fathers, prematurity, experienced separations, moments of connection, experiential approach, qualitative study, COVID-19

Introduction

Premature birth is a critical event that poses numerous challenges to newborns and their parents (Ionio et al., 2016). Existing research has largely focused on mothers' experiences, but there is growing recognition of the importance of including fathers in studies on preterm infant care and development (Provenzi and Santoro, 2016; Filippa et al., 2021). Premature births can have profound psychological implications for fathers, often evoking feelings of helplessness and anxiety due to the suddenness and unpredictability of the event (Ionio et al., 2016; Koliouli et al., 2016a). Fathers may experience stress and fear about their infants' health and survival, compounded by the unfamiliar and highly medicalized environment of the neonatal intensive care unit during the newborn's hospitalization (Koliouli et al., 2016b; Stefana et al., 2018). However, the experienced stressed may persist several months after discharge (Salomè et al., 2022). Fathers of preterm infants may also struggle with the bonding process, as traditional interactions are disrupted by infants' medical needs and the NICU setting (Mörelius et al., 2015; Koliouli et al., 2024). Feelings of exclusion from care decisions and pressure to provide emotional and financial support can further compound stress levels (Koliouli and Zaouche Gaudron, 2018). These psychological challenges can affect fathers' mental health and relationship with the newborn, highlighting the need for targeted support and inclusion in the care of preterm infants (Koliouli et al., 2022, 2024).

First-time fathers' experiences

First-time fathers experience multiple psychological implications, as they encompass a wide range of emotional and functional changes as they transition into parenthood. This major life event can affect all aspects of one's psychosocial functioning, with new fathers experiencing anxiety, which can vary significantly throughout their partner's pregnancy and postnatal period (Philpott et al., 2019). Alterations in lifestyle and relationship dynamics also pose significant challenges, with fathers often feeling strain on their emotional and physical resources, which can have repercussions not only for their well-being but also for the partner's and infant's development (Hansson and Ahlborg, 2012). Adjusting to new responsibilities, sleep deprivation, and concerns about providing effective support can contribute to the stress experienced during this period. Further complicating this transition are changes in sexual relationships and the need for rest due to the demanding care a baby requires (Hansson and Ahlborg, 2012; Leavitt et al., 2017). Recognizing the complexity of these experiences, it is crucial to support first-time fathers in their new role of fostering positive outcomes for the entire family (Jean-Dit-Pannel et al., 2021).

Consequently, transition to fatherhood in the context of premature birth comes with a unique set of challenges as first-time fathers navigate the unexpected arrival of their newborn (Benzies and Magill-Evans, 2015). Their initial experience of fatherhood may be different from what they had anticipated as they grapple with the complexities of caring for a preterm newborn. From understanding the medical needs and potential complications associated with prematurity to emotionally processing the unexpected turn of events, first-time fathers find themselves in an uncharted territory. Furthermore, the COVID-19 context has further introduced uncertainties in this uncharted territory.

COVID-19 context specificities

Transitioning to parenthood during the COVID-19 pandemic has added unique psychological challenges to first-time parents (Jean-Dit-Pannel, 2021). The combination of the typical stressors associated with the arrival of a new baby, such as adapting to new roles, altered sleeping patterns, and increased caregiving responsibilities, is further compounded by pandemic-related concerns. Transitioning to fatherhood during the COVID-19 pandemic has presented fathers with an array of challenges that distinguish their experiences from those in pre-pandemic times (Jean-Dit-Pannel and Belot, 2023). The health crisis has imposed limitations on fathers' involvement in important prenatal events, such as attending ultrasounds or being present at their child's birth, owing to hospital restrictions to limit the spread of the virus (Fonseca et al., 2023). Fathers, for example, have faced additional anxieties due to restrictions that might have prevented them from being present at prenatal appointments, delivery, and in the immediate postnatal period, significantly impacting their fatherhood experiences (Fonseca et al., 2023). The heightened risk of infection and its potential implications for the family's health introduce an added layer of stress, which may have affected the quality of father-child interactions (Adama et al., 2022; Koliouli et al., 2024). Paternal parenting stress has been linked to higher anxiety levels during the pandemic, and this was particularly pronounced in areas with higher contagion rates, reflecting a direct impact on the father's psychological well-being and the father-child relationship. This complex situation underscores the need for a responsive support system to assist new parents in managing these added stressors and to help safeguard their mental health during unprecedented times (Caporali et al., 2020; Adama et al., 2022). This has potentially hindered early opportunities to bond with their children and actively participate in the initial stages of caregiving. Moreover, expectant fathers might have had to experience the birth and early moments of their infant's life via technological means rather than in person, altering the traditional first experiences with their newborns (Jean-Dit-Panell et al., 2024). The resulting impact on first-time fathers ranges from increased stress and anxiety to feelings of disenfranchisement in parenting roles. Despite these difficulties, some fathers have found new ways to engage by being more present at home, assisting with remote learning, and spending quality time fostering their children's independence, resilience, and educational involvement (Fonseca et al., 2023). Such adaptations demonstrate the complex interplay between the challenging circumstances imposed by the pandemic and resilient responses that fatherhood can evoke.

Furthermore, the French NICUs varied in terms of imposed sanitary restrictions (Adama et al., 2022; Koliouli et al., 2024). However, they were mostly supportive about parents providing kangaroo care even during the COVID-19 period. Parents were involved in most caregiving practice, skin-to-skin contact included. It appears that the survival benefit of Kangaroo Mother Care far outweighs the small risk of death due to COVID-19. According to Minckas et al. (2021) the worst-case scenario of little probability (100% transmission in the NICU) could result in 1,950 neonatal deaths from COVID-19. Conversely, 125,680 neonatal lives could be saved with universal KMC coverage. In the same line, Kangaroo Father Care (KFC) may promote bonding of fathers with their infants and make them feel less stressed (Chavan et al., 2023).

To date, few studies have investigated the intricacies of becoming a first -time father of preterm infant, and this from a qualitative perspective (Benzies and Magill-Evans, 2015). To the best of knowledge, this is a first attempt to explore the singular context of the COVID-19 pandemic.

The aim of this paper is to delve into the emotional and psychological challenges that first-time fathers face as they navigate the complexities of having a preterm infant in the NICU and in an unprecedented sanitary context.

Research design

Given the decrease in preterm births during the first wave of the pandemic in France (Fresson et al., 2022), we chose the case study approach to explore and better understand this phenomenon, that is the experiences of first-time fathers in a dually complex contexts: experiencing premature birth and the COVID-19 lockdown restrictions. These cumulative unique life conditions draw a unique context that a case study approach is suitable as method. We used the interpretative case study approach (Stake, 1995), which focuses on understanding the subjective and interpretative aspects of the research subject, often by delving deeply into selected cases. Interpretative case studies aim to grasp the meanings that participants attribute to their experiences and understand how those meanings influence their behavior. Finally, we undertook an instrumental case study (in terms of participants) which uses a particular case to gain a broader appreciation of an issue or phenomenon (Stake, 1995; Crowe et al., 2011).

Methods

Participants

Two fathers of premature newborns met in 10 months of the infants' corrected age have participated to the study protocol.

Paul is 25 years old, he is a healthcare professional and has been in couple with his spouse for 10 years. Their baby boy was born in May 2020 at 34 weeks of amenorrhea (SA), a month and a half "too early." This birth is medically qualified as "late prematurity." Pregnancy occurred during the first lockdown. Due to this profession, he has been physically distanced from his pregnant spouse because of the risks linked to COVID-19 ("*not really knowing the risks there were with COVID-19 situation*"). Moreover, no warning signs of premature birth were observed: the pregnancy went well, and premature delivery had occurred a week after the couple's reunion and was a surprise for both parents ("*we did not expect it at all*"). The duration of hospitalization was 1 month.

Franck is 31 years old, he is an Information Technology (IT) service manager in his branch. Franck and his spouse have confronted several challenges to conceive their child. Franck did not precise whether it was an IVF, but it took them 3 years to conceive. The pregnancy also occurred during the first lockdown and the couple did not experience any cumulative separations except for the time of birth. Their twin boys were born in June 2020 at 26 weeks of amenorrhea (SA), which is qualified as "extremely premature." Franck was also the first parent who engaged in skin-to-skin practice (before the mother). They experienced 157 days of hospitalization in hospital and 2 months of neonatal care at home (providing home medical and paramedical care depending on the evolution of the baby's health).[1]

The experienced restrictions that these NICUs imposed were as per the extended family visitations: parents could practice skin-to-skin freely and get involved in caregiving practices.

Data collection

We used three data collection methods such as interviews (an interview narrative and the Clinical Interview for parents of High-risk infants) and the Edinburgh Postnatal Depression Scale to gain a comprehensive understanding of the case.

Narrative interview

The unstructured interviews began with a simple question, designed to be as broad as possible to encourage a free discussion: "Would you like to tell me about your transition to fatherhood, your experience of becoming a father of a premature newborn?" We deliberately chose to stress the experience of becoming a father before invoking the COVID-19 pandemic. Following the non-directive nature of the narrative interviews, we respected the silences of the participants, and the prompt questions were used to further develop their narratives (i.e., "*Could you please further explain? Could you give us an example? "What do you mean by this*?").

Clinical interview for parents of high-risk infants

The Clinical Interview for Parents of High-risk Infants (CLIP) (Meyer et al., 1993) is a semi-structured interview that explores the relationship of parents with the healthcare team on the one hand and with the family on the other hand, and the provided social support. In our study, we used a version adapted for parents of premature babies (Meyer et al., 1993). This tool can detect both the psychological situation of the parents (their needs, fears, etc.) and can also constitute a means of managing these difficult experiences for the parents. In other words, parents can express themselves through open questions about their experiences in the neonatology unit. This semi-structured interview explored the following axes:

A. Infant's current condition: further explore how the father perceives his baby's condition. The description of the baby's condition aims to introduce a more emotional aspect and goes beyond a simple collection of medical information, namely possible respiratory problems, breastfeeding etc.
B. Course of pregnancy: The description of the pregnancy course depends on the sensitivity of the father towards his partner, but also on his involvement from the beginning of the pregnancy.
C. Labor and delivery: This section refers to the presence of the father during labor and whether he was the first to meet the newborn.
D. Relationship with the baby and feelings as a parent: This section covers the first paternal feelings when first meeting his baby.
E. Reaction to the Intensive Care Nursery and Relationships with Staff: The purpose of this group of questions covers reactions towards the medical equipment of the unit and its relationships with healthcare. Thus, fathers were asked to identify the sources of perceived stress and the most supportive persons around them.
F. Relationship with Family and Social Support: Explore the perceived support sources among family and friends.
G. Discharge and beyond: In the section, we tried to explore paternal reflections about the future through projections as a father.

1 In France, neonatal home care has advanced in response to familial demands and is part of the evolution of neonatology towards family-centered care. Infants who are not yet mature and need neonatal care, like feeding through tubes, can continue to receive hospital care at home, with the help of specialized teams in collaboration with a neonatology unit (Montjaux-Régis et al., 2023).

Edinburgh postnatal depression scale

The Edinburgh Postnatal Depression Scale (EPDS), originally developed by Cox et al. (1987), contains 10 items with four response options, each rated 0–3. EPDS is a self-administered screening tool that is used to evaluate postpartum depression. Thus, the range is 0–30 points, with higher scores indicating more depressive symptoms. The EPDS asks if, during the last 7 days, the respondent had been able to laugh/see the funny side of things, looked forward to things with enjoyment, blamed oneself unnecessarily when things went wrong, been anxious or worried for no good reason, felt scared or panicky for no good reason, felt that things had been "getting on top" [of the respondent], had been so unhappy that it had been difficult to sleep, had felt sad or miserable, had been so unhappy that [the respondent] had been crying, and if the thought of harming oneself had occurred to the respondent. The EPDS has also been validated for fathers by Matthey et al. (2001), who demonstrated that a score of 9/10 or more was optimal for the detection of minor and/or major depression, with a sensitivity of 71.4%, a specificity of 93.8%, and a positive predictive value of 29.4% (Carlberg et al., 2018). We used the French validation by Guedeney and Fermanian (1998) and Adouard et al. (2005).

Procedure

Fathers were invited via websites and social media platforms and through the SOS Préma support organization for NICU parents in France. We expected to recruit more fathers, however solely two fathers accepted to participate.

The study protocol (interviews and EPDS) was conducted when every newborn was at 10 months of corrected age. The whole procedure was recorded for transcription, and the duration was approximatively 1 h and a half. Participants responded firstly at the narrative interview and then at the CLIP. Finally, they completed the EPDS. It is important to note that the interviews conducted in French were translated into English by the third author after the analysis and then verified by the other two authors. As noted by Temple and Young (2004), the act of translation must be acknowledged, as the researcher's sociocultural positioning is inextricably linked to the interpretation of the findings.

Data analysis

An interpretative phenomenological approach was employed with the data analyzed as follows (Smith et al., 1999). Initially, the transcripts were read and re-read several times to obtain a holistic picture of each participant's narrative. During this process, the first researcher made unfocused notes related to anything within the text that appeared interesting or significant. Following this, the transcripts were examined further, and conceptual themes were created to capture the essence of the participant's account. The emergent themes were listed, and connected themes were sought, with those related to being clustered under appropriate superordinate conceptual headings. During this data organization process, all three researchers continuously referred to the transcripts to ensure that the themes selected were representative of the participant's accounts. Themes should reflect the most salient meanings within the participants' narratives. The resultant framework, consisting of emergent experiential and psychological clusters, was used to facilitate the production of the written analysis. The iterative process continued throughout the analysis to ensure that the data were appropriately represented. In addition, an independent 'auditor' checked whether interpretations are warranted against the data. These validation criteria were adhered to in this study.

We used a phenomenological approach to focus on the lived experiences, so we followed an inductive data analysis method. However, an essential component of methodological rigor in qualitative analysis is reflexivity (Malterud, 2001) in order to being aware of our own position in producing research. In this study, all three researchers are trained psychologists in psychoanalytic/psychodynamic approaches. The study protocol was done by one researcher, so we acknowledge that collected data are dependent on the interviewer's questions and prompts (Sale, 2022). Furthermore, the data conceptualization may have been influenced by this clinical analytic process.

Ethical considerations

The study was conducted in accordance with the local legislation and institutional requirements (Department of Psychology of the University of Franche-Comté, in France). The participants provided their written informed consent to participate in this study, before the data collection procedure started. Due to the constraints posed by the ongoing pandemic, researchers secured digital letters of permission with affixed e-signatures from the participants. The participants were further verbally asked if they consented to be interviewed during the scheduled interview date. Participants were encouraged to narrate their experiences freely and honestly in response to questions. They were also given the discretion to refuse to answer a question or cease participating at any time if they wished to do so. Furthermore, considering the sensitive nature of this research, the participants were allowed to contact a trained psychologist who conducted the interviews. Finally, all names were pseudonymized to safeguard participants' anonymity.

Findings

The following analysis explores two individuals' personal experiences of becoming a first-time father during the first wave of the COVID-19 pandemic through a close examination of two superordinate themes. The first one is named "A series of separations through the experienced COVID- 19 restrictions," and the second one "Moments of connection." The first theme details the restrictions experienced on different levels of transition to fatherhood, and the second delves into the moments that connected fathers with their experienced fatherhood and the lasting latent psychoemotional implications of this period. For ease of explanation, the two themes were presented separately, although there were several interrelated elements.

A series of separations through the experienced COVID-19 restrictions

Experienced separation during pregnancy and psychoemotional reactions

Paul largely expressed that the pandemic had a strong impact on the course of the pregnancy because he was not able to experience it with his wife fully. More specifically, Paul claims that the fact of not being physically with his wife and not observing her body changing has complexified his transition to being a father.

> "*We spent a lot of time alone, away from each other, and I spent a lot of time of this pregnancy alone too, so we didn't see each other much and it was after the end of this first lockdown when she came back. So, we did not really enjoy the pregnancy together... She actually went into labor a week after she had returned to our home.*" Paul explained that his spouse was off to the parents' house to protect herself and the future infant from the COVID-19 risks "*Euh, so uh not knowing too much about the risks involved with covid in fact she, she went back to live with her parents in fact during the period when I was working.*"

Paul pointed out that he felt excluded from the course of pregnancy because of his profession (being confronted day-to-day with the COVID-19 virus) that prevented him to fully experience it. Despite his work status (that is being a healthcare professional), Paul experienced feelings of helplessness and frustration as he could not be actively involved during his spouse's pregnancy in terms of prenatal screenings and preparations.

> "*The fact of experiencing this pregnancy from afar, without being able to participate, and without having the impression that I was actively involved in this moment, it was complicated. I mean, I do have any memories of it, because I was not there* (laughs)!"

The COVID-19 context seems to have played an important role in Paul's narrative. He graphically expressed that the sanitary crisis had a strong impact on this pregnancy, as he was not able to fully experience it with his wife. He also wondered whether this context was not a potential cause of prematurity given the perceived stress during that period: "*Would the pregnancy have gone more smoothly, would it have gone further, would it have gone better, would things have been different? Was it the overall stress of pregnancy related to this covid period that was complicated? we'll never know! It certainly leaves a little taste of unfinished business (laughs).*"

Franck was neither present at prenatal screening. His narrative differs from that of the previous one. At the first appointment, their doctor (gynecologist) was 3 h later; Franck was unable to stay as he had to return to work, thinking that he would be able to attend many more ultrasound examinations afterward. Unfortunately, strict restriction measures were applied, and he was no longer able to attend. The healthcare professionals sent video recaps of the ultrasounds and prenatal screening, which further enhanced his experience of disconnection.

> "*Small disappointment this COVID-19 situation [meaning in the way that he experienced his spouse's pregnancy] because it was the first lockdown which means that it was not to join the mom to the various exams, ultrasound. In fact, strangely enough, it's frustration I am feeling today because at the time I was saying to myself: "Well, as long as everything's going well….*"

At 22 SA, the future parents rushed to the emergency room when one of the amniotic sacs ruptured. Unfortunately, Franck was unable to join his spouse because of hospital restrictions. Franck's spouse remained in the hospital for 5 days without any authorized visitors, including Franck.

> "*Uh so there too uh moment of fear and frustration because I'm dropping my wife off at the emergency entrances […] I couldn't go with her…. The restriction would not let me join her, so she stays, she and the babies for five days in the high-risk pregnancy section, with no visits, no way to see each other, no way to comfort her, and no way to support her. uh, so that was the first shock of having to abandon her to ... and seeing her from the forecourt, outside the hospital.*"

In his narratives, Franck unraveled fear, a sense of helplessness, and frustration. Indeed, several separations and disconnections before labor and delivery are noted: for instance, the 3 years to conceive, the 5 days of high-risk pregnancy hospitalization… "*there was no support or soever to be with my spouse for prenatal screening and examinations*," "*ultrasounds*," or even being able to "*attend childbirth preparation courses*."

Newborn's hospitalization and suspended paternal identity

Paul's son spent a short time in the intensive care unit and then joined the neonatal unit. He stayed there for a month and a half. During this time, Paul found it difficult to assume his new identity as father. The constant uncertainty, coupled with anxiety and the stressful experiences of the labor, here experienced as a traumatic event, also made this entry into fatherhood complicated.

> "*So, it's clear that for the first few weeks I did not really... it was complicated to get it into my head that I was a dad and that Simon had arrived.*"

As for Franck, he reminisces, relieved, the first night when his boys were born: "*during the night, it was like they tried [healthcare team] to make room for the boys*," thus providing additional space to accommodate their twins. Two hours later, they were invited to visit their children to the pediatric intensive care unit. They were shocked and stayed only 10 min: "*We're in for a phenomenal slap in the face*." The medical equipment (screens, syringes, and tubes) around his boys were unbearable to both Franck and his spouse.

> "*We see our little ones, who don't look like babies as you might imagine... They look red and are intubated, probed, and monitored. They are no more than 30 centimeters long, er... 800 grams*". Franck's wording illustrates that he has been traumatized by the medical environment.

He also pointed out that he would feel his "first feeling as a father," as he described it: "*my first paternal emotion, well, I felt like a day after their birth*." Moreover, Franck shared his first reflections on realizing that he was a father. Despite the challenges and dark thoughts that may have occurred, he was motivated to be closely present to his twins. "*And then I said to myself ... you are a dad, you have got your boys, you have got to go. And then I go back to see the kids and uh, pretty dark thoughts. (nervous laughter) I have to take care of them*." He became emotional when he verbalized the worst scenario of his newborns' hospitalization: "*If they live 3–4 days, then even for 3–4 days they need a dad. Erm...so I stay there, I do not know how long either, but a long, long time*."

It seems that paternal identity in the context of premature birth is somewhat suspended: the medicalized context impedes their transition to fatherhood because they are primarily focused on newborns' health issues, survival, and well-being. This results in a paternal preoccupation that prevents them from fully experiencing their paternal identity, as if it is on pause, waiting to see if their babies will survive. "*Looking back now, what we have been through, it is very emotional, you know*" (Franck).

Moments of connection

Labor and delivery: questions about life and death

Paul expressed his vivid memories of the moments before his spouse's labor. Firstly, he recalled the moment when the "water broke" and had to drive his spouse to the hospital. He was in complete confusion and uncertainty, stating that he was afraid for his son's life. He relates that his anxiety was linked to the uncertainty of the baby's state of health and that it was still "too early" for him to be born.

> "*So, it's still something magical... and at the same time it's a huge stress because we don't know: is he going to have after-effects uh is he uh going to survive uh is he going to be okay, is he uh and the problem is that until he arrives and until he's been examined uh we can't know... Uh so uh that, so yes we'll say that a moment, it's a fuzzy moment where we don't really know where we are, emotionally we're neither happy nor not happy uh and here we are navigating we're navigating between these two states constantly*"

Paul was present in the delivery room thanks to a midwife who decided to let him in. He had anticipated not being able to attend, so his presence was experienced as a chance, even a privilege. Despite Paul being a healthcare professional, he was very worried and stressed after the birth of his son because he manifested pulmonary difficulties.

Franck had also attended at his children's birth. He described it as "*anxious*" due to the presence of numerous resuscitators. Their newborns were intubated directly, and Franck stated that "*This is not how you imagine the birth of your child.*" He described in detail the delivery process that was stressful and challenging as their newborns were resuscitated.

> "*Well, between the birth of L and T… On one side, I could see my wife preparing to give birth to T, while on the other side, in a separate room with an open door, I could see them giving L his initial treatments. However, these were not his first treatments, as the initial care should involve cleaning and aspiration of the nose. We cleaned him up and provided the necessary resuscitation care. And, trust me, nobody is prepared for this…*"

It seems that both fathers experienced the delivery process as both magical and stressful at the same time. On one hand, there's a sense of awe and wonder, but on the other hand, there's uncertainty and anxiety about whether the newborns will experience any negative consequences, whether they will survive, and whether they will be healthy. The uncertainty that resides did not let these fathers to fully relate to the positive emotions.

Skin-to-skin and caregiving practices: fighting against detachment

Paul described that he followed his son in the NICU and he started skin-to-skin practice since day one. Paul felt that the first bond was formed through the physical contact and interaction. However, he encountered challenges in finding his place as father and played an active role in the caregiving process.

> "*It is true that we were lucky to be able to do skin-to-skin very quickly […] So, uh that was really good, it allowed us to have a real sharing contact with him right away. It is true that the nurses and pediatricians at the hospital in X (name of the town) were very supportive.*"

However, Paul experienced feelings of dispossession due to the continuous and invasive presence of both the medical staff and equipment around his son.

> "*During the ICU period, uh, after neonatal care less so, but on the other hand, it is true that in the ICU period, yes, there is so much, there is so much equipment around. […] There are so many people constantly coming to look after him that it's almost as if we are doing nothing, apart from skin-to-skin contact and trying to feed him a little from time to time when they suggest it, the rest of the time we feel like we are doing nothing. It's like being a spectator and waiting for things to unravel*"

Skin-to-skin contact and feeding the newborn were among the caregiving activities that initiated these new fathers into parenthood. Franck also participated in his child's first bath, as he described, although they had their "firsts" in the NICU, it was under exceptional conditions. "I *fed my son his first bottle using a syringe, but it was still my first bottle (smiling). The first bath was also under special conditions because he could not be separated from his breathing machine for too long, which is normal*." Franck was involved in the caregiving process, and he felt that it made him truly feel like a father. The first experiences of these fathers have a unique quality because there are several safety precautions to consider that they can cause anxiety and apprehension, enhancing the "medicalized" sense of fatherhood.

Franck also shared his experiences with the supportive role of healthcare professionals in caregiving. For instance, he was not feeling capable of having skin-to-skin on his own. Thus, the first physical contact between Franck and his twins was enabled by the healthcare staff. He described vividly that "*they did not have any reaction at first […] you have to imagine, they were under morphine […] They must be physically shocked too*." Franck exhibited active empathy towards his newborns, talking more about how they would feel instead of himself, thus enhancing his connection to them.

Nevertheless, he expressed feelings of guilt without specifying whether they were about his partner and/or twins. "*I had to stay 3–4 h with the boys and then I say to myself, I have to go check on the mom too... Since I cannot find her on the phone at all, I must go and check her. So, here we were, returning to the NICU with their mother, well it's just as complicated, but uh... It is even more complicated because of guilt*."

In his narratives, we witnessed a conflict that involved an internal struggle between Franck's real and imagined worries regarding his spouse and their twins, which had an impact on the quantity and quality of their interactions with the baby. Despite the moments of connection experienced during caregiving practices, Franck also tried to connect his twins with their mothers, build bridges, and fight against disconnections and disruptions (Gaudron et al., 2016).

> "*[A piece of advice for parents] is to spend time with their child, to create a different bond, but to create it quickly, through skin-to-skin contact, caresses, caregiving, [in prematurity] it's not an encounter as we may have in mind, but it's still an encounter with our child*."

Reflecting on perinatal experiences: the importance of temporality

In terms of temporality, we explore the changes in their experiences over time and in relation to the dynamic relationship between fathers, their infants, and spouses. Both fathers have completed the self-administered EPDS scale at 1012 months of corrected age of their newborns. Paul obtained 13 and rated very high the item that "he very often felt worried or worried without reason." Franck, on the other hand, had obtained 12 (see Table 1). These scores indicate an increased risk for postnatal depression and anxiety for up to approximately one year following the premature birth.

Reflecting on their perinatal experiences, Paul felt that it was no longer possible to state whether his son was born prematurely, meaning that his development was typical. However, he confided that he was still worried about his son's state of health and the fear of an eventual disability that has not been still manifested, even though he is currently developing well.

> "*It's difficult to remain calm… Every beginning, everything has been difficult and challenging so far… […] We are still worried about him […] maybe because of his fragility [being born prematurely]*"

During the interviews, these fears and worries about his son's long-term development are merged with the COVID-19 health worries. We might hypothesize that Paul encountered "psychoemotional residuals" in terms of obsessive, phobic, and hypochondriacal tendencies, translated by his fear of contamination, but also his fear of illness at the slightest sign in his child.

> "*Because of being born prematurely, so now every time who has anything I see that he is a little sick every time, we always put a brake on ourselves and we doubt and we say to ourselves is it going to be okay is it not serious is this and.. we think back to all these moments and we say to ourselves ah pff I hope it's not okay, it's not going to get worse. So, there's already that, I think it's difficult, it must not be difficult for parents of non-premature children, but having a premie, I think it brings even more anxiety*"

In the same line, Franck conveyed his concerns about the developmental outcomes and the emotional burden he had experienced. More specifically, the prospect of having a child with developmental delays or disabilities is a topic that really worried Franck.

> "*We know that we will have an impact on T but that we will not have a serious handicap. The possibility of having a child with a delay or a handicap that… it's something that's coming back strongly now*."

In his case, both twins had experienced hemorrhages that could possibly have an impact in their future development. Franck's worries are linked to the current health condition of his two infants. "L*, has fully reabsorbed the hemorrhage, while T had two hemorrhages in distinct locations. T has successfully reabsorbed the first hemorrhage, but still has small lesions in the parenchyma. Compared to the first images, which showed significant reabsorption, the reabsorption of the first hemorrhage is still very well-managed*." Franck has used a quite medical terminology to fully explain his infants' health condition, which is common among fathers of premature infants (Koliouli et al., 2016a). "*According to the current outlook, it will be approximately 2–3 years before we see any progress. The condition known as leukomalacia [that T has been diagnosed with] is constantly on my mind, and I must think about it numerous times each day*."

The fathers, having discussed the challenges their infants may face in the future, made a concerted effort to focus on the positive aspects of their development and to be more attentive to their current needs.

> "*He does so many things that, it's, it's a wonder every day, even if at times afterwards it's a lot of anxiety or sometimes for other things but it's still quite magical*" (Paul)
>
> "*Well now they're progressing at their own pace, at different rates for each other, but… they're making progress. At that moment, well, they are in the top form (smiles)…! […] both our children are miracles, according to the doctors*." (Franck)

Descriptive analysis of the EPDS

Paul obtained a total score of 13 when he completed this self-questionnaire 10 months and 10 days after the premature birth of his child born on May 31, 2020, during the covid-19 health crisis, at 34 weeks' amenorrhea.

Franck's scores on the EPDS scale were 12 when he completed this self-questionnaire 10 months and 11 days after the premature birth of his twins, born on June 30, 2020, during the covid-19 health crisis, at 26 weeks of amenorrhea (see Table 1).

We can observe four common responses from both fathers (Items 2, 6, 7, and 10):

TABLE 1 Description of EPDS scores.

Items			*Paul's scores*	*Franck's scores*
1. I have been able to laugh and see the funny side of things:	As much as I always could	0		
	Not quite so much now	1	1	
	Definitely not so much now	2		2
	Not at all	3		
2. I have looked forward with enjoyment to things:	As much as I ever did	0		
	Rather less than I used to	1	1	1
	Definitely less than I used to	2		
	Hardly at all	3		
3. I have blamed myself unnecessarily when things went wrong:	No, never	0		0
	Not very often	1		
	Yes, some of the time	2	2	
	Yes, most of the time	3		
4. I have been anxious or worried for no good reason	No, not at all	0		
	Hardly ever	1		
	Yes, sometimes	2		2
	Yes, very often	3	3	
5. I have felt scared or panicky for no good reason	Yes, quite a lot	3		
	Yes, sometimes	2	2	
	No, not much	1		1
	No, not at all	0		
6. Things have been getting to me	Yes, most of the time I have not been able to cope at all	3		
	Yes, sometimes I have not been coping as well as usual	2		
	No, most of the time I have coped quite well	1	1	1
	No, I have been coping as well as ever	0		
7. I have been so unhappy that I have had difficulty sleeping	Yes, most of the time	3		
	Yes, sometimes	2	2	2
	No, not very often	1		
	No, not at all	0		
8. I have felt sad or miserable	Yes, most of the time	3		
	Yes, quite often	2		2
	Not very often	1	1	
	No, not at all	0		
9. I have been so unhappy that I have been crying	Yes, most of the time	3		
	Yes, quite often	2		
	Only occasionally	1		1
	No, never	0	0	
10. The thought of harming myself has occurred to me	Yes, quite often	3		
	Sometimes	2		
	Hardly ever	1		
	Never	0	0	0
Total score			13	12

– These fathers felt less confident and joyful than usual when thinking about their futures (Item 2).
– They were able to cope with most of the events (itemtem.6);
– Sometimes, they felt so unhappy that they had trouble sleeping (Item7);
– They never thought of hurting them. (Item 10).

There was only one rating of three for Paul (4-I felt worried or concerned for no reason: yes, very often (3)).

Discussion

The aim of this study was to explore the experienced psycho-emotional challenges first-time fathers face as they navigate the complexities of having a preterm infant in the NICU and during an unprecedented sanitary context by using interpretative case study approach. The major themes that were identified offer an insight in the experiences of first-time fathers during the pandemic which were full of separations and moments of connection. The first theme is focused on the series of separations through the experienced COVID- 19 restrictions, and the second one on the "Moments of connection." However, when taking into account the temporality dimension, the different subthemes are intrinsically interrelated one to another.

More specifically, the two fathers identified several events of separations and disconnections during pregnancy which generated dysphoric emotions. For Paul, separation during his spouse's pregnancy was devastating, as he was unable to be physically present during prenatal appointments and other important milestones. COVID-19 restrictions further exacerbated his feelings of helplessness and isolation. Franck also experienced a profound sense of loss and disconnection due to the restrictions. He had only had the experience of a virtual view of his spouse's pregnancy, which, in our opinion, amplified the virtual nature of this pregnancy and his difficulty in materializing her children. Paternal experienced exclusion produces feelings of isolation, and a sense of loss, along with a disconnection from the pregnancy, is also found in existing research (Andrews et al., 2022; Poulos et al., 2022).

The medical context prioritizes the newborn's health, survival, and well-being and may divert the attention of fathers from their transition into fatherhood. Both fathers highlighted their constant uncertainty, intense worry, and challenges in interacting with newborns. These narratives align with previous research findings with larger sample sizes (Lasiuk et al., 2013; Koliouli et al., 2016a). Additionally, we uncovered fathers' nuanced concerns, preoccupations, and dark thoughts surrounding their newborns' hospitalization. It is important to recognize that when infants are hospitalized, fathers are unable to fully embrace their roles or establish their own new identity.

This series of separations have introduced additional challenges in the construction of their primipaternal identity, as they often oscillated between feelings of joy and intense worry. These fathers were initially worried about their newborns' survival and had experienced a brutal delivery process followed by their infants' long-term hospitalization. Thus, their primipaternal identity during this important phase of their transition to fatherhood is intrinsically associated with a medicalized form of connection with their newborn. This suggests a novel aspect of paternal experience in the context of premature births, as fathers are largely preoccupied by the medical assistance and follow-ups that their newborns need and, at the same time, consist of an essential part of their relationship with their newborn. In existing research, first-time fathers' experiences have mostly been viewed in the context of full-term births (Fonseca et al., 2023), not considering the additional disruptions and sources of anxiety that a premature birth holds.

The second theme, "Moments of connection," highlighted the importance of small interactions and bonding opportunities between fathers and preterm infants in the NICU. For both Paul and Franck, labor and delivery were the first moments of connection with their children. In the current literature, paternal presence during labor and delivery empowers their paternal role, increases positive feelings about fatherhood and birth, and improves maternal attitudes towards the father (Sapountzi-Krepia et al., 2015; Smith et al., 2024). However, in the context of premature birth, feelings of joy were mixed with increased stress and anxiety as our participants' newborns were transferred to intensive care. Despite the stressful and traumatic aspect, it seems that early paternal presence empowered Paul and Franck, as they could actively support their spouse and share this unique experience after a series of separations.

Skin-to-skin contact was experienced as an active way to bond and connect with their child during the restrictive measures that separated them during pregnancy. These moments provided a sense of purpose and connection for both fathers, allowing them to feel involved in their child's care and development despite challenging circumstances. Although there is little research on paternal skin-to-skin in the COVID-19 context, the existing literature suggests that paternal skin-to-skin reduces anxiety and depression in fathers and facilitates their role attainment (Olsson et al., 2017; Huang et al., 2019; Koliouli et al., 2022). However, due to the COVID-19 pandemic and the associated restrictions in hospitals, parents have faced challenges in engaging with skin-to-skin (Saus-Ortega, 2023), affecting their emotional well-being (Adama et al., 2022). It seems however that in the French NICU where the fathers of our sample had their newborns hospitalized acknowledged the importance of the kangaroo care even in pandemic times (Minckas et al., 2021).

Intersubjective temporality refers to the shared understanding of time between individuals in a social context (Rodemeyer, 2006). Through this shared comprehension of time, people are able to align their actions and perceptions within a group or community. We assumed that this concept can be applied to the transition to fatherhood by exploring how a father's experiences and perceptions about their newborn evolves as he assumes the role of the caregiver. In this case study, it is translated through the growing presence of fathers in the caregiving process. The concept of "psycho-emotional residuals" encompasses persistent and enduring anxieties and apprehensions that originate during childbirth and continue to evolve in accordance with the health status of the infant. Drawing on our knowledge of psychoemotional residuals, we might surmise that both fathers grappled with obsessive, phobic, and hypochondriacal tendencies, which manifested in fear of contamination and anxiety over their infants' health conditions (Kernberg, 2004). In a psychoanalytic approach, obsessive, phobic, and hypochondriacal tendencies are often linked to underlying psychological conflicts and unresolved issues (Kernberg, 2004). These tendencies can be seen as defense mechanisms that individuals use to cope with unconscious anxiety and fear. Fon instance, a person with hypochondriacal tendencies may constantly worry about their health and seek reassurance from others because of underlying fears of illness or death (Nissen, 2018). Moreover, these traits were accompanied by the risk of increased symptoms of post-partum depression, as the EPDS scores suggest. Paul and Franck obtained high scores that indicate an early onset of intense worry, anxiety and possible depressive symptoms. Paternal early post-partum depression signs are often overlooked during the perinatal period (Eddy et al., 2019; Wang et al., 2021), particularly in the context of premature birth.

Limitations

Our study focused on participants' subjective experiences during the first antenatal period to understand them at a specific time and place. The data collection was conducted on one session with the fathers. Thus, it would be interesting to explore lived experiences from a longitudinal perspective, and further systematic, prospective analysis on paternal lived experiences is needed. Furthermore, some methodological concerns may be pointed out: the small sample of two fathers may be restrictive and we did expect to have more participants enrolled. Nevertheless, in a case study approach, the focus is on the phenomenon rather than the number of participants (Stake, 1995; Crowe et al., 2011). Moreover, we acknowledge that a case study can largely rely on the researcher's interpretation and selection of data, thus contributing to the "researcher's bias." Nonetheless, we managed data triangulation through different sets of data collection and ensured overall supervision by experienced researchers. Another limitation might be the exclusive focus of the paternal perspective on their experiences of psycho-emotional challenges in becoming first-time fathers of premature newborns during the pandemic period. Given that meaning and experiences are co-constructed (Smith et al., 1999), it is worth considering the perspectives and lived experiences of the father's spouse and extended family as active participants in the construction of fatherhood experience. Last but not least, EPDS is a very sensitive questionnaire and results could be influenced by the moment of administration. Furthermore, accumulating research evidence shows that EPDS might not be the best suited tool to assess the risk of depression in fathers (Matthey et al., 2001; Baldoni and Giannotti, 2020; Walsh et al., 2020) and different set of self-reported questionnaires should be used to better assess the early onset signs of anxiety and/or depression among fathers.

Future research and implications for practice

Transitioning to fatherhood and fathers' mental health in perinatal settings, including premature birth, is underrepresented in research. Therefore, further research should be conducted on these subjects, and future research should focus on issues of grief and loss in perinatal settings and on the importance of moments of connection.

Our study also highlights the importance of early involvement in caregiving processes for fathers, to enable their experienced transition to fatherhood, especially in the context of premature birth. Skin-to-skin contact (which has been explored in existing literature) was practiced during the pandemic period and, as highlighted in our results, provided a sense of connection to the newborn and to the new role as a father. Thus, NICUs should consider undisrupted involvement in caregiving during premature birth, which further enhances the early bonding between the father and newborn.

From a preventive perspective, the EPDS scale is a simple tool that can provide healthcare professionals with information about the risk of anxiety and depression symptoms in NICU parents.

Conclusion

It is important to understand the fathers' unique experiences and the need to provide appropriate support during this challenging period. This case study contributes to the existing literature by exploring the range of experiences of fathers with preterm infants in the neonatal intensive care unit and during their transition to home. It examines psychosocial implications, such as stress and anxiety related to a fragile newborn and the uncertainty of the infant's health and development. Furthermore, this study extends its focus to the transition period when the preterm infant is discharged from the NICU and the family returns home. It delves into the challenges that fathers encounter during this transition, such as adjusting to new caregiving responsibilities, managing the financial burden of medical expenses, and coping with the infant's ongoing medical needs. By shedding light on the multifaceted experiences of fathers with preterm infants, this case study sought to provide valuable insights for healthcare professionals, policymakers, and support organizations to develop more comprehensive and effective support systems for fathers in similar situations.

This research not only highlights the importance of including fathers in the discourse on preterm infant care but also advocates for tailored interventions that address the specific needs of fathers during this challenging period. Specifically, recommendations are provided to enhance the involvement of fathers in the NICU and at home, emphasizing the promotion of father-infant relationships (Baldoni et al., 2021). These recommendations address the need for health care professionals to acknowledge and support fathers' emotional well-being, provide education and resources on infant care, involve fathers in decision-making processes, and establish support networks for fathers of preterm infants (Stefana et al., 2022; Bréhat et al., 2024).

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

RJ-D-P: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. CD: Conceptualization, Investigation, Methodology, Visualization, Writing – original draft. FK: Conceptualization, Formal analysis, Funding acquisition, Methodology, Resources, Supervision, Validation, Visualization, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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EDITED BY
Livio Provenzi,
University of Pavia, Italy

REVIEWED BY
Laura Cordolcini,
Eugenio Medea (IRCCS), Italy
Flora Koliouli,
Aristotle University of Thessaloniki, Greece

*CORRESPONDENCE
Marika Leppänen
✉ marika.leppanen@utu.fi

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Early psychosocial parent–infant interventions and parent–infant relationships after preterm birth–a scoping review

Marika Leppänen[1]*, Riikka Korja[2], Päivi Rautava[3] and Sari Ahlqvist-Björkroth[4]

[1]Department of Psychiatry and Public Health, University of Turku and Turku University Hospital, Turku, Finland, [2]Department of Psychology, University of Turku, Turku, Finland, [3]Department of Public Health, University of Turku, and Research Services, Turku University Hospital, Turku, Finland, [4]Department of Clinical Medicine, Turku University Hospital, Turku, Finland

Objective: Early psychosocial interventions for preterm infants and their parents are diverse. This study aimed to structure the knowledge on psychosocial parent–infant interventions and to identify gaps in the intervention studies.

Methods: We included studies on early (during first year of life) psychosocial parent–infant interventions with parent–infant relationship outcomes after preterm birth (< 37 weeks). We excluded studies that did not focus on preterm infants, failed to indicate the studied intervention and outcomes, were not written in English, were not controlled or peer-reviewed studies, or did not provide essential information for eligibility. The search included studies published between January 2000 and March 2024 in PubMed and PsycINFO. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed in reporting. Psychosocial parent–infant intervention studies were classified adapting the International Classification of Health Interventions (ICHI) and the Template for Intervention Description and Replication (TIDieR).

Results: The included 22 studies reported data from 18 different interventions with preterm infants (< 37 weeks). Studies excluded preterm infants with health risks (19/22, 86%), with very low gestational age and/or birth weight (7/22, 32%), and/or mothers with psychosocial risks (14/22, 64%). Of the 18 interventions, 12 (67%) were classified as counseling, 3 (17%) as emotional support, 2 (11%) as psychotherapeutic, and 1 (6%) as educational. The parent–child relationship was assessed using 30 different methods and varying time points up to 18 months of age. Most studies (17/22, 77%) reported positive changes in the parent–child relationship favoring the intervention group.

Conclusion: We identified four types of interventions to influence parenting behavior; the most used was counseling. All four intervention types showed positive effects on parent–infant relationships, although the preterm populations studied were selective, the effects were evaluated using different methods, and the follow-up periods were short. These findings indicate a need for studies with standardized methods, longer follow-up, and less-restricted preterm populations to develop guidelines for all families with preterm infants.

KEYWORDS

preterm born infant, psychosocial intervention, parent-infant relationship, parent-infant interaction, parenting a child with disabilities

Introduction

Preterm birth (< 37 weeks of gestation) is a stressor for infant brain development (Krugers et al., 2017) and may relate to adverse neurodevelopmental (Bhutta et al., 2002; Aarnoudse-Moens et al., 2013) and socioemotional outcomes in later life (Bhutta et al., 2002; Aarnoudse-Moens et al., 2009; Woodward et al., 2009; Burnett et al., 2011; D'Onofrio et al., 2013; Johnson and Marlow, 2013). The lower the gestational age of the infant at birth, the higher the risk for developmental problems (Elgen et al., 2012; Arpi and Ferrari, 2013), hospital readmissions, and special care (Clark et al., 2008; Larroque et al., 2008; Athalye-Jape et al., 2022). Therefore, children born preterm are fragile and need a good environment to overcome early challenges and develop well.

A preterm birth is also a challenge to transition to parenthood. It interrupts the psychological preparation for the birth, leads often to early separation from the infant, and can include psychologically stressful or even traumatic situations during labor or the neonatal intensive care unit (NICU) care of the infant (Miles and Holditch-Davis, 1997; Jotzo and Poets, 2005; Melnyk et al., 2006; Forcada-Guex et al., 2011; Baum et al., 2012; Yaari et al., 2019). Earlier studies have shown that preterm birth also relates to stress and elevated mental health symptoms in parents, which, in turn, may negatively affect the parent–infant relationship (Forcada-Guex et al., 2011; Meijssen et al., 2011; Shah et al., 2011; Korja et al., 2012; Gerstein and Poehlmann-Tynan, 2015; Hoffenkamp et al., 2015a; Ionio et al., 2017; Gerstein et al., 2019). Together, infant fragility and challenges to early parenthood can create a complex negative circle of prematurity.

A well-functioning family relationships are a protective factor for the development of a fragile preterm infant (Miceli, 2000; Gross et al., 2001; Treyvaud et al., 2012; Aarnoudse-Moens et al., 2013; Gerstein and Poehlmann-Tynan, 2015; Faure et al., 2017). The optimal time to intervene in family relationships is during early months of an infant's life and parenthood, as this is a sensitive period in infant development and the biopsychological processes of parenthood (Givrad et al., 2021). Therefore, the interventions supporting parenting and the parent–infant relationships (Muller-Nix and Forcada-Guex, 2009; Zeanah, 2009; Meijssen et al., 2011; Benzies et al., 2013; Gerstein and Poehlmann-Tynan, 2015; Givrad et al., 2021) should be important part of modern neonatal care.

There is evidence available that interventions supporting parenting or specifically emotional parent–infant relationships during NICU stay and/or the early months after discharge lead to positive health outcomes (Benzies et al., 2013; Evans et al., 2014; Yrjölä et al., 2022). In particular, interventions that include direct support for the parents or focus on the parent–infant interaction have been shown to improve outcomes such as parents' mental well-being, child rearing attitudes, and the socioemotional and cognitive development of prematurely born children (Nordhov et al., 2010; Landsem et al., 2014, 2020; Welch et al., 2015; Vohr et al., 2017). A meta-analytic review showed that 8 out of 17 different psychosocial parent–infant interventions that were tested in randomization-controlled trials and published up to 2007 were effective in improving the quality of the parent–infant relationship. These eight interventions (Mother Infant Transaction Program, State Modulation, Nursing Systems Toward Effective Parenting-Preterm, Infant Behavioral Assessment and Intervention Program, Guided Participation, Kangaroo Holding, Traditional Holding, and an individualized family-based intervention) focused mainly on cue-based and responsive parental care (Evans et al., 2014).

However, a recent systematic review of early interventions for parenting in NICU found only small and short-term effects on parental sensitivity and stress compared with usual care or basic educational guidance, possibly because of diversity, implementation failure, or methodological bias (Lavallée et al., 2021). The structural framework of psychosocial parent–infant interventions in the preterm context has also been shown to be very heterogeneous, leaving uncertainties about their effectiveness and understanding of what works for whom (Benzies et al., 2013; Cho et al., 2013; Evans et al., 2014; Puthussery et al., 2018; Givrad et al., 2021; Lavallée et al., 2021). There have been no attempts to address this heterogeneity of intervention studies, for example, whether there are different types of interventions, and if fathers or different family structures were taken into consideration. There may be different subgroups of parents and infants and thereby a need for different approaches. For example, children born very preterm are at risk for different mental and behavioral disorders than children born preterm with later gestational age (Leppänen et al., 2023) and even for out-of-home placement during early years (Alenius et al., 2020). In the group of very preterm infants maternal psychosocial factors play an important role in the actualization or mitigation of these risks (Leppänen et al., 2023). Identifying appropriate interventions for different risk groups among NICU infants and families would be important.

A detailed understanding of the structural frameworks of the interventions and the level of support they provide would be especially beneficial for the planning of health care services (Castelpietra et al., 2017). However, no model has been designed for comparing and analyzing the differences between psychosocial parent–infant interventions for preterm infants and parents. Therefore, the aim of this scoping review was to provide more structured knowledge of early psychosocial parent–infant interventions that aim to promote parent–infant relationships during the first year after preterm birth. Specifically, we intended to explore the content of the interventions according to the theories, aims, implementation, and settings of the interventions and to study the parent–infant relationship outcomes. As described earlier, psychosocial parent–infant interventions vary a lot structurally; thus, we aimed to analyze the psychosocial parent–infant interventions in detail by using classification systems to identify potential different intervention types and describe parent–infant relationship outcomes. Furthermore, we aimed to summarize the evidence and identify potential gaps in the interventions and their implementation to benefit future research and health care services for parents with preterm infants.

Methods

In this scoping review, the systematic search and reporting followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for scoping reviews (Page et al., 2021). The literature search was conducted for articles published from January 2000 to March 2020 and later for articles published April 2020 to March 2024.

Eligibility criteria

We included studies describing early (between birth and first year) psychosocial parent–infant (psychotherapy and parental) interventions for parent(s) and preterm-born infants (< 37 weeks of gestation) with studied outcomes in the parent–infant relationship and which were written in English. We excluded studies if the infants were not preterm (i.e., were born >37 weeks), did not trial interventions for parents and infants, or did not provide parent–infant relationship outcomes.

Search strategy

We reviewed the literature from 2000 to 2024 to examine the psychosocial parent–infant interventions and the parent–infant relationship outcomes of children born preterm in the 21st century, when neonatal care has reached an advanced stage. As earlier reviews did not search for psychotherapy/psychotherapeutic interventions, we included these as well. Only publications in English were included. We excluded studies that did not follow randomization control or study-control settings or essential information about the intervention to assess eligibility. Because we wanted to focus clearly on psychosocial interventions, we excluded interventions that promoted only physical closeness or one aspect of care, such as skin-to-skin contact. We also removed duplicates.

Screening the data

We searched the electronic databases PubMed and PsycINFO for all published data from January 2000 to March 2020. The search strategy comprised the following MESH headings or keywords: Premature Birth, Infant, Psychotherapy, Parent Infant Psychotherapy, and Parent Intervention. Searches were done in PubMed using the following criteria: "Premature Birth/psychology" [Mesh] OR "Infant, Premature/psychology" [Mesh] AND "Psychotherapy" [Mesh] OR "Parent Infant psychotherapy" [All Fields] OR "Parent Intervention" [All Fields] AND (("2000/01/01" [PDAT]: "2020/03/01" [PDAT]) AND English[lang]). In PsycINFO, we used "Premature Birth" OR "Infant, Premature" AND "Psychotherapy" OR "Parent Infant psychotherapy" OR "Parent Intervention" Published Date: 20000101–20,200,331; Peer Reviewed; Publication Type: Peer Reviewed Journal; English; Age Groups: Childhood (birth–12 years); Population Group: Human; and Document Type: Journal Article. The number of all included and excluded articles of the literature search is provided in Figure 1, built according to the PRISMA guidelines (2021). Because reporting of the results took a long time, a complementary and identical search was done for all published data from April 2020 to March 2024. Studies were also identified from the reference lists of the screened manuscripts. The first author screened potential studies ($n = 2,770$) using the content analysis of the study abstracts and screened for eligibility by reading the manuscripts ($n = 111$). There were 8 studies identified through citations and were screened for eligibility. After screening, potential studies were scrutinized in greater depth through the reading of 74 manuscripts by the first author, with help of the coauthors, to examine the study methods, participants, inclusion/exclusion criteria, interventions (theory, aim, and implementation), outcomes, and results to conclude whether each study was eligible. In another search, the first author screened potential studies ($n = 641$) and scrutinized 21 of these studies, 4 of which were assessed in detail for eligibility with the help of the coauthors.

Data extraction

For different types of early psychosocial parent–infant interventions, we chose four index terms from the International Classification of Health Interventions (ICHI): Parents in Health Intervention.[1] The four main types chosen were: (1) "Education to influence parenting behavior"—Providing information to improve knowledge and influence behavior concerning patterns of interaction between a parent and their child/children, including the nature and degree of monitoring and supervision; involvement and engagement; discipline; nurturing; and the expression of affection. (2) "Counseling about parenting behavior"—Providing therapeutic and/or supportive communication in relation to behavior concerning patterns of interaction between a parent and their child/children, including the nature and degree of monitoring and supervision; involvement and engagement; discipline; nurturing; and the expression of affection. (3) "Emotional support for parenting behaviors"—Providing comfort, empathy, or motivational support to the person regarding behavior concerning patterns of interaction between a parent and their child/children, including the nature and degree of monitoring and supervision; involvement and engagement; discipline; nurturing; and the expression of affection. (4) "Psychotherapy for parenting behaviors"—providing therapeutic communication, based upon the systematic application of psychological theory, in relation to behavior concerning patterns of interaction between a parent and their child/children, including the nature and degree of monitoring and supervision; involvement and engagement; discipline; nurturing; and the expression of affection. In this manuscript, we use abbreviated versions of the models' names: education, counseling, emotional support, and psychotherapy.

To categorize the interventions into the four different intervention types, we looked at the aims and theoretical backgrounds of the interventions but especially the implementation in terms of what was done, how it was done and who did it. In addition, whether there was a focus on reading infants' cues or providing emotional support to parents or on the parent–infant relationship or psychotherapeutic approach. The ICHI definitions were applied to the practice with preterm infants (see results and discussion for examples).

All authors of this paper studied the psychosocial parent–infant interventions separately and used a common Microsoft Excel model to capture each intervention's theory and content. A consensus (a minimum of two reviewers) was then reached to assign each study to one of the four intervention categories.

However, there were still details in the implementation of the interventions that separated the 18 individual interventions from each other, and we added the subtype classification to structure this information. This classification is shown in Table 1, which presents the four main types and the six subtypes. The first author used the Template for Intervention Description and Replication (TIDieR) checklist (Hoffmann et al., 2014) to structure the studied interventions

1 https://icd.who.int/dev11/l-ichi/en

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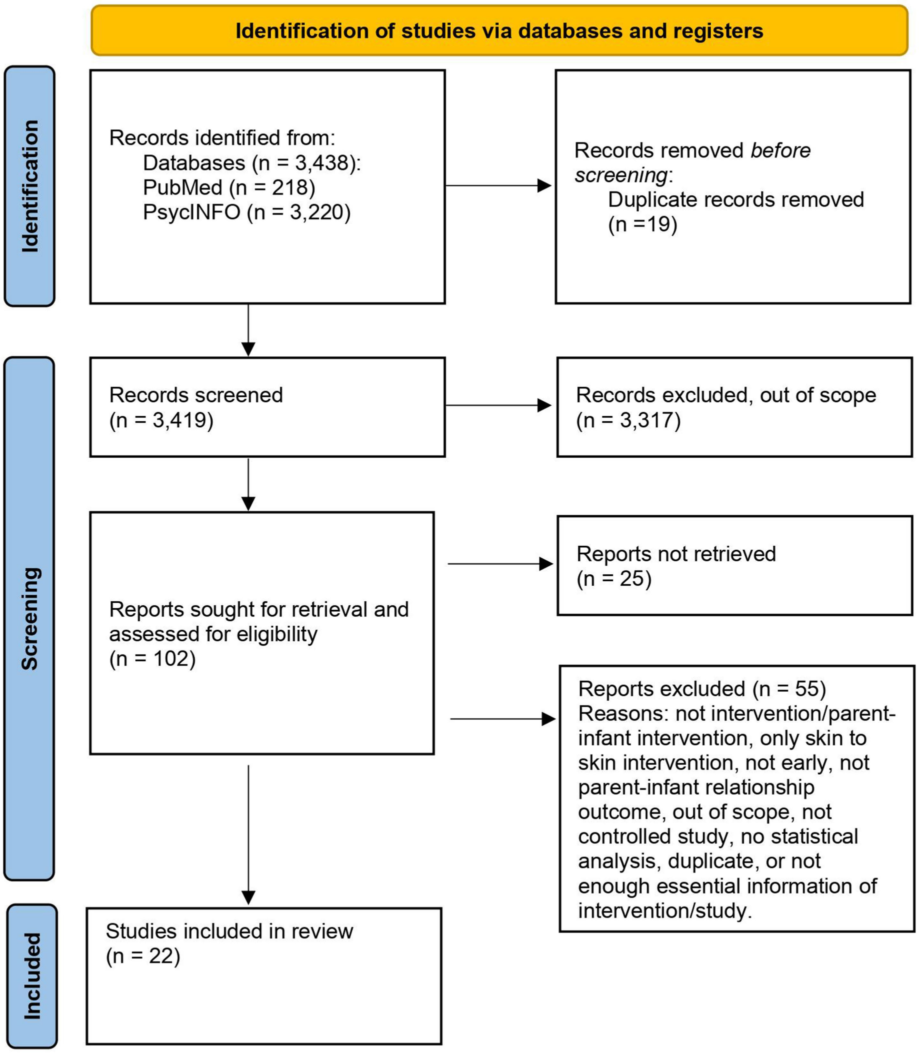

FIGURE 1
Flow diagram of included studies.

using more detailed qualitative and structural information. The TIDieR checklist's details, such as name, why (theory, aim), what (materials/counseling, general/individualized), who (intervention provider's education/training), and how (implementation, e.g., online/face-to-face), as well as where, when, and how much (environment, frequency) and how well the planned compared to the actual work done were described, were used for subtype classification. We also described the parent–infant relationship outcomes of the studies, and in relation to early parental psychosocial parent–infant intervention types. Data are available on request.

Results

Sources

We describe the selection of sources for evidence in the flow diagram shown in Figure 1.

This review included 22 studies, with 17 (Whipple, 2000; Brisch et al., 2003; Melnyk et al., 2006, 2008; Olafsen et al., 2008; van der Pal et al., 2008; Newnham et al., 2009; Meijssen et al., 2010, 2011; Nordhov et al., 2010; Ravn et al., 2012; Borghini et al., 2014; Hoffenkamp et al., 2015b; Castel et al., 2016; Evans et al., 2017; Beebe et al., 2018; Petteys and Adoumie, 2018) identified from PsycINFO and/or PubMed and 5 (Browne and Talmi, 2005; Kaaresen et al., 2006; Schroeder and Pridham, 2006; Glazebrook et al., 2007; Cho et al., 2013) identified through citation search in relevant articles. Two of the interventions were trialed with two different studies and parent–infant relationship outcomes (Melnyk et al., 2006, 2008; Meijssen et al., 2010, 2011), and one intervention was trialed three times (Kaaresen et al., 2006; Olafsen et al., 2008; Nordhov et al., 2010). Thus, there were 18 different early psychosocial parent–infant interventions but 22 studies with parent–infant relationship outcomes (Table 2). Out of all 22 studies, 19 (86.4%) were randomized-controlled studies and 3 (13.6%) were case–control studies. All included studies were quantitative with gathering and analysis of qualitative data. In total, 1,964 infants with their mothers and in some cases with their fathers were included in the final analyses (both the study and control). There were 128/1,964 term-born infants as controls, and the rest of the children were preterm-born infants (study and control). The inclusion and exclusion criteria

TABLE 1 Classification of early psychosocial parent–infant interventions to influence parenting behaviors.

Education	Counseling	Emotional support	Psychotherapy
Subtype 1	Subtype 1 (or more)	Subtype 4	Subtype 5
Creating Opportunities for Parent Empowerment (COPE) (Melnyk et al., 2006, 2008)	*Family Based Intervention* (Browne and Talmi, 2005)* *Baby Triple P (BTP)* (Evans et al., 2017)**	*Modifications of MITP* (Kaaresen et al., 2006; Olafsen et al., 2008; Nordhov et al., 2010) *Early Intervention (EI)* (Borghini et al., 2014)	*Triadic Parent–Infant Relationship Therapy(TRT)* (Castel et al., 2016)
	Subtype 2	Subtype 5	Subtype 6
	Guided Participation (GP)(Schroeder and Pridham, 2006) *Mother–Infant Transaction Program (MITP)* (Ravn et al., 2012) *Mindfulness-Based Neurodevelopmental Care* (Petteys and Adoumie, 2018) *Newborn Individualized Developmental Care and Assessment Program (NIDCAP)* (van der Pal et al., 2008) *Family Nurturing Intervention (FNI)* (Beebe et al., 2018)	*Japanese Infant Mental Health Program (JIMPH)* (Cho et al., 2013)	*Early Preventive Attachment Oriented Psychotherapeutic* (Brisch et al., 2003)
	Subtype 3		
	Parent Baby Interaction Program (PBIP) (Glazebrook et al., 2007) *Infant Behavioral Assessment and Intervention Program (IBAIP)* (Meijssen et al., 2010, 2011) *Modification of Video Interaction Guidance (VIG)* (Hoffenkamp et al., 2015b) *Modifications of MITP* (Newnham et al., 2009)***		
	Subtype unknown		
	Parent Training in Music and Multimodal Stimulation (Whipple, 2000)****		

*Two different intervention groups, one without in-person contact; **Only 67% received the full protocol, for instance 11% received only audio material and phone calls; ***The number of intervention sessions unclear, 7 + 2 in protocol, but the order and pace of the content were adjusted to mothers' needs; ****provider was unclear. Unknown, If there was missing relevant information about the intervention (dose, provider, other). Subtype 1, Only education material, no in-person contact, with very few contacts (1–4). Subtype 2, Short in-person support (1–4 sessions), counseling might notice infant's individuality, and provider could take individual account of caretaking of this infant. A provider could be a health care worker with or without any specific training/supervision. Subtype 3, Longer counseling (> 5 sessions) and could last after discharge or shorter intervention with a specific tool (less than 6 months), provider had special training in program that aimed to enhance parent–infant relationship, the provider had supervision available, and intervention aimed to support parents to find infant's unique characteristics, cues, and how parents could respond to and support infant better. Subtype 4, Similar to subtype 3, but also included possibility for more intense, but maximum 6 months, psychosocial support. Subtype 5, Similar to subtype 4, but psychosocial support lasted longer than 6 months.

of the studies, the participation of mothers and fathers, the content of the interventions, and outcomes related to the parent–infant relationship were themes that were studied and are presented in Table 2.

Participants

The studies defined prematurity by gestational age (GA) and/or birth weight in these local cohorts (Table 2). In most of the studies, GA was defined simply as <37 weeks (15/22, 68.2%), but five (22.7%) of these studies excluded immature infants of <26 weeks (Melnyk et al., 2006, 2008; Beebe et al., 2018), < 28 weeks (Castel et al., 2016), and < 30 weeks (Ravn et al., 2012) of GA. However, 6/22 (27.3%) of the studies included only very preterm infants (very low birth weight or very low GA) (Brisch et al., 2003; Glazebrook et al., 2007; Van der Pal et al., 2008; Meijssen et al., 2010, 2011; Evans et al., 2017). One (4.5%) study included only extremely low GA infants (≤ 29 weeks) (Schroeder and Pridham, 2006). Moreover, 19/22 (86.4%) of the studies excluded infants because of health impairment other than prematurity (listed in Table 2; Whipple, 2000; Browne and Talmi, 2005; Kaaresen et al., 2006; Melnyk et al., 2006, 2008; Schroeder and Pridham, 2006; Glazebrook et al., 2007; Olafsen et al., 2008; van der Pal et al., 2008; Newnham et al., 2009; Meijssen et al., 2010, 2011; Nordhov et al., 2010; Ravn et al., 2012; Cho et al., 2013; Borghini et al., 2014; Castel et al., 2016; Evans et al., 2017; Beebe et al., 2018). Furthermore, 14/22 (64.0%) of the studies excluded infants and mothers if there was any adversity in the mother's psychosocial situation (Whipple, 2000; Browne and Talmi, 2005; Melnyk et al., 2006, 2008; Schroeder and Pridham, 2006; van der Pal et al., 2008; Newnham et al., 2009; Meijssen et al., 2010, 2011; Ravn et al., 2012; Borghini et al., 2014; Castel et al., 2016; Evans et al., 2017; Beebe et al., 2018). Only a few studies systematically included fathers in the interventions (Kaaresen et al., 2006; Melnyk et al., 2006, 2008; Olafsen et al., 2008; van der Pal et al., 2008; Nordhov et al., 2010; Hoffenkamp et al., 2015b; Castel et al., 2016). Additionally, all of the studies required that parents could communicate in the official language of the country where the study was performed.

Interventions

All of the interventions provided psychosocial parent–infant intervention for mothers, and the father participated in 11/22 (50%) of the studies (Table 2). Intervention was provided only during hospital stay in eight (36.4%) of the studies (i.e., seven of the interventions, 38.9%) (Browne and Talmi, 2005; Melnyk et al., 2006, 2008; Schroeder and Pridham, 2006; van der Pal et al., 2008;

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TABLE 2 Early psychosocial parent–infant interventions and parent–infant relationship outcomes.

Author, parent–infant pair (indicated separately (*) if father also participated), number of infants in final analysis, inclusion and exclusion criteria, country	Name, background theory, content, and provider	Study design, parent–infant relationship outcome measures and results (mentioned separately if included both parents)
o Whipple (2000) o Parent–infant pairs* o 20 (intervention: 10, passive control: 10). o GA ≤ 37 weeks, birthweight ≤2,500 grams, clinically stable and referred to this intervention with the mother's consent. o United States	o *No name.* Based on music therapy and earlier studies on how environmental factors, physiological responses, and stress influence the development of the infant and how parents can relieve the infant's state through learning to read the infant's cues and by appropriate stimuli. o Both groups received education sessions in the NICU. The intervention group also had individual parent training through music therapy up to one month after discharge. The first session (15–30 min) was for music and multimodal stimulation, including massage techniques, education of signs of an infant's overstimulation, and techniques to avoid overstimulation. The second session (30 min) included education on tactile stimulation and the soothing of the infant. If the parent was insecure, the provider arranged a third session if needed ($n = 4$ parents). o Provider not clearly indicated.	o Case–control study o After two sessions of observation (*Pre- and Post-Stress Level, Appropriate Parent Score,* both parents) and questionnaires (*Parent–Neonate Interaction Survey*). o In the intervention group, the stress level of infants decreased, parents' appropriate use of music in interaction increased, and parents spent more time with their infants than in the control group ($p < 0.05$). There was no difference at follow-up about one month after discharge.
o Browne and Talmi (2005) o Parent–infant pairs o 84 (intervention: 28 + 31, active control: 25). o GA ≤ 36 weeks, without congenital anomaly or need for surgery, expected length of stay ≥2 weeks. Mother >17 years, documented presence with infants in NICU, no major medical complications in delivery, English speaking and reading ability. o United States	o *No name.* Based on parent–infant interaction and its regulative meaning for preterm infants and how to support parents in finding and responding to an infant's cues. o One (45 min) session in NICU; two intervention groups and one group as control: ■ Group 1 Demonstration and Interaction: Demonstration of the infant's reflexes, attention/interaction, motor capabilities, and sleep/wake states by systematic Assessment of Preterm Infant Behavior protocol. ■ Group 2 Education: Only electronic or written educational material. Content: The strengths and skills of preterm infants (stress, consoling an unhappy baby, bringing a baby to an alert state, sleep, and self-comforting skills) and the typical thoughts and feelings of the parent. ■ Group 3 Controls: A 30–45-min discussion regarding follow-up care for preterm infants. o Experimenter.	o Randomized-controlled study (RCT) o One month after discharge, questionnaires (*Knowledge of Preterm Infant Behavior, Parenting Stress Index*) and video observation on interactions during feeding (*Nursing Child Assessment of Feeding Scale*). o Knowledge was highest in Group 2 and was higher in Group 1 than in the controls ($p < 0.001$). Interaction during feeding was best in Group 1, then in Group 2, and finally in controls ($p < 0.05$). Control mothers expressed the greatest stress in accepting the infant. Morbidity of the infant and the age of the mother are associated with outcomes.
o Schroeder and Pridham (2006) o Parent–infant pairs o 16 (intervention: 8, active control: 8) o GA ≤ 28 weeks, appropriate for GA in weight. Mothers ≥18 years, English speaking. o United States	o *Guided participation (GP).* Based on earlier studies on parents' representations of the infant and the influence on the parent–infant relationship. GP aims to support the development of mothers to be more attuned and with adaptive expectations and intentions. o Six education sessions from 30 weeks of GA (45 min, weekly in NICU), separate protocols for intervention and control groups, controls got more general information regarding prematurity and mothers in intervention group got more individual support on how to care for her own preterm infant to support their parent–infant relationship. The provider videotaped two mother–infant caregiving interactions, where the mother was holding the infant at 32 weeks and feeding the infant at 35 weeks of GA. o Research nurse.	o RCT o At baseline (at 29 weeks of GA) interview and at follow-up video assisted interview (at 32–33 and 35–36 weeks of GA) and questionnaire (*Internal Working Model of Relating to the Baby*, *Relationship Competencies Assessment*). o Mothers in the intervention group were more attuned and adaptive to their infants' needs than mothers in the control group ($p < 0.02$).

(Continued)

TABLE 2 (Continued)

Author, parent–infant pair (indicated separately (*) if father also participated), number of infants in final analysis, inclusion and exclusion criteria, country	Name, background theory, content, and provider	Study design, parent–infant relationship outcome measures and results (mentioned separately if included both parents)
o Melnyk et al. (2006) and Melnyk et al. (2008) o Parent–infant pairs* o 251 (intervention: 138, active control: 113). o GA 26–34 weeks, birthweight <2,500 grams (appropriate for GA in weight), anticipated survival, singleton, no severe handicapping condition. Mother and father ≥18 years, no other infant in NICU, English speaking. o United States	o *Creating Opportunities for Parent Empowerment (COPE)*. Based on theories of self-regulation and control of infants and parenting of critically ill infants. COPE is an educational-behavioral program that provides information on the appearance and behavioral characteristics of preterm infants and how parents can participate in their infants' care. o Four phases including audiotapes and written material with educational information and behavioral activities. Phase I started at 2–4 days after admission to NICU (info and tasks to note special characteristics and milestones of their infant), Phase II after 2–4 days after phase I with information and advice to identify cues of their infant of stress, interaction readiness, Phase III 1–4 days before discharge and included information about infant, interaction, and how to smooth transition from hospital to home, and Phase IV at home one week after discharge with material on how to foster a positive parent–infant relationship and the development of the preterm child. The control group received at same time general information, such as audiotaped and written information about hospital services and discharge. o Research nurse delivered recorded audio-visual educational and written material (workbook).	o RCT o Questionnaires at baseline (*Parental Stressor Scale-Neonatal Intensive Care, Parental Belief Scale-NICU*), and in the follow-up, where the latter was repeated 1–4 days before discharge to both parents, and observation 3–6 days after baseline (*The Index of Parental Behavior in NICU*). o The observer found more positive interaction, mothers reported less stress, and both parents had more positive beliefs about infants in the intervention compared to the control group ($p < 0.05$).
o Glazebrook et al. (2007) o Parent–infant pairs o 232 (intervention: 112, passive control: 121) o GA < 32 weeks without life-threatening morbidity. o United Kingdom	o *Parent Baby Interaction Program (PBIP)*. Based on studies about how preterm birth influences parents and about parental stress and sensitivity in the parent–infant relationship. PBIP aims to enhance parents' observations of their baby and sensitivity to an infant's cues. Activities are tactile, verbal, and observational. o Weekly sessions from the first week after birth could continue six weeks after discharge, but the number of sessions varied (mean eight at hospital and two at home). Controls got treatment as usual. o Trained research (neonatal) nurses.	o RCT o At three months of age, the questionnaire (*Parenting Stress Index*) and observation of maternal interaction (*Nursing Child Assessment Teaching Scale, Home Observation for Measurement of the Environment*). o There was no difference between the groups, and there was no statistical comparison.
o Ravn et al. (2012) o Parent–infant pairs o 106 (intervention: 56, passive control: 50). o GA 30–36 weeks and if length of hospital stay was expected to be >8 days, parents spoke Norwegian and had no history of drug/alcohol abuse or severe psychiatric disorders. o Exclusion: congenital anomalies, neurological sequelae, hearing loss, or chromosomal disorders. o Norway.	o *Mother Infant Transaction Program (MITP)*. Based on earlier studies on prematurity and its effect on the sensitivity of parents and infants. MITP aims to help parents, through instruction, observation, modeling, and education, to appreciate their infant's unique characteristics and make the parents more sensitive and responsive to their infants' physiological and social cues, particularly those that signal stimulus overload. o Seven one-hour sessions daily 7–10 days before discharge, which included sessions to be acquainted with the child, recognition of infant's cues, and how to care for the infant, and four home visits during first three months (play, temperament). Controls got standard care (not specified). o Neonatal nurses trained and supervised by a psychologist specialist.	o RCT o Administered *Parenting Stress Index*, short version, *Infant Behavior Questionnaire* at 6 months and *Parenting Stress Index* and long version of *Infant Behavior Questionnaire* at 12 months. Breastfeeding was observed at 9 months. o There was no difference in experienced stress between the two groups at 6 and 12 months ($p < 0.05$). Mothers experienced less positive behavior in their infants at 6 and 12 months in the intervention group compared to the controls ($p < 0.05$). Intervention associated with longer breastfeeding ($p < 0.05$).

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TABLE 2 (Continued)

Author, parent–infant pair (indicated separately (*) if father also participated), number of infants in final analysis, inclusion and exclusion criteria, country	Name, background theory, content, and provider	Study design, parent–infant relationship outcome measures and results (mentioned separately if included both parents)
o Kaaresen et al. (2006), Olafsen et al. (2008), and Nordhov et al. (2010) o Parent–infant pairs* o 214 (intervention: 71, passive preterm controls: 69, passive term controls: 74). o Birthweight <2000 grams. Exclusion: non-survivors, triplets, Down syndrome, or if parents did not speak Norwegian. o Norway.	o *Early Intervention* (*EI*) is a modified version of MITP, based on the transactional model of development, which considers a disturbed pattern of parent–infant interaction to be a major influence on the child's development. The aim of EI is to educate parents to appreciate and recognize their infant's unique characteristics, temperament, and developmental potential and to promote dyadic reciprocity by modeling skills, providing verbal instruction and direct observation, offering emotional support when appropriate, and reinforcing the mother's own initiative. o Seven one-hour intervention sessions daily before discharge and four home intervention sessions at 3, 14, 30, and 90 days after discharge. Content as in Ravn et al. (2012) but EI also offered an initial session to ventilate and express negative feelings, and both mothers and fathers were enrolled. Controls had treatment as usual. o A trained nurse supervised by a coordinating nurse and a senior child psychologist.	o RCT o Questionnaires: At 6 months (*Parenting Stress Index*[1], *Infant Behavior Questionnaire*[2], *Child-Rearing Practices Report*[3] for mothers), 12 months (*Parenting Stress Index*[1] for both parents, *Infant Behavior Questionnaire*[2], *Child-Rearing Practices Report*[3] for both parents), and 24 and 36 months (*Child-Rearing Practices Report*[3] for both parents). o Fathers and mothers were less stressed in the intervention versus control groups ($p < 0.05$).[1] Maternal stress was negatively associated with a child's negative temperament at six months in the intervention group but not for controls or at 12 months ($p < 0.05$).[2] There were more nurturing child rearing attitudes after intervention at 12 and 24 months when compared to the preterm control group ($p < 0.05$).[3]
o Newnham et al. (2009) o Parent–infant pairs o 68 (intervention: 35, passive control 33). o GA < 37 weeks. Exclusion: if congenital abnormality, gross neurological damage, ≥ triplets, or if mother was non-English speaking or had drug dependency. o Australia.	o *Modification of the Mother–Infant Transaction Program (MITP)* is a program designed to enhance parent sensitivity with their own hospitalized preterm infants and to encourage them to use well-researched stimulation activities. The adapted MITP differs from these programs in that it trains mothers to combine and take responsibility for all approaches, to recognize and support individual infant needs, and to initiate positive stimulation (using well-researched activities) based on the mother's learned appreciation of the infant's regulatory and stimulation needs. o During NICU stay, five sessions to learn to identify disorganization/stress of infant and how to apply findings in care; home intervention session at one month and follow-up at three months to recognize temperament of infant and how to parent a child. Controls got treatment as usual. o Provider not indicated.	o RCT o At 3- and 6-months questionnaires (*Parenting Stress Index, Short Temperament Scale for Infant*) and observation (*Synchrony Scale*) o Compared to controls, mothers who participated in the intervention were more sensitive ($p < 0.05$) and infants attentive at three months and alert at three and six months ($p < 0.01$). Dyadic interaction was more synchronous at three months, there was more mutual attention in infants at six months, and mothers had less stress over infant ($p < 0.01$).
o Van der Pal et al. (2008) o Parent–infant pairs* o 128 (intervention: 63, active control: 65). o GA < 32 weeks, parents living in catchment area. o Exclusion: major congenital anomaly or the mother being drug addicted. o The Netherlands.	o *The Newborn Individualized Developmental Care and Assessment Program (NIDCAP).* Based on earlier studies on the wellbeing of preterm infants and families and the synactive theory of development, parents observe infant's behavior with the help of a provider using four subsystems (autonomic, motor, state organization, attention-interaction). It aims to support parents in being active in their infant's care and in helping the infant's regulation. o The intervention started 48 min after birth, every 7 to 10 days. In one hour of observation, parents paid attention to the infants' approach and avoiding behavior in four subsystems, 10 min before, during, and after caregiving. This was recorded on a sheet, and with this information, the provider summarized the infant's approach and avoidance behavior and provided guidance for the parents on how to interact with their infants. Controls got the basic elements of developmental care (nest, positioning aids, dose not told). o A developmental specialist.	o RCT o At 9 months (*Infant Behavior Questionnaire Revised*) and 12 months (*Parental Stress Index, short version*) *questionnaires for* both parents. o There was no statistically significant difference in the perception of infant behavior characteristics and parenting stress between the groups.

(Continued)

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TABLE 2 (Continued)

Author, parent–infant pair (indicated separately (*) if father also participated), number of infants in final analysis, inclusion and exclusion criteria, country	Name, background theory, content, and provider	Study design, parent–infant relationship outcome measures and results (mentioned separately if included both parents)
o Meijssen et al. (2010, 2011) o Parent–infant pairs o 112 (intervention: 57, passive control: 55). o GA < 32 weeks and/or birthweight <1,500 grams and surviving. o Exclusions: severe congenital abnormalities, mothers with illicit drug use or severe physical or mental illness, non-Dutch speaking, or participation in other studies. o The Netherlands.	o *Infant Behavioral Assessment and Intervention Program (IBAIP).* Based on the theory of self-regulatory competence in enhancing social interaction and learning competence. IBAIP is a post-discharge preventive intervention program for infants at risk and their parents. Its goal is to guide parents through observation to support their infants' self-regulatory competence and social interactions. o 6–8 home intervention sessions, provider used observational tool of IBAIP to see and help parents to see baby's responses to sensory information. After sessions, parents received a report on the infant's neurobehavioral and developmental progress, providing suggestions on how to support the infant's explorations and self-regulatory competence by responsive parenting and environment modification. Later, parents were encouraged to gradually reduce their support. Controls got treatment as usual. o Experienced pediatric physical therapists trained in IBAIP.	o RCT o At six months observation* (*Still Face*) and at 18 months half-structured interview (*Working Model of Child Interview*). o Mothers in intervention showed less intrusive behavior than controls in still face observation ($p = 0.04$), but there were no differences in other relationship outcomes regarding mother's representation on child and attachment.
o Cho et al. (2013) o Parent–infant pairs o 66 (intervention: 26, active control: 40). o GA < 36 weeks, hospitalized in the intensive care unit, no longer in critical condition, having no chromosomal anomalies, neurological disease, requiring no medical treatment other than internal medicine after hospital discharge, having a Japanese mother, and singleton. o Japan.	o *Japanese Infant Mental Health Program (JIMPH).* Based on infant mental health studies and European Early Promotion Project and on importance of early parent–infant interaction and relationship on child's development, maternal mental health, and their relationship. JIMPH aims to promote maternal mental health, mother–infant interaction (cue and developmental guidance), social support to the mother, and stress reduction relevant to maternal parenting and child development. o Six sessions until 12 months of age (one at the care unit and five after discharge). Intervention included work with interpersonal relationships, teaching how to respond to cues of infant, and interaction. Controls received treatment as usual and guidance regarding discharge of preterm infant and three post discharge intervention sessions by different helpers (nursing, public health, midwifery). o JIMPH helper (nurse/public health nurse/clinical psychologist with training in JIMPH).	o Case–control study o At 12 months questionnaire (*Parenting Stress Index, Japanese version*) and observation week before discharge (*Nursing Child Assessment Feeding Scale*). o Mothers' interaction scale increased after intervention when compared to the control group ($p < 0.05$), but there was no difference in experienced stress.
o Brisch et al. (2003) o Parent–infant pairs* o 68 (intervention: 32, passive control: 36) o < 1,500 grams and GA ≤ 35 weeks. o Exclusion: non-surviving, discharged, lacking common language or participation in other study. o Germany.	o *No name.* Based on different approaches from earlier studies combined with psychotherapeutic work. The aim of multimodal psychotherapeutic intervention is to improve parents' coping and parent–infant interaction. o Five supportive group therapy sessions in NICU, five individual attachment-oriented psychotherapy sessions for mother and father, one home visit session to promote parental self-compliance within 1 week after discharge, and at 3 months parental sensitivity training for infants' cues. Controls got treatment as usual and daily talks with medical staff and nurses. o Psychotherapist and a nurse from the NICU.	o Case–control study o At 14 months, parent–infant observations (*Strange Situation Procedure*) were conducted. o There were no differences in attachment styles between the groups, but there were different amounts of neurologically impaired infants in the groups. Neurologically impaired infants benefited more from intervention for their attachment style than did controls.
o Borghini et al. (2014) o Parent–infant pairs o 85 (intervention: 26; preterm control: 29; term control: 30). o GA < 33 weeks. o Exclusion: non-surviving, malformation, severe brain finding, neonatal abstinence syndrome, non-French-speaking family, or mental illness of parent. o Switzerland.	o *Early Intervention (EI).* Based on systematic family theory and transactional preventive intervention (the Neonatal Behavioral Assessment Scale, the Clinical Interview for Parents of High-Risk Infants, the Interaction Guidance). EI aims to improve parents' observation, attention, and understanding of preterm characteristics and to promote parent–infant interactions. o At GA of 33-week joint observation, 42-week Neonatal Behavior Assessment Scale followed by interview to allow emotion expression, and at 4 months, three videotaped free play sessions, one week apart, followed by interaction guidance. Preterm controls got information about their infant and relationship at 33 weeks of GA, and preterm and term controls participated in Neonatal Behavior Assessment Scale at 42 weeks without therapeutic guidance; these were without therapy intervention. o Interaction guidance therapist (with nurse).	o RCT o At 4 months, observation of parent–infant interaction (*CARE index*). o Intervention increased sensitivity of mother ($p < 0.05$) and co-operation of infant ($p < 0.0001$) when compared to pre-and post-intervention interaction. Mothers of preterm infants without interventions were more controlling than intervention and term-born control mothers ($p < 0.002$).

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TABLE 2 (Continued)

Author, parent–infant pair (indicated separately (*) if father also participated), number of infants in final analysis, inclusion and exclusion criteria, country	Name, background theory, content, and provider	Study design, parent–infant relationship outcome measures and results (mentioned separately if included both parents)
o Hoffenkamp et al. (2015a) o Parent–infant pairs* o 150 (intervention: 75, passive control: 75). o GA < 37 weeks (both ≥32 weeks and < 32 weeks to balance the degree of prematurity). o Exclusion: poor understanding of the Dutch language and previous experience with a video-feedback intervention. o The Netherlands.	o Modification of *Video Interaction Guidance (VIG)*. Based on earlier studies on early interaction and its association with development and parental responsiveness. This is aimed at being achieved through behaviorally focused intervention with positive feedback to facilitate bonding, attuned parental interactive behavior, and the well-being of parents, and the protocol is based on individual needs. o At the first week after birth, there were three video sessions: a 15-min video during daily care routines at the first, third, and sixth postpartum days with the day after review with parents. The provider took video during daily moments, edited videos to focus on the infant's contact initiatives and parents' positive responses to these signals, and then viewed these micro-moments with parents, offering reflection and positive feedback. Controls got treatment as usual. o VIG professionals.	o RCT o Questionnaire for both parents (*Postpartum Bonding, My Baby and I, Yale Inventory of Parental Thought and Actions, Parental Stress Scale; NICU*) at one week, 1-, 3-, and 6-months, and parent–infant observations at 1 and 6 days, 3- and 6-months (*National Institute of Child Health and Human Development Early Care Research Network*). o When compared to controls, intervention enhanced sensitivity (mother $p < 0.004$, fathers $p < 0.04$) and less withdrawn behavior in mothers ($p < 0.01$) in the short term. Intervention also increased bonding, especially in fathers, and lasted up to six months ($p < 0.02$). However, the intervention did not diminish intrusive behavior or stress in the parents.
o Castel et al. (2016) o Parent–infant pairs o 89 (intervention: 33, passive preterm control: 32, passive term control: 24). o GA 28–36 weeks, without congenital anomaly or other disability seen early. Siblings were included. Term control infants born at the same time were identified retrospectively from the birth register. Parents >18 years, French speaking, without psychiatric history. o France.	o *Triadic Parent–infant Relationship Therapy (TRT)*. Based on earlier studies on prematurity; parents' wellbeing, stress, and triadic relations; attachment theory; and child's development. TRT aims to improve triadic relationships during the first 18 months by alleviating parents' stress, supporting their confidence, and expressing emotions. o Twenty-two sessions with emotional sharing, supporting triadic relations and mental health of parents, and promoting understanding of infant and its development: twice per month for the first four months, then follow-up once a month on ward for up to 18 months. Controls got treatment as usual. o A clinical psychologist.	o RCT o For both parents at discharge, a 3-, 9-, and 18-month questionnaire (*Parenting Stress Index, short*). o Both mothers and fathers in the intervention group reported less stress at 18 months than at the beginning of the intervention and parents in the control group ($p < 0.05$).
o Evans et al. (2017) o Parent–infant pairs o 120 (intervention: 61, passive control 59). o GA < 32 weeks. o Exclusion: non-surviving, major congenital anomalies, parents unwilling to participate at 24 months, non-English speaking mother, or infant was transferred to foster care. o Australia.	o *BabyTriple P (BTP)* is a modification of the Triple P – Positive Parenting Program. Based on earlier studies on the importance of infant's environments for development and social learning theory, which include education of preterm infant's characteristics and teaching strategies of parenting. The aim of the program is to strengthen parents' knowledge, confidence, and skills. o Four lesson sessions during NICU (if transferred to other hospital, by video) with content including survival skills, partner support, positive parenting, and responding to your baby. Continuing until post discharge. Four phone calls to help put theory in practice, tip sheets were mailed every 3 months, and text messages were sent until 12 months. Controls got treatment as usual. o Facilitator with completed BTP training.	o RCT o At six weeks and 12 months, parent–infant interaction observation (*Emotional Availability Scales*) and questionnaire (*Maternal Postnatal Attachment Scale*). o There were no differences in the interaction variables. No difference in attachment was reported at six weeks, but at 12 months the mothers in the intervention group reported a higher attachment than the controls ($p < 0.02$).

(Continued)

TABLE 2 (Continued)

Author, parent–infant pair (indicated separately (*) if father also participated), number of infants in final analysis, inclusion and exclusion criteria, country	Name, background theory, content, and provider	Study design, parent–infant relationship outcome measures and results (mentioned separately if included both parents)
o Beebe et al. (2018) o Parent–infant pairs o 71 (intervention: 39, passive control: 32). o GA 26–34 weeks, mother without drug abuse/severe mental illness, English speaking, and no single adult home. o Exclusion: birth weight < third percentile for GA, congenital anomaly, and family without two adults. o United States	o *Family Nurture Intervention (FNI).* Based on studies on separation, the regulatory framework, hidden regulatory sub-processes (olfaction, touch, vocal senses), and autonomic co-conditioning between mother and infant. FNI aims to overcome the negative effects of maternal deprivation on neonatal care units. It involves parents being active in nurturing and enabling emotional closeness, bonding, and autonomic co-regulation. o Starts after birth and continues through neonatal care unit stay; the dose of the intervention varies according to the availability of the infant, the mother, and the family, with an average of six hours per week. Nurture specialists encouraged bonding by cloth suffused by the infant's smell and vice versa, and by holding. Enables parents to contact their child (eye, emotional speaking and singing, touch). Controls received standard care, such as education and, if they wanted, skin-to-skin care. o Nurture specialists.	o RCT o At four months, observation of mother and infant (coding of gaze, vocal affect, touch). o There were no differences in behavior compared to the intervention and control groups in mean, but mothers touched their infants more often and infants used more vocal affects in intervention than control group ($p < 0.001$).
o Petteys and Adoumie (2018) o Parent–infant pairs* o 55 (intervention: 28, passive control 27). o GA < 35 weeks, length of hospital stay > 14 days, parents agreeable to spend a minimum of one hour by infant weekly, and English-speaking. o United States	o *No name.* Earlier studies on mindfulness and stress reduction, need for attunement, and psychoeducation of parents in preterm characteristics. Mindfulness-based neurodevelopmental care programs include education on mindfulness techniques (focused breathing, personal awareness, and nonjudgment of themselves and infants), principles of attunement and interaction, and neurodevelopmental care training for preterm infants to recognize infant cues. o One individual education session (30–60 min) with mindfulness techniques, how to be present for infant, how to wait for cues of infant in care and interaction, then call with research team at least every other week during NICU care. Controls received treatment as usual. o Trained research team.	o RCT o Within seven days, anticipated hospital discharge questionnaires for both parents (*Parental Stressor Scale: Neonatal Intensive Care Unit, Mother-to-Infant Bonding Scale*) and parents recorded how much time they spent in care and interaction with their infant (*Parent–infant Interaction Log*). o There was no difference in bonding or overall parental stress between the intervention and control groups. However, parental stress decreased during intervention in the intervention group ($p < 0.02$) but not in the control group. The Parental–Infant Log did not provide applicable information to the study because of missing information.

RCT = Randomized control trial, GA = gestational age, age corrected for prematurity until 24 months, GP = Guided participation, COPE = Creating Opportunities for Parent Empowerment, PBIP = Parent–Baby Interaction Program, MITP = Mother–Infant Transaction Program, EI = Early Intervention, NIDCPA = Newborn Individualized Developmental Care and Assessment Program, IBAIP = Infant Behavioral Assessment and Intervention Program, JIMPH = Japanese Infant Mental Health Program, VIG = Video Interaction Guidance, TRT = Triadic Parent–infant Relationship Therapy, BTP = Baby Triple P, FNI = Family Nurture Intervention. [1,2,3]Symbols are used to mark each trial of the studied intervention. *Fathers participated in the intervention with mother. In studies by: Melnyk et al. (2006, 2008) a total of 258 mothers and 154 fathers were included, but the number of fathers in the final cohort was not reported. In Kaaresen et al. (2006), Olafsen et al. (2008), and Nordhov et al. (2010) there were 70 mothers and 61 fathers in intervention groups at 12 months, in preterm controls 67 mothers and 51 fathers, and in term controls 72 mothers and 58 fathers. In Van der Pal et al. (2008) there were nine fathers in the intervention group who completed the observation, and five in the control group. In Hoffenkamp et al. (2015a) there were 150 families (150 mothers and 144 fathers), but the exact number of families eligible for trial participation was not feasible. In Petteys and Adoumie (2018), 83.7% of parents were mothers versus 16.3% fathers. In Brisch et al. (2003) there was no exact number of fathers provided. In Glazebrook et al. (2007) it was mentioned that PBIP can involve the whole family, but the mother was the principal recipient of the intervention; there was no number provided for fathers.

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Hoffenkamp et al., 2015b; Beebe et al., 2018; Petteys and Adoumie, 2018). Three (13.6%) studies implemented interventions only after discharge (i.e., 2/18 interventions, 11.1%) (Meijssen et al., 2010, 2011; Borghini et al., 2014). Interventions were provided longitudinally in 12 (54.5%) of the studies (i.e., 9/18 interventions, 50.0%) (Brisch et al., 2003; Kaaresen et al., 2006; Melnyk et al., 2006, 2008; Glazebrook et al., 2007; Olafsen et al., 2008; Newnham et al., 2009; Nordhov et al., 2010; Ravn et al., 2012; Cho et al., 2013; Castel et al., 2016; Evans et al., 2017). The number of in-person sessions in the analyzed interventions varied during hospital stay, up to 10 (13/22 studies gave exact numbers, their mean number of sessions = 3.4) and after discharge, up to 22 (15/22 studies gave exact numbers, mean = 3.1). These variations in the number of intervention sessions seem to be related not only to the intervention *per se* but also to the health of the infant or other conditions, such as hospital transfers. Only one of the interventions lasted over a year (18 months) (Castel et al., 2016).

To gain an overview, most of the interventions based their theory on preterm infants' need for sensitive regulation by parents (12/22 (54.5%) studies; 10/18 (55.5%) interventions) (Whipple, 2000; Browne and Talmi, 2005; Melnyk et al., 2006, 2008; Glazebrook et al., 2007; van der Pal et al., 2008; Newnham et al., 2009; Meijssen et al., 2010, 2011; Ravn et al., 2012; Beebe et al., 2018; Petteys and Adoumie, 2018). The interventions also considered one or more of the following aspects in their background and planning of the intervention: parental stress (2/22 (9.0%) studies; 2/18 (11.1%) interventions) (Glazebrook et al., 2007; Petteys and Adoumie, 2018), parental representations (1/22 (2.5%); 1/18 (5.5%)) (Schroeder and Pridham, 2006), the importance of the parent–infant relationship for the development of the child (6/22 (27.3%); 4/18 (22.2%) interventions) (Kaaresen et al., 2006; Olafsen et al., 2008; Nordhov et al., 2010; Cho et al., 2013; Hoffenkamp et al., 2015b; Evans et al., 2017), the parent–infant relationship in general (2/22 (9.0%); 2/18 (11.1%)) (Cho et al., 2013; Beebe et al., 2018), and multimodal psychotherapeutic theory (3/22 (13.6%) studies; 3/18 (16.7%) interventions) (Brisch et al., 2003; Borghini et al., 2014; Castel et al., 2016). In almost all the studies (19 (86.4%) of the studies and 15 (83.3%) of the interventions), the provider of the intervention was a staff member (a nurse, a physiotherapist, or a clinical psychologist) or an individual from a research team with education in intervention. Only one intervention was delivered by a psychotherapist who worked with a nurse (Brisch et al., 2003). In two studies, the provider was not clearly stated in the manuscript (Whipple, 2000; Newnham et al., 2009).

All early psychosocial parent–infant interventions were first classified into four main types: the education type included one (4.5%) intervention that was trialed twice with different outcomes; counseling included 12 interventions (67%); emotional support included three interventions (17%), in which one was trialed three times; and two interventions were classified as psychotherapy (11.1%).

One multimodal music therapy intervention (Whipple, 2000) described the intervention but did not clearly indicate the type of provider used, and we classified the study type as unclear. One (5.6%) education intervention (Melnyk et al., 2006, 2008), which was trialed twice and had three contacts before discharge and one after discharge, was implemented with written and audiotaped material only, and was classified as subtype 1. Two of the interventions (11.1%) had variation in delivery of the intervention (two different intervention groups and in others only 67% received the full protocol, and the remaining studies used other methods, e.g., phone calls and video presentations) (Browne and Talmi, 2005; Evans et al., 2017) and were therefore classified according to the lowest subtype used in the intervention, as subtype 1. We classified five (27.8% of the interventions) counseling interventions (Schroeder and Pridham, 2006; van der Pal et al., 2008; Ravn et al., 2012; Beebe et al., 2018; Petteys and Adoumie, 2018) as subtype 2 because they included up to four personal intervention sessions with individual approaches. Subtype 3 included all methods used in subtypes 1–2, in addition to providing over five sessions, being based on a specific theory, and training providers to implement the intervention, covering four counseling interventions (22.2%) (Glazebrook et al., 2007; Newnham et al., 2009; Meijssen et al., 2010, 2011; Hoffenkamp et al., 2015b). Subtype 4 offered a possibility for longer psychosocial support than in subtype 3, but for less than 6 months; there were two emotional support interventions suitable for this subtype (11.1%) (Kaaresen et al., 2006; Olafsen et al., 2008; Nordhov et al., 2010; Borghini et al., 2014). Subtype 5 included longer psychosocial support than in subtypes 1–4; there was one emotional support and one psychotherapy intervention that fulfilled these criteria (11.1%) (Cho et al., 2013; Castel et al., 2016). One intervention contained individual psychotherapy sessions for parents and specific parent–infant care but also multilevel support and peer support, and we classified it as subtype 6 (5.6% of the interventions) (Brisch et al., 2003).

Parent–infant relationship outcomes in relation to early psychosocial parent–infant interventions

Almost half of the studies (10/22, 46.0%) reported parent–infant relationship outcomes for both parents and child (Whipple, 2000; Kaaresen et al., 2006; Melnyk et al., 2006, 2008; Olafsen et al., 2008; van der Pal et al., 2008; Nordhov et al., 2010; Hoffenkamp et al., 2015b; Castel et al., 2016; Petteys and Adoumie, 2018), while the remaining studies reported outcomes for either mother or child only. Moreover, parent–infant relationship outcomes were studied by 30 different methods (Table 2) by observations (16/22, 76.7%) (Whipple, 2000; Brisch et al., 2003; Browne and Talmi, 2005; Melnyk et al., 2006, 2008; Schroeder and Pridham, 2006; Glazebrook et al., 2007; Newnham et al., 2009; Meijssen et al., 2010, 2011; Ravn et al., 2012; Cho et al., 2013; Borghini et al., 2014; Evans et al., 2014; Hoffenkamp et al., 2015b; Beebe et al., 2018) and/or questionnaires (19/22, 86.4%) (Whipple, 2000; Browne and Talmi, 2005; Kaaresen et al., 2006; Melnyk et al., 2006, 2008; Schroeder and Pridham, 2006; Glazebrook et al., 2007; Olafsen et al., 2008; van der Pal et al., 2008; Newnham et al., 2009; Meijssen et al., 2010, 2011; Nordhov et al., 2010; Ravn et al., 2012; Cho et al., 2013; Evans et al., 2014; Hoffenkamp et al., 2015b; Castel et al., 2016; Petteys and Adoumie, 2018). Assessments of the intervention outcomes had varying time points: during neonatal intensive care (1/22, 4.5%) (Petteys and Adoumie, 2018); straight after intervention session (2/22, 9.0%) (Whipple, 2000; Schroeder and Pridham, 2006); days to weeks after discharge (2/22, 9.0%) (Melnyk et al., 2006, 2008); 1 month after discharge (1/22, 4.5%) (Browne and Talmi, 2005); at the age of 3 months (1/22, 4.5%) (Glazebrook et al., 2007), 4 months (2/22, 9.0%) (Borghini et al., 2014; Beebe et al., 2018), 6 months (4/22, 18.2%) (Newnham et al., 2009; Meijssen et al., 2010; Ravn et al., 2012; Hoffenkamp et al., 2015b), 9 months (1/22, 4.5%) (Castel et al., 2016), 12 months (3/22, 13.6%) (van der Pal et al., 2008;

Ravn et al., 2012; Evans et al., 2014), or 18 months (3/22, 13.6%) (Brisch et al., 2003; Meijssen et al., 2011; Castel et al., 2016), or 24 to 36 months of corrected age (3/22, 13.6%) (Kaaresen et al., 2006; Olafsen et al., 2008; Nordhov et al., 2010). Many of the studies (17/22, 77.3%) reported at least some positive change in the intervention compared to controls.

The findings of parent–infant outcomes in the four main intervention types

Education

This type included only one intervention but was trialed twice by Melnyk et al. (2006, 2008). They reported results about this COPE intervention with audiovisual or written material on preterm infants and parenting. This RCT study with 260 families found a positive effect of the intervention on better interaction behavior between mother and father, mothers' decreased stress concerning the infant and environment, and mothers' and fathers' better beliefs about infants compared to controls. The parent–infant outcomes were assessed during NICU care and about 1 week before discharge. The interaction behavior was measured using the Index of Parental Behavior in the NICU. The study did not include infants with very low gestational age (< 26 weeks) or severe handicapping conditions, or twins or multiples, and mothers had to be over 17 years.

Counseling

This type included 12 interventions in which one intervention was trialed twice. Nine out of 13 studies (69.2%) and 8 of 12 interventions (66.7%) classified to this type reported some positive changes in the parent–infant relationship: improved parent–infant interaction (Whipple, 2000; Browne and Talmi, 2005; Newnham et al., 2009; Meijssen et al., 2010, 2011; Hoffenkamp et al., 2015b; Beebe et al., 2018), lessened parental stress (Browne and Talmi, 2005; Newnham et al., 2009; Petteys and Adoumie, 2018), improved maternal attunement to infant and adaptability (Schroeder and Pridham, 2006), or bonding and increased time spent with the infant during hospital stay (Whipple, 2000) compared to controls and assessed before or at six months or less. In three following counseling interventions, there were both positive and unchanged parent–infant relationship outcomes. In Meijssen et al.'s (2010, 2011) studies, the mothers' behavior improved, but their representation of attachment did not change. In a study by Hoffenkamp et al. (2015a), the intervention improved sensitive behavior and bonding but not intrusive behavior or stress. In a study by Evans et al. (2017), there were no changes in observed interaction or in attachment at 6 weeks, but attachment at 12 months was better than in controls. Of these studies, 8/13 (61.5%) (Browne and Talmi, 2005; Schroeder and Pridham, 2006; Newnham et al., 2009; Meijssen et al., 2010, 2011; Hoffenkamp et al., 2015b; Beebe et al., 2018; Petteys and Adoumie, 2018) were RCT, and one of the studies (7.1%) (Whipple, 2000) was a case–control study. The size of the study cohorts varied between $N = 16–112$ in nine studies with positive parent–infant outcomes (Whipple, 2000; Browne and Talmi, 2005; Schroeder and Pridham, 2006; Newnham et al., 2009; Meijssen et al., 2010, 2011; Hoffenkamp et al., 2015b; Beebe et al., 2018; Petteys and Adoumie, 2018). Of these nine studies, one (11.1%) excluded very preterm (Beebe et al., 2018) and six (66.7%) sick preterm infants (Whipple, 2000; Browne and Talmi, 2005; Newnham et al., 2009; Meijssen et al., 2010, 2011; Beebe et al., 2018). and two (22.2%) mothers of young age (Browne and Talmi, 2005; Schroeder and Pridham, 2006) and four (44.4%) with health problems (Newnham et al., 2009; Meijssen et al., 2010, 2011; Beebe et al., 2018). However, three of the studies included only very preterm infants (Schroeder and Pridham, 2006; Meijssen et al., 2010, 2011). Interventions included 1–6 sessions (Whipple, 2000; Browne and Talmi, 2005; Schroeder and Pridham, 2006; Newnham et al., 2009; Hoffenkamp et al., 2015b; Petteys and Adoumie, 2018) or individually varied numbers of sessions (Beebe et al., 2018). The follow-up lasted until NICU discharge (Whipple, 2000; Petteys and Adoumie, 2018) or until one month after discharge (Browne and Talmi, 2005), 36 weeks of GA (Schroeder and Pridham, 2006), four months (Beebe et al., 2018) or six months of age (Newnham et al., 2009; Meijssen et al., 2010, 2011; Hoffenkamp et al., 2015b). Parent–infant relationship evaluation was assessed by questionnaires (Whipple, 2000; Browne and Talmi, 2005; Schroeder and Pridham, 2006; Newnham et al., 2009; Petteys and Adoumie, 2018) and observations (Whipple, 2000; Browne and Talmi, 2005; Schroeder and Pridham, 2006; Newnham et al., 2009; Meijssen et al., 2010, 2011; Hoffenkamp et al., 2015b; Beebe et al., 2018).

In total, 4/13 (30.8%) of these studies (i.e., 4/12 (33.3%) interventions) found no difference in interaction, responsiveness, attachment, or parenting stress (Glazebrook et al., 2007; van der Pal et al., 2008; Ravn et al., 2012; Evans et al., 2017) or found negative results in parent–infant relationship outcomes in parenting stress, how the mother experienced the infant, and maternal attachment (Ravn et al., 2012; Evans et al., 2017). The cohorts included 106–242 parent–infant pairs. In the studies with negative or no difference, all four studies excluded sick preterm infants (Glazebrook et al., 2007; van der Pal et al., 2008; Ravn et al., 2012; Evans et al., 2017), and in 3/4 (75%) of the studies mothers with health issues were excluded (van der Pal et al., 2008; Ravn et al., 2012; Evans et al., 2017). However, three (75%) of the studies included only very preterm infants (Glazebrook et al., 2007; van der Pal et al., 2008; Evans et al., 2017). The interventions included seven (Ravn et al., 2012) or varying numbers of intervention sessions (Glazebrook et al., 2007; van der Pal et al., 2008) or had no-person but material delivery (Evans et al., 2017). The follow-up lasted until 3 months in one study (Glazebrook et al., 2007) and about 12 months of age of the child in the remaining three studies (75%) (van der Pal et al., 2008; Ravn et al., 2012; Evans et al., 2017). Outcomes were evaluated by questionnaire in all four studies (Glazebrook et al., 2007; van der Pal et al., 2008; Ravn et al., 2012; Evans et al., 2017) and by observation of the parent–infant relationship in three-quarters of the studies (Glazebrook et al., 2007; Ravn et al., 2012; Evans et al., 2017).

Emotional support

This type included three different interventions in which one was trialed three times. All of the studies and interventions in this group (100%) had a positive result in parent–infant relationship outcomes (in sensitivity of mother, co-operation of the infant, interaction, less stress, and attitudes toward the infant) among 4- and 24-month-old children (Kaaresen et al., 2006; Olafsen et al., 2008; Nordhov et al., 2010; Cho et al., 2013; Borghini et al., 2014). In one study, there were positive changes in observed interactions but no changes in parental stress (Cho et al., 2013). Three out of five of these studies (60%) (Kaaresen et al., 2006; Olafsen et al., 2008; Nordhov et al., 2010;

Borghini et al., 2014) were RCT and one (Cho et al., 2013) was a case–control study. The size of the study cohorts varied between 66 and 214. All five studies excluded unhealthy preterm infants (Kaaresen et al., 2006; Olafsen et al., 2008; Nordhov et al., 2010; Cho et al., 2013; Borghini et al., 2014) but included all gestational ages, and 4/5 of the studies excluded mothers with young age or health problems (Kaaresen et al., 2006; Olafsen et al., 2008; Nordhov et al., 2010; Borghini et al., 2014). The number of intervention sessions varied between five and six (Cho et al., 2013; Borghini et al., 2014), and there were more sessions at home after discharge (Kaaresen et al., 2006; Olafsen et al., 2008; Nordhov et al., 2010). The follow-up period varied from 4 to 36 months of age. The parent–infant relationship was assessed by questionnaires in 4/5 of the studies (Kaaresen et al., 2006; Olafsen et al., 2008; Nordhov et al., 2010; Cho et al., 2013) and by observation in 2/5 of the studies (Cho et al., 2013; Borghini et al., 2014).

Psychotherapy

This type included two different interventions and separate studies. One study (50%) found a positive correlation to the parent–infant relationship (Castel et al., 2016). Parents in this study (Castel et al., 2016) reported less stress after intervention at 18 months than those in the control group. There was no other parent–infant relationship outcome measure in this study. The study included 84 parent–infant pairs; the infants were preterm (GA 28–36 weeks, excluding the most preterm infants) without congenital anomaly or other disability, and the mothers were over 18 years, without psychiatric disease. This high-frequency intervention (22 sessions) aimed to improve triadic relationships through parental stress alleviation, supporting their confidence and emotional expression and parents in the control group. In a study by Brisch et al. (2003), there were 87 parent–infant pairs; the infants were only very preterm (<1,500 grams and GA ≤ 35 weeks), surviving beyond the intervention. This multimodal psychotherapeutic intervention included group therapy, individual attachment-oriented psychotherapy sessions for mother and father, one home intervention session to promote parental self-compliance within 1 week after discharge, and, at 3 months, parental sensitivity training for infants' cues. The mother's attachment to the infant was evaluated at 14 months. There were no differences between controls and mothers in the intervention (Brisch et al., 2003).

Discussion

The aim of this scoping review was to provide structured knowledge of early psychosocial parent–infant interventions that seek to promote parent–infant relationships after preterm birth. We also aimed to summarize the evidence considering parent–infant relationships and identify potential gaps in existing interventions and/or in the used outcomes. Previous reviews on psychosocial parent–infant interventions have shown heterogeneity (Benzies et al., 2013; Evans et al., 2014; Givrad et al., 2021) but have not provided answers on how the variation in psychosocial parent–infant interventions could be understood.

To analyze and impose a structure on the content of the interventions, we classified the studied interventions into four main types and six subtypes, adapting existing intervention classification models, namely the International Classification for Health Interventions (ICHI) by the World Health Organization and the Template for Intervention Description and Replication (TIDieR) checklist for better reporting of interventions. Based on the classification, the most common type of early psychosocial parent–infant intervention to influence parenting behavior was found to be counseling, followed by emotional support. The least common types were psychotherapy for parenting behavior and education to influence parental behavior. Positive intervention effects on the parent–infant relationship were reported in 16 of 22 studies, particularly in single education (Melnyk et al., 2006, 2008), in 8/13 of the counseling interventions (Whipple, 2000; Browne and Talmi, 2005; Schroeder and Pridham, 2006; Newnham et al., 2009; Meijssen et al., 2010, 2011; Hoffenkamp et al., 2015b; Beebe et al., 2018; Petteys and Adoumie, 2018), in 3/3 of the emotional support interventions in which one was trialed three times (Kaaresen et al., 2006; Olafsen et al., 2008; Nordhov et al., 2010; Cho et al., 2013; Borghini et al., 2014), and in 1/2 of the psychotherapy interventions (Castel et al., 2016). Our results are in line with earlier studies on the positive outcomes of parental interventions (Benzies et al., 2013; Evans et al., 2014).

ICHI definitions of different types of early parent–infant psychosocial interventions were applied to the practice with preterm infants, and the following examples are from analyzed and classified interventions. These were applicable to intervention targeted at preterm infants and their parents. Education interventions concentrated on educating parents of the typical characteristics in preterm infants and how parents can participate in their infants' care. Counseling about parenting behavior provided individual observations and guidance for parents on how to see cues in their own preterm infant and how to consider cues when interacting with their child. Emotional support for parenting behavior promoted parents' mental health and parent–infant interaction and psychotherapy for parenting behavior focused on dyadic/triadic relationships through emotional sharing, supporting relationships and the mental health of parents, and promoting understanding of the infant's development. Psychotherapeutic elements such as individual or group sessions were offered to deal with experiences during the birth of the child or an individual's own childhood.

Study characteristics

This study included 22 studies with 18 different early psychosocial parent–infant interventions, in which about half were implemented longitudinally, starting on the NICU and lasting after discharge. The studies used 30 different outcome measures of the parent–infant relationship, measured mainly after hospital discharge (21/22) and up to 18 months of age.

We identified multiple gaps in studies on early psychosocial parent–infant interventions, especially those related to the populations included in the interventions. In total, 86.4% of the studies excluded parent–infant pairs because of some health impairment in the infant (Whipple, 2000; Browne and Talmi, 2005; Kaaresen et al., 2006; Melnyk et al., 2006, 2008; Schroeder and Pridham, 2006; Glazebrook et al., 2007; Olafsen et al., 2008; van der Pal et al., 2008; Newnham et al., 2009; Meijssen et al., 2010, 2011; Nordhov et al., 2010; Ravn et al., 2012; Cho et al., 2013; Borghini et al., 2014; Castel et al., 2016; Evans et al., 2017; Beebe et al., 2018) and/or health or other adverse sociological risk in the mother (64.0%) (Whipple, 2000; Browne and Talmi, 2005; Melnyk et al., 2006, 2008; Schroeder and Pridham, 2006; van der Pal et al., 2008;

Newnham et al., 2009; Meijssen et al., 2010, 2011; Ravn et al., 2012; Borghini et al., 2014; Castel et al., 2016; Evans et al., 2017; Beebe et al., 2018). Thus, the effectiveness of most the intervention is not studied with the preterm infants and their parents with high or multiple risk factors. In future intervention studies these groups would require more attention, because typically multiple risk factor exposure is more harmful than singular risk exposure for child development (Evans et al., 2013; Leppänen et al., 2023). Further, all of the studies required parents to be able to communicate in the official language of the country where the study was performed, thereby likely excluding recently immigrated populations. Fathers were not evaluated for inclusion criteria as mothers, which may be one of the explanations why mothers and fathers seemed to benefit differently from the interventions.

In the reviewed interventions, there were extreme but also moderate preterm infants, which may have influenced the results. The environment (neonatal intensive care unit) where preterm infants may be for quite a long time before discharge may be a challenge for psychosocial care. A need for other treatments and the transfer of infants was reported to affect implementation in some interventions (Newnham et al., 2009; Evans et al., 2017), and these kinds of prematurity and intensive care-related factors may have resulted in the observed variations in the number of sessions implemented. In 18 individual interventions, there were 30 different parent–infant outcome measures at varying age points of the infants, which makes comparison of the results difficult. In these studies, the parent–infant outcomes were often not the primary outcomes of the studies and therefore likely to be underpowered. In the future, the power of parent-infant outcomes should be considered when designing an intervention study and at least adequately discussed in the reports. Evans et al. (2014) described the contents of early psychosocial intervention and statistically compared outcome variables between study and control groups. They found that part of the interventions, especially those with education/counseling of cues and how to interact with infants, seemed to be beneficial for parent–infant relationships. However, both interventions and outcome methods, as well as follow-up times, have varied strongly in reviewed and earlier studies, details have been missing, and numbers have been small in studies, leaving uncertainties (Benzies et al., 2013; Givrad et al., 2021). A recent systematic review by Lavallée et al. (2021) on early parenting intervention after preterm birth on parental sensitivity and parental stress before and after 6 months of age found mostly low or very low quality of evidence. They discussed that this could be explained by implementation failure, risk of bias, the small number of participants, and substantial heterogeneity (Lavallée et al., 2021), which is in line with our observations.

The interventions

The most common type of early psychosocial parent–infant intervention in our study was counseling about parenting behavior (13/22 of the studies and 12/18 of the interventions). This kind of intervention provides therapeutic and/or supportive communication in relation to behavior concerning patterns of interaction between a parent and their child/children. Nine out of 13 (69.2%) studies of the counseling type reported some significant effects on the parent–infant relationship (improvements in parent–infant interaction bonding, less parental stress, increased time spent with the child during hospital stay compared to controls), with outcomes assessed within the first 6 months of infant age. The remaining 4 of 13 studies and of 12 interventions did not report any positive intervention effects. The studies with less positive outcome results seemed to differ in that they had larger cohorts and longer follow-ups compared to studies with positive outcomes. Two of the studies with counseling interventions excluded very preterm infants, and six included only this population. Based on the subtype categories, it appears that the moderate-dose counseling interventions (subtypes 1 to 3) had a positive but maybe short effect on the parent–infant relationship. However, among the counseling interventions, intervention components, such as the amount of training/supervision of the intervention providers or the length of the intervention, did not seem to influence the results. This is interesting but may be explained by missing information about the extent to which the participants receive the intervention as intended. Intervention studies in the future, even those using an RCT design, should monitor adherence during the intervention delivery and report it (Giovanazzi et al., 2022). In three counseling interventions (in addition to one emotional intervention) that included several different measures and age points, only some of the outcomes were positive for the intervention (Meijssen et al., 2010, 2011; Hoffenkamp et al., 2015b; Evans et al., 2017). It would be important for further studies to identify the measures that are sensitive for measuring the effect of a short counseling intervention on the parent–infant relationship. Furthermore, it is important to report negative results to avoid intervention causing harmful effects.

The next most common intervention type found was emotional support to influence parenting, caretaking, or interaction, where 5/5 and 3/3 of individual interventions and studies had a positive result in parent–infant relationship outcome (e.g., improvements in maternal sensitivity, co-operation skill of the child, interaction, less parenting stress, and attitudes toward the child) assessed between 4 and 24 months of age. Emotional support provides comfort, empathy, or motivational support to the person regarding behavior concerning patterns of interaction between a parent and their child/children. Many of the emotional support interventions included the possibility of more intense and/or longer-lasting psychosocial support than the counseling interventions did (Subtype 4). All interventions included also sessions after discharge, and also very and extreme preterm infants were included to these emotional interventions. Furthermore, all emotional support interventions included providers who received education for intervention delivery. The providers, if they were staff members, also collaborated or were supported by a specialist, such as a psychologist. NICU staff have reported that they experience the provision of emotional support to parents as a demanding task (Turner et al., 2014). Therefore, it is crucial to have a specialist with appropriate education who can collaborate on or support the delivery of parenting interventions with emotional support. Although some studies have reported less stress, one of the studies did not find an intervention effect on parenting stress (Cho et al., 2013). The outcomes were assessed between 4 and 36 months of the child's age, utilizing mostly RCT study designs and relative sample sizes. Based on this scoping review, all interventions classified as emotional support interventions were all shown to be effective. However, we cannot conclude why these interventions were all effective. Thus, our conclusion is that there is a need for studies that compare different types of interventions rather than only studying the effect of one intervention at a time. Furthermore, the active ingrediencies of the interventions should be reported in detail and impact mechanisms of interventions studied, not only the outcomes.

Less common intervention types were education and psychotherapy, with 2/22 (9.0%) of the studies and 2/18 (7.7%) of the interventions being psychotherapy and 1/18 (5.5%) being education-based. Education aims to improve knowledge to influence behavior concerning patterns of interaction between a parent and their child/children, including the nature and degree of monitoring and supervision, involvement and engagement, discipline, nurturing, and the expression of affection. An education intervention study by Melnyk et al. (2006, 2008) delivered education materials to parents but had a positive effect on parent–infant interaction as it diminished stress and improved parents' representations of their child/children at 1 week before discharge. Unfortunately, no later outcomes were reported. This intervention also excluded most preterm infants. One of two psychotherapy interventions by Castel et al. (2016) reported less parental stress when a child was 18 months old. There were no other outcomes assessed, although that intervention lasted until 18 months and with an educated provider and background theory of the interventions to improve triadic relationships (between mother, father, and infant). Thus, the quality of the parent–infant or triadic interaction was not evaluated as an outcome in the study. In another psychotherapeutic intervention study by Brisch et al. (2003), only the attachment quality of the child was evaluated after a very multimodal intervention that could have also eased parental stress and anxiety, and improved parental representations, which were evaluated in other studies. Although child attachment was a well-founded choice for the main outcome of this intervention with an attachment-oriented approach, the narrow choice of outcomes may leave invisible some of the important effects. This study found that effect was only present in a subgroup of preterm infants, those with neurologic delay seemed to benefit from the intervention (Brisch et al., 2003). Both psychotherapeutic interventions included only very preterm infants, although not extremely preterm infants (< 28 weeks) (Castel et al., 2016). It may be that preterm infants and their parents with comorbidities, psychotherapeutic interventions are appropriate.

We found some constraints in the reviewed studies that may affect the generalization of the results. We do not know how the exclusion of mothers and infants with additional risks has influenced the studied outcome. However, some of the different intervention types showed that some subgroups benefited more from interventions than other parents in the study. Hoffenkamp et al. (2015a) reported that mothers who were traumatized benefited more from video-based interaction guidance than those who were not. And above discussed finding by Brisch et al. (2003), that if an infant had a neurological impairment, intervention improved maternal attachment, which is line with earlier results on attachment study By Korja et al. (2012) on preterm infants and parents. Prematurity *per se* might not be a risk for attachment. Overall, future interventions should pay more attention to subgroups of preterm infants and parents who may be at even greater risk of parent–infant relationship problems than preterm infants and parents without comorbidities. Previous reviews have also recommended the identification of families at risk (Benzies et al., 2013; Evans et al., 2014; Givrad et al., 2021). Psychosocial risks are known to accumulate in families with preterm infants and influence the outcomes of preterm-born children (Schothorst et al., 2007; Nosarti et al., 2012; Leppänen et al., 2023). However, adequate parent–infant emotional interaction can be protective (Yrjölä et al., 2022). Therefore, when infants and parents with cumulative risks are included in intervention trials, interventions should be tailored to meet the different and probably targeted needs of the families.

The included studies used over 30 different outcome measures; some seemed to fit well with the content of the intervention, while others did not. Pilot studies should be used to identify the sensitive outcomes of an intervention to ensure a better choice of outcomes. Standardized outcome sets could also be co-created between researchers and parents. Only 5/18 (Kaaresen et al., 2006; Glazebrook et al., 2007; Olafsen et al., 2008; Meijssen et al., 2010, 2011; Nordhov et al., 2010; Hoffenkamp et al., 2015b) of the interventions clearly reported the parent–infant relationship outcome as the primary outcome in their study. Another identified gap in previous research is related to the lack of knowledge about the intervention's effects on fathers. In the future, the inclusion of fathers in the intervention studies should be encouraged, and the content of the intervention should be modified based on existing knowledge about early fatherhood. Further, the intervention effect on the father–infant relationship could be analyzed separately in a review.

Limitations

Our goal was to include various types of interventions in this scoping review; however, our inclusion criteria, as stipulated in the study methodology, necessitated the exclusion of many interventions, which might have influenced the overall picture of early parental interventions. As we aimed to scope the field broadly and to identify existing gaps, we did not follow any specific quality assessment tool for the inclusion of studies. This may have influenced our observations.

We could not extract all details from a few manuscripts for classification, even though we searched the data—for example, we searched earlier publications on the intervention—and this might have influenced how we classified the interventions. As there were no readily available classification systems, our system provides a pilot for the development of other classifications in future studies. We excluded interventions that included only skin-to-skin care to concentrate more on psychological support. Skin-to-skin care *per se* has been reported as beneficial for parents and infants (Neu and Robinson, 2010; Holditch-Davis et al., 2014). We used only PubMed and PsycINFO as data sources; extension to other databases and gray literature could have expanded the picture of what kind of early psychosocial parent–infant interventions there might be. For example, in a recent complementary search we identified new types of interventions, including online/app-based interventions for parents, but these were excluded. Generally, this study could not consider other social and health care services offered to families in each NICU, hospital district, and community that might supplement interventions but were not studied in this scoping review. In the future, there is a need to describe all levels of support in different phases and environments. This field has no established terms (i.e., types and subtypes), and we used new terms compared to earlier reviews (Benzies et al., 2013; Evans et al., 2014).

Conclusion

This scoping review study provided systematic information on studies of early psychosocial parent–infant intervention in the context of neonatal intensive care. The included interventions were classified using the ICHI, provided by the World Health Organization, and their implementation was evaluated using the TIDieR structure for reporting interventions. The most common intervention types in the studies were consultation about parenting and emotional support for parenting. Psychotherapy and education intervention types were less common. All types of interventions were shown to be beneficial for the parent–infant relationship, particularly in populations of preterm infants, without accumulating risk factors and with short-term follow-up times. But we think that in future studies, it would be of great benefit to conduct fidelity analyses of the intervention delivery (Ibrahim and Sidani, 2016) to understand how well the intervention succeeded.

Due to the heterogeneity of the outcomes and interventions used, it is hard to make comparisons between the interventions. To obtain reliable and comparable data, standardized study protocols (e.g., time of measurement and length of follow-up) and outcome measures are needed in the future. It would be important to have a long-term follow-up to study whether early outcomes are maintained. For example, synchronicity between child and parent may be a potential stable factor to measure (Feldman, 2012). The biomarkers of parenting could also be interesting proximal outcomes of parenting interventions in NICU context (Hajal and Loo, 2021). There is also a need for more intervention studies that include subpopulations of preterm infants and their parents with accumulating risks. However, it is important to carefully consider the type of intervention that is appropriate for these subpopulations. It may be that emotional support and psychotherapeutic types of interventions involving multiprofessional collaboration are more likely to be beneficial for families with accumulation risks than education or consultation. This study may help NICU professionals understand the differences between various psychosocial interventions for parenting. It may also have implications for the development of health care services for families with preterm infants.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

ML: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. RK: Conceptualization, Investigation, Methodology, Supervision, Writing – original draft, Writing – review & editing. PR: Conceptualization, Methodology, Project administration, Supervision, Writing – review & editing. SA-B: Conceptualization, Investigation, Methodology, Supervision, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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EDITED BY
Livio Provenzi,
University of Pavia, Italy

REVIEWED BY
Maria Spinelli,
University of Studies G. d'Annunzio Chieti and Pescara, Italy
Alexandra Ullsten,
Centre for Clinical Research and Education, Karlstad, Sweden

*CORRESPONDENCE
Katrin Mehler
✉ katrin.mehler@uk-koeln.de

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Does early skin-to-skin contact have a long-term effect on the emotional and behavioral development of very preterm infants?

Patricia Trautmann-Villalba[1], Eva Heine[2], Angela Kribs[2] and Katrin Mehler[2]*

[1]Institute of Peripartal Interventions, Frankfurt, Germany, [2]Department of Paediatrics, Faculty of Medicine and University Hospital Cologne, Cologne, Germany

Introduction: Premature birth may impair a sensitive, responsive, enjoyable, and regulating parenting style, potentially leading to behavioral, cognitive, and emotional deficits in children. Additionally, the emotional bond between the parent and infant may be disturbed due to the restrictions and difficulties at the neonatal intensive care unit (NICU), further negatively impacting child development. Skin-to-skin contact (SSC) directly after birth is strongly recommended also for preterm or low birth weight infants since there is high-certainty evidence that SSC has positive effects on neonatal and maternal health as well as on the quality of the parent–child relationship. The aim of this study was to examine the effect of skin-to-skin contact immediately after childbirth on the development of emotional and behavioral problems in children born preterm entering school.

Methods: This study is part of a randomized controlled delivery room skin-to-skin study (*Deisy Study*). A total of 33 children (aged 6–8 years) were assessed at school start. The German version of the CBCL/6-18R was used to evaluate the presence of behavior problems.

Results: The perceived parental stress 6 months after discharge was the variable that most contributed to the variance explanation. SSC immediately after childbirth was not significant in the prediction of emotional and behavioral problems at school start.

Limitations: The study was conducted in a small study group. Partners' variables were not included. Information regarding sociodemographic variables and bonding quality was collected 6 months (corrected age) after birth. The measurement of children's behavioral problems is not objective and corresponds to the parents' perception.

Clinical Trial Registration: https://clinicaltrials.gov, deisy study NCT01959737, deisy follow up NCT03366285.

KEYWORDS

premature infant, preterm infant, skin-to-skin contact, behavior problems, school-age, parental stress, bonding, depressive symptoms

1 Introduction

The idea that the birth of a child is one of the most fulfilling and satisfying experiences in life is widespread. However, reality shows that this assumption is not always true for all parents. The time during pregnancy and after birth is a very intense, stressful phase for all parents, and it is associated with a number of challenges, regardless of whether or not particular difficulties arise.

In the case of a preterm birth, that is, the birth that occurs before the 37th week of gestation (World Health Organization, 2023a,b), parents face a very critical period due to a double burden. They must manage the expected crisis of welcoming a new child while also dealing with the trauma of potential danger and separation due to the high-risk state of the newborn and potential admission to a neonatal intensive care unit (NICU) (Arizu et al., 2024). Prematurity is a well-known risk factor for long-term medical and developmental deficits such as sensory, motor, cognitive, and behavioral impairments and delays (Shaw et al., 2023; Twilhaar et al., 2018) but could also have a negative impact on parental mental health (Ionio et al., 2024; Roque et al., 2017) and on the parent–child relationship, including bonding, interaction, and attachment (Mira et al., 2024; Shaw et al., 2023).

These circumstances have an important effect on parents' emotional state that can lead to feelings of sadness, grief and loss, insecurity, a high level of stress, and depressive or anxiety symptoms regardless of the baby's clinical severity. Pisoni et al. (2019) found that mothers at the NICU reported elevated postnatal depressive symptoms and high stress levels, even when their preterm infants had low perinatal risk and normal neurological examinations. A recent systematic review of parental mental health studies following preterm birth (Sandnes et al., 2024) found that ∼20% of the mothers of extreme or very low birth weight infants showed depression, anxiety, post-traumatic symptoms, and a high level of parenting stress in the first 2 years after birth. In this context, depressive symptoms appear to be the most common symptoms with rates as high as 40% in the early postpartum period among women with premature infants (Vigod et al., 2010). Parents of preterm babies are likely to experience up to 18 times higher mood disorders compared to parents of full-term babies (Carson et al., 2015; Helle et al., 2015). Even though most studies included only mothers, partners also experienced symptoms of depression and anxiety during the 12 first months and decreasing symptoms of post-traumatic stress disorder (PTSD) between 12- and 24-months corrected age (CA). However, the occurrence of these symptoms is lower in partners (Sandnes et al., 2024).

The very special emotional state that parents experience in the NICU, associated with the routines and conditions there, makes it difficult to establish and develop a parent–baby relationship. In a recent study, Ionio et al. (2024) found that feelings of tension, anger, and confusion experienced by the mother tend to negatively affect the quality of the bond with her child. With respect to interactive maternal behaviors, studies have shown that the experience in the NICU has a negative effect on these and the quality of the bond. This effect was mediated by the presence of depressive symptoms, the level of perceived stress (Gerstein et al., 2019), and not having had SSC immediately after childbirth (Mira et al., 2024). Even though there is no universally recognized description of the procedure, continuous and prolonged SSC initiated immediately after birth has been strongly recommended by the World Health Organization as routine care for all preterm and low birth weight infants after delivery since there is high-certainty evidence of its benefits (World Health Organization, 2022, 2023b). A number of positive effects on the baby's health, for example, the reduction of risk of neonatal death and the prevention of infections (Conde-Agudelo and Díaz-Rossello, 2016), the improvement of infants' vital signs (Zengin et al., 2023), or the reduction of pain (Campbell-Yeo et al., 2019), as well as on maternal health (Scime et al., 2019; Pathak et al., 2023) and on the quality of the parent–child relationship, have been described in the literature (Lilliesköld et al., 2023). Recently, an expert panel who developed a "Skin-to-Skin Pragmatic Implementation Guide" also highlighted the positive influence of SSC on an infant's sucking behavior, maternal breastfeeding self-efficacy and self-confidence, as well as the positive maternal perception of the breastfeeding birth parent (Brimdyr et al., 2023). In previous studies conducted in a German level III NICU, we have reported that a group of premature children who maintained SSC for 1 h immediately after birth showed a higher quality of mother–child interaction at 6 months (CA) compared to a group of children with similar characteristics who only maintained visual contact (VC) with their mothers for 5 min after birth. In addition, SSC mothers scored lower in depression scores and presented a better quality of bonding than those who only had VC (Mehler et al., 2020, 2024). Comparing the SSC group to a group of full-term infants and their mothers, SSC dyads showed similar interactional behaviors as term dyads. In contrast, the interactional behaviors in the VC group were significantly reduced (Heine et al., 2023).

Children born preterm are up to three times more likely to receive a psychiatric diagnosis at school age than those born full term. The most common diagnoses include emotional disorders, conduct disorders, attention-deficit/hyperactivity disorder, and autism spectrum disorder (Bhutta et al., 2002; Larsen et al., 2024; Treyvaud et al., 2014). In this context, temperament can play an important role: the meta-analysis conducted by Cassiano et al. (2020) supports the affirmation that preterm children present less regulated temperament than full-term children, which, in turn, could lead to a higher activity level and lower attentional focusing and persistence. In the same direction, Martins et al. (2021) reported that 18- to 36-month-old toddlers, who were born preterm and showed more negative affectivity, presented more behavior problems on the CBCL scores (total, externalizing, and internalizing) compared to full-term toddlers. This aspect is relevant since infant temperament is an independent risk factor for higher levels of parental stress (Gray et al., 2013). Parental stress, depression, and anxiety were found to be a significant and independent predictor of child cognitive and behavioral development of preterm infants, although most studies have focused on short-term rather than long-term effects (Greene et al., 2018; Mughal et al., 2017; Neri et al., 2017; Zelkowitz et al., 2011).

Due to the demonstrated benefits of SSC on the development of preterm infants and maternal mental health, we hypothesized that children who were born between the 25th and 32nd week of gestation and receive SSC in the delivery room (DR-SSC) may present lower levels of behavioral and emotional problems at the start of school, which may be irrespective of maternal depressive symptoms, bonding quality, and parental stress.

2 Materials and methods

2.1 Participants

This study is part of a randomized controlled delivery room skin-to-skin study (*Deisy Study*, Mehler et al., 2020) conducted at a level III NICU at the University Children's Hospital of Cologne with the purpose of evaluating a standardized SSC intervention to improve the quality of the mother–child interaction and bonding. To enhance the neurodevelopment of these preterm infants and to reduce possible behavior problems, firstborn singletons between 25 and 32 weeks of gestation were included in the initial sample. After initial stabilization (approximately 45 min), the infant was transported to the room where the mother was cared for. In 2013, when the trial was conducted, neither physical nor short visual contact between parents and their preterm newborns was the standard of care in most neonatal departments. In our study, infants who received standard care had 5 min of visual contact with their parents. Visual contact allowed them to see but not to touch or kiss their infant. Dyads randomized into the intervention group received 60 min uninterrupted SSC, supervised by the neonatal team (detailed information in Mehler et al., 2020). Eighty-eight newborns constituted the initial sample (DR-SSC $n = 45$, VC $n = 43$). Two data collections were planned: at 6 months corrected age (CA) and between 6 and 8 years, the time when children enter school, to assess the long-term effects of the DR-SSC on their behavior. Data collection took place between 2018 and 2021. Figure 1 shows the design of the initial and the follow-up trial, and the respective data collection used in this study.

From 2020, the restrictions due to the COVID-19 pandemic made home visits difficult. Therefore, the study group was greatly reduced. No significant differences were found between participants at the 6- to 8-year follow-up and non-participants regarding neonatal characteristics, maternal age and educational variables, family income, single parenthood, maternal depressive symptoms at child's discharge, nor in the quality of bonding or parental stress at the age of 6 months. In the study at school start, 33 children participated (SSC $n = 16$, VC $n = 17$). The sociodemographic and neonatal characteristics of the sample are shown in Table 1.

The study was approved by the Ethics Committee of the University of Cologne and was conducted in accordance with the 1964 Declaration of Helsinki. The study is registered under the number NCT03926923.

2.2 Instruments

To identify depressive symptoms, quality of bonding, parental stress, and child behaviors, self-reporting methods were used.

TABLE 1 Characteristics of the study group and their mothers ($N = 33$)[a].

	VC	SSC	*p*
Gender Female (%)	10 (58.8)	10 (62.5)	0.556
Gestation (weeks)	29.2	28.8	0.550
Birth weight (in grams)	1,143.6	1,236.9	0.513
10-min Apgar score	8.47	8.50	0.884
Days at the hospital	60.1	63.8	0.691
Firstborn (%)	11 (68.8)	10 (62.5)	0.592
Age-appropriate school enrollment (%)	12 (70.6)	12 (75.0)	0.859
Maternal age	37.8	39.2	0.480
High school degree (mother)	13 (81.3)	15 (93.8)	0.300
Professional qualification (mother)	15 (93.8)	16 (100)	0.500
Single parent	1 (5.9)	3 (18.8)	0.335
Perceived social support	4.5	4.4	0.824
CES-D	10.1	12.6	0.480
PSI total score	55.1	55.8	0.871
PBQ total score	10.7	9.1	0.582

[a]N and % for nominal variables/M for continuous variables.
CES-D, Center for Epidemiological Studies Depression Scale; PSI, Parental Stress Index; PBQ, Postpartum Bonding Questionnaire.

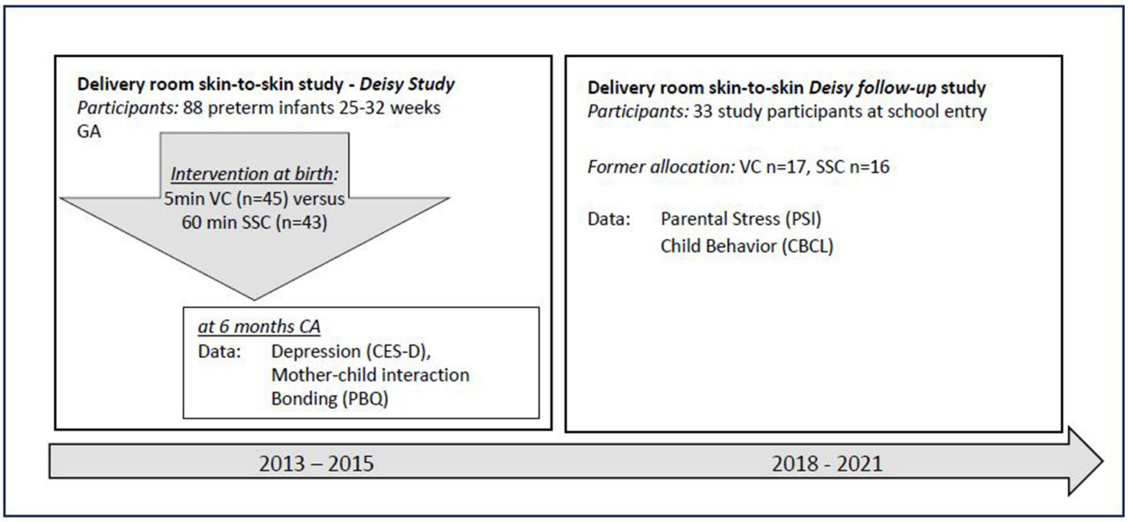

FIGURE 1
Timeline of the initial and the follow-up delivery room skin-to-skin study. GA, gestational age; VC, visual contact; SSC, skin-to-skin contact; CA, corrected age.

The assessment time is presented in Figure 1. Sociodemographic data (e.g., parental age, level of education, financial situation, employment, and number of children) and basic data on neonatal course were collected at birth.

2.2.1 Center for epidemiological studies depression scale (CES-D)

Depressive symptoms were assessed with the German version of CES-D, long form (Hautzinger and Bailer, 1993). This instrument consists of 20 self-descriptive statements in the first person relating to the past week. The items refer to typical affective, cognitive, somatic, and social depressive symptoms. The possible answers range from "0—rarely/not at all" to "3—mostly/all the time". All 20 items added together build a total score (range of 0–60), and 4 items are scored reversely. Higher values indicate a higher level of depressive symptoms. Clinical cutoffs are also available. For this study, only the total value is used. The German version of CES-D has good overall psychometric proprieties and internal reliability (Cronbach's alpha 0.85–0.92).

2.2.2 Postpartum bonding questionnaire (PBQ)

The PBQ was originally developed to assess the emotional bond between a mother and her child (Brockington et al., 2001, 2006), but meanwhile, the PBQ has been also frequently used for partners. The PBQ is a self-report screening instrument and consists of 25 positive and negative statements rated on a scale of 0 to 5. Positive statements are scored as "marked" and negative statements as "reversed". The sum of all values constitutes a general score; in addition, three subscales could be built: impaired bonding, rejection and anger, and anxiety about care. For all scales, a higher score indicates more bonding difficulties. The German version yields a good internal consistency (Cronbach's alpha 0.85) (Reck et al., 2006). Brockington et al. (2001) proposes cutoff points for each scale to identify problematic bonding for this study; however, we only used the scores.

2.2.3 The parenting stress index (PSI)

The PSI (Abidin, 1995) is a widely used instrument to assess stress specifically associated with parenting. The self-report items are related to the parent's perception of difficulties in the parental role, the parent–child interaction, and specific infant characteristics, which make it difficult to cope with the child (e.g., the baby is perceived as irritable, agitated, and moody). The German version (Hofecker Fallahpour et al., 2009) contains 12 subscales with four items each. Items are scored on a 5-point Likert scale. The scales indicate the source of stress and cover the following aspects: distractibility/hyperactivity, mood, acceptability, demand, and adaptability in the child domain and attachment, social isolation, parental competence, depression, health, personal limitations, and partner relationship in the parent domain. Two partial scores and total scores could be built. Although cutoff values were established to identify parents with significant levels of distress, only the total score values were included in the analysis. The German version demonstrated very good internal consistency, with a Cronbach's alpha of 0.95 for the total score and 0.91 to 0.93 for the subscales.

2.2.4 Child behavior checklist/6-18 (CBCL/6-18)

The Child Behavior Checklist/6-18 is an internationally widely used, standardized tool for assessing behavioral and emotional problems of school-age children (6–18 years). The German version (Döpfner et al., 2024) consists of a 118-item questionnaire and is administered to parents using a 3-point scale (0 = not true to 2 = very true) to rate how true each item is. Scores could be calculated for eight clinical subscales (Withdrawn/Depressed, Somatic Complaints, Anxious/Depressed, Rule-Breaking Behavior, Aggressive Behavior, Social Problems, Thought Problems, and Attention Problems). These subscales can be grouped into two higher-order factors: internalizing and externalizing problems (Cronbach's alpha of 0.90 and 0.94, respectively) and added up to a total problem score (Cronbach's alpha of 0.97).

2.3 Statistical analysis

For data management and statistical analysis, SPSS (Version 28, IBM, Armonk, NY, USA) was used. Pearson's chi-square and univariate ANOVA were used to test the similarity of the study group with the drop-out group, likewise to prove the homogeneity among the SSC and the VC groups.

Means and standard deviations for the CES-D, PBQ, and PSI scores were calculated, and Spearman's rho coefficients were used to determine the association between these variables (CES-D, PSI, and PBQ) as well as the association between the variables and the CBCL scores.

A stepwise hierarchical regression analysis was performed to assess the significance of DR-SSC in the prediction of emotional and behavioral problems (CBCL total score) while controlling for neonatal course and maternal variables, including depressive symptoms, parental stress, and bonding. In the first step, maternal age and child gender were included, followed by the APGAR score at 10 min after birth and the number of hospitalization days. After that, the CES-D score, the PBQ, the PSI variables, and finally skin-to-skin contact were introduced (forced) into the model.

The level of significance for all tests was two-sided and set at a $p = 0.05$.

3 Results

3.1 Depressive symptoms, parental stress, and bonding

Descriptive statistics for depressive symptoms, parental stress, and bonding (at 6 months CA) are presented in Table 1. Maternal depressive symptoms were significantly correlated only with the parent domain score of the PSI. On the other side, higher scores in the child domain were associated with more rejection and anger and more anxiety about care. Interestingly, the only PBQ scale that correlated with the PSI parent domain was impaired bonding. Both domains were strongly associated. Contrary to our expectations, no PBQ scale correlated significantly with depressive symptoms. Furthermore, higher parental stress (PSI total score) is associated with a poorer maternal bond to her child (PBQ total scores). All results are shown in Table 2.

TABLE 2 Descriptive statistics and intercorrelations (6 mo. CA).

	M	SD	Range	1.	2.	3.	4.	5.	6.	7.
1. CES-D	10.5	8.95	0–35	-						
2. PSI Child Domain	57.7	10.22	32–70	0.219	-					
3. PSI Parent Domain	54.52	9.61	30–70	**0.375***	**0.883*****	-				
4. PSI Total Score	56.06	10.58	30–70	0.310	**0.957*****	**0.970*****	-			
5. PBQ Impaired bonding	5.57	4.37	0–15	0.264	0.342	**0.362***	0.340	-		
6. PBQ Rejection and anger	2.23	3.06	0–14	0.247	**0.442***	0.242	0.340	**0.728*****	-	
7. PBQ Anxiety about care	2.07	1.62	0–7	0.068	**0.442***	0.341	**0.380***	**0.448***	**0.464***	-
8. PBQ Total Score	9.87	7.7	0–34	0.219	**0.475****	**0.393***	**0.424****	**0.922*****	**0.872*****	**0.631*****

***p < 0.001; **p < 0.01; *p < 0.05.
CES-D, Center for Epidemiological Studies Depression Scale; PSI, Parental Stress Index; PBQ, Postpartum Bonding Questionnaire. Bold means statistically significant.

TABLE 3 Descriptives for CBCL scores and correlation with CES-D (Center for Epidemiological Studies Depression Scale), PSI (Parental Stress Index), and PBQ (Postpartum Bonding Questionnaire).

Variables	CBCL internalizing	CBCL externalizing	CBCL total score
1. CES-D	0.147	0.164	0.116
2. PSI child domain	0.362*	0.623***	0.802***
3. PSI parent domain	0.348*	0.598***	0.687***
4. PSI total score	0.394*	0.607***	0.748***
5. PBQ impaired bonding	0.241	0.455*	0.433*
6. PBQ rejection and anger	0.163	0.295	0.390*
7. PBQ anxiety about care	0.136	0.317	0.380*
8. PBQ total score	0.290	0.446*	0.511**
M (S)	56.61 (6.55)	54.33 (9.91)	57.36 (8.55)
Min–Max	45–70	35–73	40–74
>cutoff	*N* = 5	*N* = 3	*N* = 5

N = 33.
***p < 0.001; **p < 0.01; *p < 0.05.

TABLE 4 Skin-to-skin contact and Child Behavior Checklist Score at school start—stepwise (forward) regression analysis.

	CBCL total score					
	ß	T	R^2	R^2adj.	F	p
Model 1						
PBQ total score	0.418	2.394				
			0.175	(0.145)	5.731	**0.024**
Model 2						
PBQ total score	0.084	0.667				
PSI child domain	0.773	6.107				
			0.661	(0.635)	25.365	**<0.001**
Model 3						
PBQ total score	0.087	0.657				
PSI child domain	0.772	5.931				
DR-SSC	−0.010	−0.083				
			0.661	(0.621)	16.267	**<0.001**

Excluded variables: maternal age, gender of infant, 10-min Apgar score, hospitalization days, and maternal depressive symptoms.
PBQ, Postpartum Bonding Questionnaire; PSI Parental Stress Index; DR-SSC, delivery room skin-to-skin contact. Bold means statistically significant.

3.2 CBCL scores and maternal depression, parental stress, and bonding at school entry

No significant associations were found between maternal depressive symptoms and any CBCL score. However, both PSI domains (parent and child) presented a high level of association with all CBCL scores: Higher perceived stress was associated with a higher number of externalizing and internalizing behaviors, with a stronger association observed for externalizing behaviors. In relation to the values observed with the PBQ, no scale presented a significant association with internalizing behaviors, while the impaired bonding scale and the PBQ total score correlated with the externalizing and the total score. The CBCL total score was strongly associated with all aspects of the PSI and the PBQ (Table 3).

3.3 The role of skin-to-skin contact immediately after childbirth in the prediction of emotional and behavioral problems at school start

Maternal age, gender of infant, Apgar score, hospitalization days, and maternal depressive symptoms—included in the analysis for control—were not significant in any of the models. Even though the PBQ total score reached significance in the first model, this significance was lost in the next step, when the PSI variables were entered. The PSI child domain was the only variable that attained significance and remained significant after the forced inclusion of DR-SSC, which was not significant. The last model explained 66% (R^2 0.661, R^2cor 0.621) of the variance (<0.001). The results of the stepwise regression analysis are shown in Table 4.

4 Discussion

The aim of this study was to examine the effect of SSC immediately after childbirth on the development of emotional and behavioral problems in children born preterm entering school. It was hypothesized that children receiving DR-SSC would have fewer behavioral and emotional problems than children receiving only VC in the delivery room. We expected that the positive effect of SSC observed by different authors and in our own previous studies could also be maintained in the long term. However, this hypothesis could not be demonstrated: SSC immediately after childbirth was not significant in the prediction of emotional and behavioral problems at school start. Neither the depressive symptoms nor the quality of bonding variable contributed the most to the variance explanation, but the perceived parental stress at 6 months CA variable did, which was an unexpected result. A fundamental aspect of the interpretation of the results is the small sample size, which unfortunately does not allow for more complex analyses and can mislead the results.

The fact that DR-SSC was not the explanatory factor for the behavioral and emotional problems observed in school-aged children could be understood (among others), through the feeling of being a family and belonging together that first becomes evident to parents as time passes—a comment that is often heard in contact with these parents in daily clinical practice. Parents of premature children often say that they do not perceive this feeling of belonging until the moment their children are discharged, unlike parents of children born full term and without problems, who can engage in the parental role and, for example, hold their children immediately after birth (Schuetz Haemmerli et al., 2020). Therefore, DR-SSC, an intervention that has a high impact at that specific moment in family life, might lose this effect over time and with the adjustment of parental feelings and family life.

The lack of association between maternal depressive symptoms and the level of behavioral and emotional problems of children at school entry could be explained in the same direction. Although depressive symptoms have been widely demonstrated to be a risk factor for the presence of children's behavioral and emotional problems (even regardless of prematurity), it is important to consider that the depressive data we used for our analyses were collected a long time before. The existing literature for the specific case of parents of premature children indicates that in most cases, depression gradually declines over time (Barkmann et al., 2018; Genova et al., 2022; Pace et al., 2016). This trend was also observed in our study (Mehler et al., 2020). However, depressive symptoms remain associated with parental stress (parent domain), a phenomenon that could be explained by the inverse relationship between parents' perception of the demands of parenting and the personal available resources to cope with them. This lack of confidence has been described even for depressive parents of full-term children (Aviles et al., 2024; Pazzagli et al., 2023; Reck et al., 2016; Sandnes et al., 2024).

Similarly, parental stress plays an important role in the development of an emotional bond with the baby: The higher the stress perceived by the birth parents, the worse the bond quality to their preterm infants. Our results showed a strong association between the Parental Stress Index with the observed values of the PBQ at 6 months. The child domain score, which comprises negative characteristics of the infants, is related to the PBQ-Subscales Rejection and Anger, Anxiety about care, and the PBQ Total Score. It could be hypothesized that these children were already more irritable, agitated, moody, etc. at the age of 6 months and that is why their mothers had difficulties in establishing a good bond with them, which in turn would allow us to think that these negative characteristics continue even at the age of entering school. In addition, the PBQ-Subscale Impaired Bonding, which indicates some kind of occasional delay in, or temporary loss of maternal feeling about the infant but not established rejection or anger (Brockington et al., 2001, 2006), is the only subscale associated with the parent domain score. Further maternal bonding and parenting stress were still significantly associated with CBCL scores at school beginning but not with depressive symptoms. These results are in line with those by Fransson et al. (2020), who pointed out the mediating role of postpartum bonding difficulties in this context. This association between parental stress and PBQ scores could explain the loss of significance when the parental stress variable was entered into the regression model, although the bonding quality plays an important role in the development of behavioral problems.

Finally, the role of perceived parental stress could be better understood from a differentiated perspective of parental stress in the context of prematurity and the COVID-19 pandemic. Chronic but also acute stressors have the potential to increase the demands of parenting and thus parenting stress (Aviles et al., 2024). In their review, Sandnes et al. (2024) reported increased stress levels in the first 2 years after birth in 15–56% of parents of premature infants; however, only a few studies have focused on parental stress into school age or longer. Nevertheless, parenting stress following preterm birth can remain high until the age of 7 years and could be mainly caused by children's difficulties (Treyvaud et al., 2014) or characteristics, such as temperament or chronic physical and/or mental health conditions (Deater-Deckard and Panneton, 2017). In any case, parenting stress can increase the risk of a child's negative behavioral and emotional outcomes in the present and/or over the years, certainly not only by children born preterm (Crnic et al., 2005; Deater-Deckard and Panneton, 2017; Han and Lee, 2018; Neece et al., 2012; Ribas et al., 2024; Spinelli et al., 2020). Considering that part of the data related to children's problem behaviors was carried out during the COVID-19 pandemic, it is possible to speculate that this high-stress situation had an impact on both the level of parental stress and the CBCL scores. All of this allows us to hypothesize that the level of parental stress in these families could have remained high in these years and thus explain the strong effect of this variable on the behavioral problems of children upon entering school. In addition, this fact may have led to a selection bias in the group that participated in this part of the study. On the one side, parents could have facilitated participation in the study to obtain a founded professional opinion if they have noticed an increase in problematic behaviors by their children or, on the other, to address doubts and obtain specialized guidance if necessary.

5 Limitations

Clear limitations of this study should be mentioned. Even though the study group does not differ in relation to sociodemographic and perinatal variables from the original group, the participating families represent <40% of it. A major deficit was not having included information about the partner (as a possible moderating factor) and not having collected current information. Furthermore, the children's behaviors were only evaluated with a global instrument (CBCL/6-18), which does not collect objective information but instead the perception of the parents. One can speculate that the DR-SSC could have long-term effects on other areas of development or that its effect could be much more differentiated than that which could be assessed with the instruments used.

6 Conclusion

The extensive existing literature has shown that DR-SSC, even for very premature children, is safe and feasible and has important benefits for both the babies and their parents. Although in this study its long-term effect could not be demonstrated in relation to the presence of behavioral problems upon entering school, other results are still interesting. Parental stress and its long-term influence on the emergence of behavioral problems is an important piece of information, especially for the support and follow-up programs for families with children born prematurely. In the long-term perspective, maternal stress seems to be much more important than having had skin-to-skin contact immediately after birth. Since premature birth is a situation of extreme vulnerability for the entire family, a comprehensive and careful approach that also includes psychoeducation, coping with stress, parental empowerment, and at least family mental health is required. Since in Germany, there are numerous care programs for premature children and their families, the affected families normally receive the necessary support throughout the different evolutionary stages. Medical, psychological, financial, and social familial support is guaranteed by law.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Ethics Committee of the University of Cologne, Germany. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

KM: Conceptualization, Data curation, Funding acquisition, Supervision, Writing – review & editing. EH: Data curation, Formal analysis, Writing – review & editing. AK: Conceptualization, Supervision, Writing – review & editing. PT-V: Data curation, Formal analysis, Supervision, Validation, Writing – original draft.

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EDITED BY
Livio Provenzi,
University of Pavia, Italy

REVIEWED BY
Benedetta Ragni,
Libera Università Maria SS. Assunta, Italy
Christine Tuden Neugebauer,
Texas Tech University Health Sciences Center, United States

*CORRESPONDENCE
Haixia Fang
✉ fhx13979835482@163.com

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Assessing the needs of grandparents of preterm infants in neonatal intensive care units: a cross-sectional study

Huamin Huang[1], Jingyun Tao[1], Ying Lei[1], Rui Chen[1] and Haixia Fang[2]*

[1]Pediatric Department, the Second People's Hospital of Jingdezhen, Jingdezhen, Jiangxi, China,
[2]Emergency Department, the Second People's Hospital of Jingdezhen, Jingdezhen, Jiangxi, China

Background: Globally, there is an increasing trend in the incidence of premature births and low birth weight. Neonatal intensive care unit (NICU) care has become indispensable for these newborns. Nevertheless, this mode of care poses substantial economic, psychological, and health challenges to the families of preterm infants. Despite abundant evidence concerning the parents' needs in the NICU, the needs of grandparents—vital family members—are frequently disregarded. This exploratory study aimed to assess the grandparents' needs of preterm infants in the NICU, exploring the impact of demographic elements on these needs to offer guidance for clinical care practices.

Methods: This study employed a cross-sectional design and the Chinese version of the NICU Family Needs Inventory (NICU-FNI) to investigate the needs of grandparents. A total of 280 grandparents participated in the study, providing data by completing structured questionnaires related to their demographic profiles and needs. Statistical analyses were utilized to analyze the data, including descriptive statistics, chi-square tests, Pearson's correlation, and multiple linear regression.

Results: Six items about Assurance emerged as significant among the top 10 important needs, with two items for Information, one for Proximity, and one for Support; among the least important needs, nine items related to Comfort and Support were identified. The subscale "Assurance" achieved the highest mean score of 4.07 ± 0.49, followed by the subscales of "Information" and "Proximity," registering mean scores of 3.50 ± 0.47 and 3.50 ± 0.46, respectively. This explorative study identified a correlation between the needs for Assurance and employment status, place of residence, gestational age, and birth weight ($p < 0.05$). Employment status, place of residence, and gestational age were identified as significant correlates for Assurance ($p < 0.05$).

Conclusion: The foremost need identified by grandparents is Assurance of quality care for preterm infants, closely followed by the demand for thorough Information and the ability to be in Proximity to the infant. This exploratory study highlights that mitigating the strain on families with preterm infants, as well as recognizing and meeting the needs of grandparents, is of paramount importance.

KEYWORDS
preterm infants, neonatal intensive care unit, grandparents, critical illness, family needs, China

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Introduction

The neonatal intensive care unit (NICU) offers life-saving care; however, the exorbitant expenses and intricate caregiving procedures can impose considerable emotional and psychological burdens on the entire family, precipitating conditions such as depression, anxiety, and trauma (Geng et al., 2022; Grunberg et al., 2022). Generally, neonates necessitating urgent medical intervention are admitted to the NICU (Chow et al., 2015). Such infants are commonly characterized by preterm birth (i.e., occurring prior to 37 weeks of gestation), low birth weight, and/or the presence of severe medical ailments (Chow et al., 2015). As per the WHO's "Global Report on Preterm Births," the worldwide occurrence rate of preterm or low birth weight deliveries increased from 9.6% in 2005 to 11.1% in 2012 (WHO, 2012). Furthermore, in a 2011 nationwide survey in China, the preterm birth incidence was recorded at 7.1% (Zou et al., 2014). Following the relaxation of China's two-child policy in 2015, the surge in advanced maternal age, multiparous women, and multiple gestation pregnancies has significantly led to an escalation in the preterm birth rate (Yang et al., 2017; Zhang et al., 2021).

Parents of premature infants are frequently confronted with a variety of challenges pertaining to economic, psychological, and physical health. Upon the admission of their infants to the NICU, these parents often undergo emotions of anxiety, depression, guilt, and a sense of helplessness, potentially adversely (Kim, 2018; Lorié et al., 2021). Identifying and addressing parental needs in the NICU is a crucial factor in achieving the best outcomes for newborns and their families. Specifically, parents of preterm infants have emphasized the significance of obtaining infants' health information and guidance (Arockiasamy et al., 2008; Harris et al., 2024), trusting medical staff (Bernaix et al., 2006), and benefiting from Support from staff to meet their needs (Bernaix et al., 2006; Pepper et al., 2012).

The emergence and evolution of the concept of "family-centered care" has led to active parental involvement as primary caregivers in the care of preterm infants, representing critical factor in enhancing the post-discharge survival quality of preterm infants; the majority of research on the family needs in NICU has mainly concentrated on newborn parents (Arockiasamy et al., 2008; Diffin et al., 2013), particularly on mothers of preterm infants (Govindaswamy et al., 2020). Usually, mothers may suffer physical discomfort after delivery, making it impossible to care for the baby; fathers serve as the initial point of contact between the family and the NICU staff and are the ones who decide on the need for emergency treatment (Arockiasamy et al., 2008; Johnson, 2008). Nevertheless, grandparents play a pivotal role in the family, especially for parents of preterm infants in single-child households. In China, they hold an especially significant position, often enjoying relatively high economic status and social standing (Zhang et al., 2022). Moreover, there is a high prevalence of grandparents living with their grandchildren in China. These resident grandparents play a vital role in raising the children, particularly once the child has passed their first birthday. While caring for the children, grandparents often work with healthcare professionals to ensure the children's wellbeing. This includes regular health checkups, vaccinations, and monitoring of the children's development, requiring the active involvement and cooperation of the grandparents (Chen et al., 2011; Chen and Lewis, 2015). Chinese fathers often rely on grandparents for support to reduce their stress, considering the mother's need for care. Grandparents are viewed as the most trusted individuals (Sun et al., 2024).

Studies have demonstrated that, in the context of a family member's acute severe illness, the concept of family resilience is instrumental in facilitating adaptive responses and preserving familial equilibrium in the face of both internal and external crises (Gao et al., 2022; Shao et al., 2023; Walsh, 2016). The critical role of grandparents in enhancing family resilience is unmistakable; they provide support and comfort to younger parents, thereby strengthening the family's collective resilience through shared confrontations with adversities (Lambiase et al., 2024). In the high-pressure environment of the NICU, grandparental support helps alleviate the emotional strain on parents, increases familial cohesion, and enhances the family's ability to navigate hardships (Brødsgaard et al., 2017). Hence, grasping the needs of grandparents with a premature infant in the NICU is of utmost importance; healthcare professionals should be adequately prepared to meet grandparents' needs by offering the necessary support and assistance. Such proactive measures can significantly reduce the grandparents' emotional burden, by extension, on the parents, establishing a constructive dialog between patient families and healthcare providers, thereby reducing the incidence of medical disputes (Brødsgaard et al., 2017; Jain et al., 2021; Sun et al., 2024). This exploratory study aims to investigate the unique needs of grandparents with preterm infants in the NICU. The primary aim is to generate initial insights that will assist healthcare professionals in understanding how to provide more tailored and effective support and to offer foundational information to regulatory authorities as a basis for potential considerations in developing NICU policies.

Materials and methods

Study design and setting

The NICU-Family Need Inventory (NICU-FNI) is a specialized adaptation of the Critical Care Family Needs Inventory (CCFNI) by Ward (2001), incorporating the research by Jacono et al. (1990) and Kirschbaum (1990), explicitly designed to address the needs of parents with NICU infants. The NICU-FNI is divided into five domains (Leske, 1991; Ward, 2001): Support (interpersonal and emotional needs); Comfort (personal and physical comfort); Information (pragmatic information about the infant); Proximity (remain in the range of infant); and Assurance (experience confidence about the infant). The NICU Family Needs Inventory comprised 56 items to measure the importance attributed to parents' needs using a 5-point Likert scale incorporated into each item: 5 = extremely important, 4 = important, 3 = moderately important, 2 = unimportant, and 1 = extremely unimportant. Zhang et al. (2016) translated the NICU-FNI scale into Chinese and evaluated the reliability and validity of the scale, with results indicating Cronbach's alpha coefficient of 0.957 for the translated NICU-FNI scale, a test–retest reliability of 0.875, and a content validity index (CVI) of 0.934. The correlation coefficients between each dimension and the total score ranged from 0.753 to 0.872, thus demonstrating good reliability and validity in the preliminary testing of the Chinese version of the NICU-FNI scale among parents with a premature infant in the NICU in China. In this study, we utilized the Chinese version of the NICU-FNI scale (Zhang et al., 2016) and re-evaluated its reliability and validity. The findings indicated Cronbach's alpha coefficient of 0.963 and a test–retest reliability of 0.792 for the NICU-FNI scale, demonstrating good reliability and validity in preliminary testing among grandparents of premature infants in the NICU in China. Building on previous studies (Ward, 2001; Zhang et al., 2016), this questionnaire (see Supplementary material) was developed in two parts: the first part collected demographic information on grandparents, mothers, and newborns, while the second part consisted of the Chinese version of the NICU-FNI scale (40 items).

Study population and sample size

The cross-sectional study was conducted at the Obstetrics and Gynecology office of the Second People's Hospital of Jingdezhen between February and December 2023. Stringent selection procedures identified a cohort of grandparents visiting infants hospitalized in the NICU as the study sample. In order to uphold the strictness and precision of the research, obstetric nurses were tasked with issuing research invitations to them and delivering comprehensive research information sheets in print format. Upon reception of the information sheets, these grandparents were asked to read and comprehend the contents diligently. Following this, we instructed the grandparents who agreed to participate in the research to complete a questionnaire survey. The inclusion criteria for this study were grandparents whose premature grandchildren were still receiving treatment in the NICU at the time of questionnaire completion. Using the mother's admission number for preterm infants or the infants' own admission numbers as unique identifiers, one grandparent was chosen to participate in the survey. In cases involving twins, two grandparents were chosen for the study. Exclusion criteria included grandparents of infants whose grandchildren had completed NICU treatment and were discharged and grandparents who did not understand Chinese.

We calculated the sample size using the Power Analysis and Sample Size (PASS) Version 15.0 software (NCSS, LLC, Kaysville, Utah, USA). A sample of 258 participants, each responding to 40 items, achieves 90% power to detect the difference between the coefficient alpha under the null hypothesis of 0.80 and the coefficient alpha under the alternative hypothesis of 0.85. This is accomplished using a two-sided *F*-test with a significance level of 0.05 (Bonett, 2002). Considering the estimated 10% non-response rate, we calculated the expected sample size to be 287 participants.

Ethical clearance for this research was granted by the Ethics Committee of the Second People's Hospital of Jingdezhen, documented by Approval No: 2023-LLLW-07. Moreover, it conformed to the Declaration of Helsinki principles, guaranteeing that informed consent was obtained from all participants.

Statistical analysis

Utilizing descriptive statistics, the study summarized survey responses, representing data in tables with counts and percentages for response categories, assessing response frequency differences across groups using a chi-square test, conducting a one-way ANOVA for comparisons among three or more groups, and investigating correlations between dependent and independent variables through Pearson's correlation analysis. Univariate linear regression and multivariate multiple linear regression analyses were conducted to find factors relevant to identifying grandparents' needs. All statistical analyses were performed using SPSS statistical software (version SPSS 20.0, IBM SPSS Inc., Chicago, IL, USA). *p*-values <0.05 were considered to indicate statistical significance.

Results

Demographics of the respondents

The questionnaires were distributed to 287 grandparents, with 280 completed and returned. All respondents belonged to independent families associated with the NICU, meaning that each family had only one grandparent complete the questionnaire, resulting in a response rate of 97.6%. As shown in Table 1, among these 280 participants, grandmothers constituted 50.7%. The mean age of participants was 59.6 years (S.D. = 7.2 years). Regarding age groups, the proportions were as follows: ≤55 years (26.4%), 56–60 years (30.4%), 61–65 years (23.2%), and > 65 years (20.0%). In terms of place of residence, 45.0% of the grandparents lived in towns or cities, whereas 55.0% resided in the countryside. In terms of education level, the proportions were as follows: college and above (18.6%), junior high school/technical secondary school (27.5%), junior middle school (26.8%), and primary school and below (27.1%). Furthermore, employment status

TABLE 1 Demographics of grandparents ($n = 280$).

Characteristics	Frequency (*n*, %)	*p*-value
Sex		
Male	138 (49.3)	0.811
Female	142 (50.7)	
Age group (years)		
≤55	74 (26.4)	0.086
56–60	85 (30.4)	
61–65	65 (23.2)	
>65	56 (20.0)	
Place of residence		
Town/city	126 (45.0)	0.094
Countryside	154 (55.0)	
Education level		
College and above	52 (18.6)	0.102
Junior high school/technical secondary school	77 (27.5)	
Junior middle school	75 (26.8)	
Primary school and below	76 (27.1)	
Employment status		
Employed full-time	66 (23.6)	0.532
Employed part-time	62 (22.1)	
Unemployed	75 (26.8)	
Retired	77 (27.5)	

All calculations were performed using the one-way ANOVA, except for sex and place of residence, which were evaluated using the chi-square tests.

distribution includes full-time employment (23.6%), part-time employment (22.1%), unemployment (26.8%), and retirement (27.5%).

As shown in Table 2, the distribution of newborn characteristics revealed significant variations in gestational age, birth weight, and admission diagnosis. Gestational age categories were as follows: 28–34 weeks (9.3%), 34–37 weeks (27.9%), and over 37 weeks (62.9%), showing a statistically significant difference ($p < 0.001$). Birth weight categories included under 1,500 g (1.4%), 1,501–2500 g (34.3%), and over 2,501 g (64.3%), with a notable statistical significance ($p < 0.001$). In terms of admission diagnosis, the frequencies were as follows: neonatal jaundice (37.9%), neonatal infectious pneumonia (36.4%), neonatal hypoxic–ischemic encephalopathy (10.7%), premature infants (8.6%), neonatal respiratory distress syndrome (5.0%), and neonatal asphyxia (1.4%). The differences in admission diagnoses were also found to be statistically significant ($p < 0.001$).

The most and least important needs of grandparents

The 10 most and least important aspects, based on the results from the NICU-FNI scale, can be found in Table 3. Among the top 10 most important needs, six items for Assurance emerged as a significant factor, with grandparents expressing a strong desire for their infant to receive the best care even in their absence from the hospital. Additionally, grandparents emphasized the importance of being informed about their baby's condition and treatments, having their questions answered honestly, and receiving explanations in a clear and understandable manner. The need for Proximity and Information regarding the baby's progress also ranked high. On the other hand, among the 10 least important needs, aspects related to Comfort and Support were prominent. Specific requirements, such as restroom availability in the waiting room and private areas in the hospital, were ranked lower in importance. Overall, the findings highlight the crucial role of Assurance, Information, and Support in addressing the needs of grandparents in the NICU while suggesting that certain Comfort-related factors may be of lesser priority.

TABLE 2 Characteristics of the preterm infants in neonatal intensive care units ($n = 280$).

Newborn characteristics	Frequency, *n* (%)	*p*-value
Gestational age, weeks		
28–34	26 (9.3)	<0.001
34–37	78 (27.9)	
>37	176 (62.9)	
Birth weight, g, *n* (%)		
<1,500	4 (1.4)	<0.001
1,501–2,500	96 (34.3)	
>2,501	180 (64.3)	
Admission diagnosis		
Neonatal jaundice	106 (37.9)	<0.001
Neonatal infectious pneumonia	102 (36.4)	
Neonatal hypoxic–ischemic encephalopathy	30 (10.7)	
Premature infants	24 (8.6)	
Neonatal respiratory distress syndrome	14 (5.0)	
Neonatal asphyxia	4 (1.4)	

Comparisons between groups were performed using the one-way ANOVA.

NFNI subscale scores and their rankings

Among the identified subscales, "Assurance" received the highest mean score of 4.07 ± 0.49, ranking it as the most important need for grandparents in the NICU setting. This underscored the significance of providing reassurance and emotional Support to grandparents during this difficult time. The subscales "Information" and "Proximity" obtained identical mean scores of 3.50 ± 0.47 and 3.50 ± 0.46, respectively, indicating their equal importance in the second and third positions. These findings highlight the value of clear and comprehensive Information about the infant's condition and the opportunity for grandparents to be physically close to their grandchild. The "Support" subscale had a mean score of 3.10 ± 0.39, placing it fourth in importance. This suggests that grandparents greatly benefit from various forms of Support, such as emotional, practical, and social support, while their grandchild is in the NICU. Finally, the "Comfort" subscale received the lowest mean score of 2.90 ± 0.53; it ranked fifth, indicating that although Comfort is still important, it may be less prioritized by grandparents than other needs. In conclusion, grandparents in the NICU setting primarily value Assurance, followed by the need for Information and Proximity. Support is also crucial, whereas Comfort holds a slightly lower priority. These findings shed light on the needs of grandparents and emphasize the importance of addressing them to provide optimal Support and care during their grandchild's NICU stay (Table 4).

Correlation between grandparents' needs and demographic characteristics

In Table 5, we identify statistically significant correlations between the needs of grandparents and their demographic attributes, as well as those of preterm infants. Specifically, the age of the grandparents is positively associated with the need for Proximity ($r = 0.143$; $p < 0.05$), suggesting older grandparents have more demand for proximity to preterm infants. The educational attainment of grandparents is positively related to the need for Information ($r = 0.135$; $p < 0.05$), yet inversely related to the need for Proximity ($r = 0.159$; $p < 0.01$), revealing that grandparents with lower education levels may seek less Information but desire greater Proximity to their grandchildren. The employment status of grandparents is associated with Assurance ($r = 0.122$; $p < 0.05$), Proximity ($r = 0.219$; $p < 0.01$), and Support ($r = 0.138$; $p < 0.05$), suggesting that retired grandparents may seek a more profound connection with grandchildren. The place of residence of grandparents is positively associated with the need for Assurance ($r = 0.179$; $p < 0.01$), Proximity ($r = 0.168$; $p < 0.01$), and Comfort ($r = 0.118$; $p < 0.05$), indicating that grandparents residing in rural areas may exhibit a greater need for these aspects than those in urban settings.

Regarding the attributes of preterm infants, there is a negative correlation between gestational age and the grandparents' needs for Assurance, Information, Support, and Comfort, as well as the overall

TABLE 3 Ten most and least important needs of grandparents according to NICU-FNI scale scores ($n = 280$).

Ten most important needs of grandparents	NICU-FNI subscale	Mean score (x ± SD)
To be assured that the best care possible is being given to my infant even in my absence from the hospital	Assurance	4.28 ± 0.54
To be assured that the best care possible is being given to my infant	Assurance	4.25 ± 0.52
To know the expected outcome for my infant	Assurance	4.24 ± 0.52
To have my questions regarding my infant answered honestly	Assurance	4.23 ± 0.48
To have the medical staff provide an explanation in simple terms	Assurance	4.21 ± 0.54
To know how my infant is being treated medically	Information	4.21 ± 0.51
To know specific facts concerning my infant's progress	Proximity	4.18 ± 0.55
To know the expected outcome for my infant	Assurance	4.17 ± 0.57
To know the expected outcome	Information	4.14 ± 0.45
To have explanations of the NICU environment before entering for the first time	Support	4.14 ± 0.55
Ten least important needs of grandparents		
To have a bathroom near the waiting room	Comfort	2.87 ± 1.04
To have a place to be alone while in the hospital	Support	2.86 ± 0.94
To have friends/family nearby	Support	2.84 ± 1.14
To have classes about premature infant's special care needs	Information	2.83 ± 1.02
To be able to talk to other parents whose infant is in the neonatal intensive care unit or has had a similar situation	Support	2.83 ± 0.87
To have a support group of other families available	Support	2.79 ± 0.94
To be allowed to have my infant's siblings visit	Support	2.76 ± 0.94
To have friends/family nearby	Support	2.75 ± 1
To have someone to be concerned with my health	Support	2.68 ± 1.05
To have a telephone in the waiting room	Comfort	2.13 ± 0.89

The Neonatal Intensive Care Unit Family Need Inventory Scale is categorized into five dimensions: Assurance, Information, Proximity, Support, and Comfort. NICU, neonatal intensive care unit; NICU-FNI, NICU-Family Need Inventory.

need score. This indicates that as the gestational age of a premature infant at birth increases, the needs of the grandparents decrease. The birth weight is inversely related to the need for Assurance ($r = -0.263$; $p < 0.01$) and Information ($r = -0.214$; $p < 0.01$), potentially indicating heightened concern among grandparents for the health issues pertaining to infants with lower birth weights.

TABLE 4 Mean importance of neonatal family needs inventory subscales for grandparents.

NICU-FNI subscale	Mean score (x ± SD)	Ranking of important needs
Assurance	4.07 ± 0.49	1
Information	3.50 ± 0.47	2
Proximity	3.50 ± 0.46	3
Support	3.10 ± 0.39	4
Comfort	2.90 ± 0.53	5

NICU, neonatal intensive care unit; NICU-FNI, NICU-Family Need Inventory.

Multiple linear regression analysis of needs among grandparents

Multiple linear regression analysis was employed to elucidate the determinants of grandparents' needs. Six family needs models were identified for the analysis (covering the grandparents' needs), focusing on the mean scores of NICU-FNI, including the needs for Assurance, Information, Proximity, Support, and Comfort.

The results from the multiple regression models, which analyzed the needs of grandparents across different dimensions, identify key predictors that are associated with various aspects of Support in the NICU as depicted in Table 6. The mean score model highlights significant associations between the mean score and employment status ($p = 0$), place of residence ($p = 0.038$), and birth weight ($p = 0.001$). This indicates that grandparents who are retired, live in rural areas, and have grandchildren with lower birth weights have greater needs. In the domain of Assurance, the predictors of significance were employment status ($p = 0.005$), place of residence ($p = 0.027$), and gestational age ($p = 0$), indicating that grandparents who are retired and residing in rural locales, along with their grandchildren of lower birth weights, possess an augmented need for Assurance. The Information model revealed that the level of education ($p = 0.006$) and gestational age ($p = 0$) exert significant impacts on the need for Information, indicating that grandparents possessing higher educational qualifications and their grandchildren with reduced birth weights exhibit a more substantial need for Information. The Proximity model identified employment status ($p = 0.002$) and place of residence ($p = 0.008$) as significant predictors, suggesting that grandparents who are retired and reside in rural areas have an increased need for Proximity. In the Comfort model, gestational age ($p = 0$) was the only factor identified as a significant predictor, whereas the Support model showed no significant predictors.

TABLE 5 Statistically significant correlations between grandparents' needs and demographic characteristics.

Characteristics	Assurance	Information	Proximity	Support	Comfort	Mean score
Sex	−0.026	−0.019	−0.081	−0.06	−0.032	−0.058
Age	−0.034	−0.046	0.143*	0.045	−0.036	0.015
Education level	−0.096	0.135*	−0.159**	−0.002	−0.028	−0.042
Employment status	0.122*	0.087	0.219**	0.138*	0.084	0.174**
Place of residence	0.179**	0.05	0.168**	−0.007	0.118*	0.144*
Gestational age	−0.394**	−0.300**	−0.098	−0.157**	−0.242**	−0.330**
Birth weight	−0.263**	−0.214**	0.013	−0.018	−0.082	−0.159**

Values represent the Pearson's correlation coefficient; "*" means $p < 0.05$, "**" means $p < 0.01$. Abbreviations: NICU, neonatal intensive care unit; NICU-FNI, NICU-Family Need Inventory.

The findings highlight the importance of considering specific factors when addressing the diverse needs of grandparents in the NICU, providing valuable insights for tailored Support interventions.

Discussion

The care provided in the neonatal intensive care unit (NICU) is vital for preterm infants (Cao et al., 2021). However, this type of care presents significant economic, psychological, and health challenges for the families of preterm infants (Geng et al., 2022; Grunberg et al., 2022). Despite ample evidence regarding the needs of parents in the NICU, the needs of other family members, such as grandparents, are often overlooked (Adama et al., 2022; Maleki et al., 2022). Grandparents, however, play a crucial role in providing support to the family (Hillis et al., 2021), and it is important to understand their needs in order to improve NICU care practices. This study aimed to provide a comprehensive investigation of the needs of this particular group, thereby making an additional contribution to the existing body of literature.

The findings of this study reveal that grandparents' foremost concern is the Assurance of the infant's safety and wellbeing. Studies involving parents of preterm infants in the NICU have consistently identified Assurance as the top priority (Alsaiari et al., 2019; Govindaswamy et al., 2020). Similarly, family members of critical care patients have emphasized the importance of Assurance (Kang et al., 2020), and nurses have also deemed Assurance as the most critical need for family members of patients admitted to critical care units (Khatri Chhetri and Thulung, 2018). It is both expected and understandable that all family members, including grandparents and parents, prioritize health assurance for these infants, recognizing it as a crucial necessity.

In the hierarchy of importance among the remaining four dimensions, the needs of grandparents of preterm infants in the NICU are prioritized as follows: Information, Proximity, Support, and Comfort. In comparison, the needs of Saudi parents of preterm infants are ranked as Proximity, Information, Comfort, and Support (Alsaiari et al., 2019), while another study focused on the needs of fathers, ranking them as Proximity, Information, Support, and Comfort (Govindaswamy et al., 2020). The variations in family member inclusion across research studies and differences in hospital policies regarding visitation for preterm infants in the NICU may elucidate this discrepancy. In Saudi hospitals, parents are permitted to visit their infants around the clock; thus, Alsaiari et al. excluded two Proximity-related items from the NICU-FNI scale: "to be able to visit my infant at any time" and "to see my infant frequently" (Alsaiari et al., 2019). In China, NICUs employ a closed management approach alongside the traditional practice of "sitting the month." This results in minimal opportunities for mothers of premature infants to observe their newborns after birth, and even fewer opportunities for other relatives to have contact with the baby at that time (Ling et al., 2022). Consequently, our research emphasizes the heightened significance of Information and Proximity for grandparents. Prior research suggests that the Information needs of family members of patients in critical care are the second most significant, irrespective of the family's educational or cultural background (Kang et al., 2020; Wesson, 1997). Studies indicate that family members of patients admitted to critical care units frequently seek Proximity and Information as coping mechanisms to alleviate anxiety (Baharoon et al., 2017; Wang et al., 2018). This aligns with the family resilience framework, which underscores the importance of clear communication and emotional closeness as factors that bolster resilience. When family members are well-informed and have opportunities for meaningful involvement, they are better equipped to manage the emotional and psychological stress associated with NICU experiences (Walsh, 2016).

The results of this study reveal a significant negative correlation between the gestational age of preterm infants and the grandparents' need for Assurance, Information, Support, and Comfort, as well as the overall need score. This suggests that as the gestational age of a premature infant at birth increases, the needs of the grandparents decrease. It is worth noting that previous studies have indicated a similar trend: as an infant spends more time in the NICU, family members place less emphasis on seeking Information about the infant (Nicholas, 2018; Alsaiari et al., 2019). Furthermore, the psychological stress, anxiety, and fear experienced by family members are found to escalate as the infant's condition deteriorates. However, when there is an improvement in the infant's health, these negative emotions gradually subside (Heidari et al., 2012; Jackson et al., 2003). This inverse relationship between the severity of the infant's condition and the emotional state of the family members could be attributed to the fact that the occurrence and severity of multiple diseases are linked to gestational age and birth weight. Conditions such as respiratory distress syndrome (Mikolajcikova et al., 2022), bronchopulmonary dysplasia (Trembath and Laughon, 2012), and necrotizing enterocolitis (Battersby et al., 2017) are more likely to occur in infants with lower gestational age and birth weight.

The needs related to Support (interpersonal and emotional) and Comfort (personal and physical) are the lowest priority for

TABLE 6 Multiple regression model explaining grandparents' needs.

	Unstandardized coefficients		Standardized coefficients	*t*	*p*	VIF
	B	standard error	Beta			
The model that explains grandparents' needs for mean score						
(Constant)	3.355	0.134		24.964	0	
Employment status	0.059	0.017	0.194	3.533	0	1.02
Place of residence	0.081	0.039	0.117	2.087	0.038	1.075
Gestational age	−0.295	0.047	−0.564	−6.215	0	2.798
Birth weight	0.2	0.062	0.297	3.211	0.001	2.912
The model that explains grandparents' needs for Assurance						
(Constant)	4.273	0.189	–	22.633	0	–
Employment status	0.067	0.024	0.156	2.861	0.005	1.02
Place of residence	0.122	0.055	0.124	2.227	0.027	1.075
Gestational age	−0.377	0.067	−0.51	−5.654	0	2.798
Birth weight	0.149	0.088	0.156	1.698	0.091	2.912
The model that explains grandparents' needs for Information						
(Constant)	4.164	0.155		26.781	0	
Education level	−0.07	0.025	−0.159	−2.796	0.006	1.006
Gestational age	−0.27	0.068	−0.379	−3.994	0	2.811
Birth weight	0.077	0.087	0.084	0.891	0.374	2.8
The model that explains grandparents' needs for Proximity						
(Constant)	2.9	0.121		24.067	0	
Age group	0.025	0.027	0.059	0.921	0.358	1.234
Education level	0.04	0.026	0.093	1.545	0.124	1.102
Employment status	0.079	0.026	0.192	3.061	0.002	1.197
Place of residence	0.147	0.055	0.159	2.666	0.008	1.071
The model that explains grandparents' needs for Support						
(Constant)	3.342	0.112		29.941	0	
Education level	−0.003	0.022	−0.009	−0.145	0.885	1.005
Gestational age	−0.093	0.035	−0.157	−2.648	0.009	1.005
The model that explains grandparents' needs for Comfort						
(Constant)	3.246	0.174		18.624	0	
Place of residence	0.078	0.064	0.072	1.219	0.224	1.042
Gestational age	−0.184	0.048	−0.228	−3.838	0	1.042

grandparents. Concerning the hospital infrastructure, elements such as the Proximity of a bathroom to the waiting area, the provision of a solitary space within the hospital, and the presence of a phone in the parental waiting room are not the foremost considerations of grandparents. This underscores grandparents' tendency to place the Comfort and Support needs of the mother and baby above their personal needs, a perspective that aligns with findings on paternal needs (Ireland et al., 2016).

This study does not negate the fact that parental involvement in newborn care within the NICU is a currently favored healthcare approach (Zanoni et al., 2021). Furthermore, decisions regarding emergency treatment for NICU patients and communication with doctors position parents as taking a leading position among family members (Govindaswamy et al., 2020). However, upon the admission of their newborn to the NICU, parents often experience anxiety, depression, guilt, and helplessness due to their unpreparedness and lack of parenting experience, the unpredictability associated with their preterm infant's stay in an unfamiliar NICU environment, the closed management system of the NICU, the uncertainty of their infant's medical condition, prognostic worries, and substantial hospital expenses (Diffin et al., 2016; Whittingham et al., 2014). These challenges often result in their inability to understand nurses' explanations or engage in the caregiving process (Ladani et al., 2017). Moreover, fathers particularly wish for grandparents to assist in alleviating their stress, as mothers require care following childbirth, thereby positioning grandparents as their most trusted allies (Aliabadi et al., 2014). Hence, grandparents could serve as a vital communication bridge between nurses and parents, lowering the communication burden on nurses and fostering a collaborative relationship, ultimately contributing to improved care and expectations for the newborn (Wigert et al., 2013).

As with any survey-based research, our study has certain limitations. First, because of the cross-sectional design of this study, we are unable to assess changes in the needs of grandparents of preterm infants in the NICU over time. Additionally, our sample was limited to grandparents from a specific region in China, which may limit the broader applicability of our findings. Third, the self-completion nature of the questionnaires introduces the potential for bias due to social desirability. Given these factors, it is important to interpret the research findings with caution.

Conclusion

This study aimed to broaden the scope of research concerning the needs of grandparents with preterm infants in NICU, complementing the existing studies that have predominantly centered on the needs of parents. The research reveals that grandparents primarily desire Assurance regarding the safety and health of their grandchild, indicating a substantial level of concern about the quality of care. Additionally, secondary needs related to Information and Proximity were identified.

The findings demonstrate a significant negative correlation between the gestational age of preterm infants and the grandparents' needs for Assurance, Information, Support, and Comfort. As the gestational age increases, the expressed needs of grandparents tend to diminish, supporting previous findings that suggest family members experience less anxiety and a decreased demand for information as infants stabilize.

The results underscore the critical role grandparents play within the family support system and highlight the necessity of recognizing and addressing their needs in clinical practice. Recognizing these needs is essential not only for alleviating family stress but also for enhancing overall care quality within NICUs. By emphasizing family-centered care, the study advocates for policies and practices that acknowledge and support the involvement of grandparents during such challenging times.

While this research provides valuable insights, its cross-sectional design constrains the ability to monitor changes in needs over time. Moreover, the sample was limited to a specific region in China, potentially affecting the generalizability of the findings. Future research should employ longitudinal designs to assess the evolution of grandparents' needs and to explore these needs across diverse cultural and healthcare contexts.

In conclusion, this study serves as a call to action for healthcare providers and policymakers to integrate the needs of grandparents into NICU care practices, ensuring they receive appropriate support, communication, and engagement during challenging periods for the entire family. This approach could enhance the psychological wellbeing of families and improve the quality of care in NICUs.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by the Second People's Hospital of Jingdezhen, documented by Approval No: 2023-LLLW-07. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

HH: Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. JT: Formal analysis, Investigation, Methodology, Validation, Writing – original draft, Writing – review & editing. YL: Investigation, Methodology, Writing – original draft, Writing – review & editing. RC: Investigation, Methodology, Writing – review & editing. HF: Conceptualization, Investigation, Methodology, Supervision, Validation, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyg.2024.1433391/full#supplementary-material

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Livio Provenzi,
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REVIEWED BY
Alessandra Raspanti,
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Christine Tuden Neugebauer,
Texas Tech University Health Sciences Center, United States

*CORRESPONDENCE
Yolanda Sánchez-Sandoval
✉ yolanda.sanchez@uca.es

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Health-related quality of life in children born preterm at school age: the mediating role of social support and maternal stress

Melissa Liher Martínez-Shaw[1,2], Kari Anne I. Evensen[3,4,5], Sandra Melero[1,2] and Yolanda Sánchez-Sandoval[1,2]*

[1]Department of Psychology, Faculty of Education Sciences, University of Cadiz, Cádiz, Spain, [2]Instituto de Investigación e Innovación Biomédica de Cádiz (INiBICA), Cádiz, Spain, [3]Department of Clinical and Molecular Medicine, Norwegian University of Science and Technology, Trondheim, Norway, [4]Children's Clinic, St. Olavs Hospital, Trondheim University Hospital, Trondheim, Norway, [5]Department of Rehabilitation Science and Health Technology, Oslo Metropolitan University, Oslo, Norway

Research on health-related quality of life (HRQoL) of school-aged children born preterm (< 37 weeks of gestational age) is scarce and there are few studies examining the relationship with medical and family factors. The aims were to analyze HRQoL in a sample of 8-year-old children born preterm with very low birth weight (VLBW), to test a proposed theoretical model that examines the relationship with medical and socio-family factors, and to explore the mediation effects of maternal factors between perinatal variables, demographic characteristics and HRQoL. A total of 147 VLBW children and 116 mothers were assessed. The measures included for assessment were self-and parent-reported HRQoL, functional social support, maternal stress, socio-family risk index and neonatal medical risk index. Mediation analysis was applied to investigate mediation effects of the maternal factors. Mean self-and parent-reported KIDSCREEN scores were 55.1 (*SD* 10.1) and 58.2 (*SD* 9.1), respectively, indicating better HRQoL than the normed sample with a mean of 50 ($p < 0.001$). The total effect of the initial theoretical model was not significant, thus another partial model was validated. Socio-family risk index significantly influenced HRQoL (direct effect), and this relationship was mediated by functional social support and maternal stress (indirect effects). School-aged VLBW children and their parents reported better HRQoL than the mean reference value on KIDSCREEN-10 and -27. Maternal stress and social support had a mediating effect on the children's HRQoL. These results could be used to tailor interventions in these families.

KEYWORDS

preterm children, health-related quality of life, socio-family risk index, social support, maternal stress, mediation analysis

1 Introduction

In the last years, the survival rates following the birth of extremely low birth weight (ELBW; < 1,000 g) infants have increased (Arpino et al., 2010), although the risk of neonatal morbidities has also increased with decreasing gestational age and very low birth weight (Manuck et al., 2016; Mukherjee et al., 2023; Platt, 2014). Different health difficulties are more frequent in these children than in term-born children (Larroque et al., 2008; Marsh et al., 2023; Taylor and O'Shea, 2022; Chung et al., 2020). Extremely preterm infants are at risk of deficits with potential consequences in functionality regarding general health. Nevertheless, the impact of the unhealthy condition on the well-being of these children and their families has been poorly described (Vederhus et al., 2010; Shaw et al., 2023).

This effect can be studied on health-related quality of life (HRQoL), which is a dynamic, multidimensional, and subjective concept, associated with health status in physical, emotional, and social functioning (Hays and Reeve, 2008). HRQoL assessments provide valuable additional information to traditionally reported medical evaluations (Saigal and Doyle, 2008). Some HRQoL assessments following individuals born preterm or with low birth weight and their families have applied multi-dimensional health profile measures, including physical, psychological, and social well-being (Pal et al., 2020; Petrou et al., 2020).

Research on quality of life during the school years of very preterm or very low birth weight (VLBW) children is scarce. Two separate systematic reviews about HRQoL in preterm children include only one study each at school age (Vieira and Linhares, 2016; Zwicker and Harris, 2008). The first study (Saigal et al., 1994a; Saigal et al., 1994b) compared the HRQoL of extremely low birth weight children (ELBW) with that of a reference group, showing that the global long-term burden experienced by children with ELBW was higher, with the latter presenting more functional limitations. In the second study, the health score of ELBW children was similar to that of normal birth weight children, while parents reported significantly poorer health for their ELBW children (Hack et al., 2011).

In addition to the studies included in the systematic reviews, Peart et al. (2021) studied HRQoL in a sample of 8-year-old extremely preterm children compared with three cohorts of term-born children with different birth years. In this study, parent-reported HRQoL was lower for children born extremely preterm with respect to all control groups (Huhtala et al., 2016) concluded that HRQoL was not significantly different for healthy VLBW children at 8 years of age when compared to a control group.

Few studies have examined factors related to a better or worse HRQoL for these children during their school years. Studies included in Mottram and Holt (2010) found that preschool preterm children with lower GA had lower scores in HRQoL. Other studies have found no differences in HRQoL related to GA in preschool children (Schiariti et al., 2007), or in birth weight in healthy preterm VLBW children at school age (Huhtala et al., 2016) compared with full-term children.

There is little evidence of the mechanism through which the effects of neonatal morbidities are transmitted to HRQoL in preterm children. One study found that, among children born extremely preterm, perinatal, and neonatal morbidity was mostly unrelated to HRQoL (Vederhus et al., 2010). Recent studies have clarified the mediating effects of bronchopulmonary dysplasia (BPD) and severe non-respiratory morbidity between GA and HRQoL (Kim et al., 2023). More specifically, the mediation analysis revealed that BPD and severe non-respiratory morbidity contributed to significant reductions in HRQoL, with indirect effects translating into HRQoL score decrements for both at the gestational ages studied (<26, 26–27, and 28–29 weeks). The effect was more detrimental when the GA was lower. In this case, as the authors indicate, the worse HRQoL score is mainly due to the complications of preterm birth rather than the preterm birth itself.

Furthermore, studies about families of children with neurocognitive developmental disorders and disabilities (NDD) have highlighted a clear relationship between children's quality of life, parents' quality of life, and family environment, concluding that the importance of family well-being in the well-being of the child should be recognized (Puka et al., 2020). The similarity in parental quality of life among parents of children with different NDD indicates that quality of life is influenced by parental and family characteristics rather than by the disease or specific factors (Hatzmann et al., 2008; Puka et al., 2018). To the best of our knowledge, little is known about how family variables influence the quality of life of children born preterm at school age. Much more is known about maternal stress before or immediately after delivery (Hoffman et al., 2016). Another study highlighted the importance of social support as a protective factor for perinatal depression in the 2 years following postpartum and adverse child development (Milgrom et al., 2019). Socioeconomic level, ethnicity, family conflicts, maternal distress and maternal education are some risk factors identified for development in studies about children born prematurely (Moreira et al., 2014). There is greater knowledge of how family variables behave when children are newborns or toddlers, but not how they behave in the long-term during school age. It remains unclear how these variables act on each other as these children grow up, as well as the real impact on their quality of life, knowing their true mediating role.

Therefore, we aimed to (1) study HRQoL in a sample of children born preterm with VLBW at 8 years of age, (2) examine the relationship between medical and socio-family factors and HRQoL, and (3) explore the mediation effects of maternal factors between perinatal variables, socio-family characteristics and HRQoL.

We proposed a theoretical model, testing a direct effect of neonatal medical and socio-family variables, as well as a mediating effect of maternal variables, on the HRQoL of preterm children (see Figure 1). This model draws on other studies (Hatzmann et al., 2009; Isa et al., 2016; Wang et al., 2022), although they did not refer specifically to preterm samples at school age. According to the model, risk factors related to children's perinatal status and socio-family situation have direct negative effects on their HRQoL. Additionally, parental stress and perceived support would play a mediating role in the association between risk factors and quality of life. This model can be applied not only to the general quality of life, but also to its subdimensions. Within this model, partial models will be considered if the theoretically proposed model is not confirmed.

We tested the following hypotheses: (1) children in the study will show lower HRQoL than the normed mean, (2) there will be a negative association between neonatal medical and socio-family risk and the level of HRQoL, and (3) this relationship would be mediated by the level of stress and the support perceived by the mothers.

2 Methods

2.1 Participants

This prospective two-wave study was conducted from a cohort of children born preterm with very low birth weight (<1,500 g). These children were admitted to the neonatal intensive care unit (NICU) of the Puerta del Mar Hospital in Cádiz (Spain) between the years 2011 and 2014. The exclusion criterion was the presence of major congenital malformations, chromosomal abnormalities, or congenital infections.

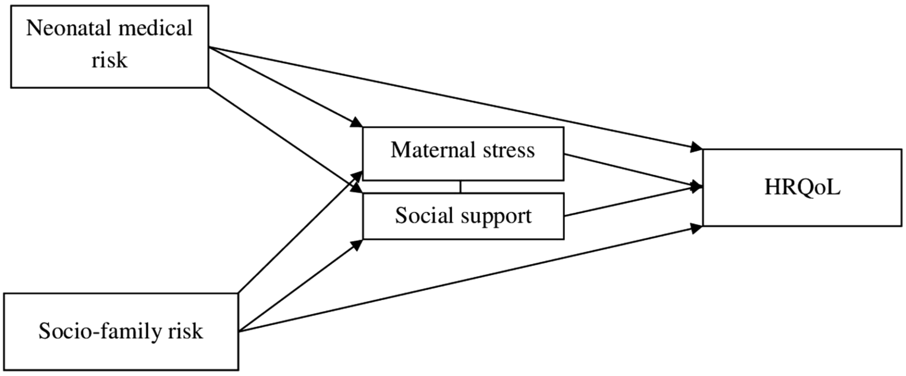

FIGURE 1
Hypothetical model of mediation analysis among neonatal medical risk, socio-family risk and HRQoL.

A total of 199 children were eligible for the assessment, of whom 147 children and 116 mothers were finally included (Figure 2). Demographic variables such as GA, birth weight (BW), sex, perinatal variables and maternal age at birth were collected at the time of birth of the child. Children's age at present and family characteristics (family structure, education level, employment status, family income and language spoken at home) were collected at the 8-year follow-up assessment. All demographic characteristics are included in Table 1.

2.2 Measures

The self-reported HRQoL of children was assessed using a generic measure, i.e., the KIDSCREEN-10 (Ravens-Sieberer et al., 2010), which consists of 10 items with a 5-point response scale. This instrument provides a single score of HRQoL. These values were computed into Rasch scores and transformed into t-values ($M = 50$ and $SD = 10$). The internal consistency of the scale was acceptable ($\alpha = 0.719$).

KIDSCREEN-27 (Ravens-Sieberer et al., 2007) was also used, which assesses the proxy report HRQoL through parental response. It consists of 27 items with a 5-point Likert scale. The subscales of this instrument are physical well-being, psychological well-being, autonomy and parent relationship, social support and peers, and school environment. The reliability was excellent ($\alpha = 0.913$), and the subdimensions had an internal consistency of 0.824, 0.768, 0.817, 0.615 and 0.751, respectively, going from questionable to good. Higher scores on KIDSCREEN measures indicate a better HRQoL.

The Duke-UNC Functional Social Support Questionnaire (Bellón et al., 1996; Broadhead et al., 1988) assessed parents' self-perceived social support. It consists of 11 items with a 5-point Likert scale. This scale provides a global score (good internal consistency; $\alpha = 0.886$) and two subscales (affective support and confidant support). Higher scores indicate more perceived support. The first subscale assesses perceived support as a relational catalyst (acceptable internal consistency; $\alpha = 0.765$) and the second subscale assesses as a source of strength (good internal consistency; $\alpha = 0.847$).

The Spanish version of the Parental Stress Scale (PSS; Berry and Jones, 1995; Spanish adaptation by Oronoz et al., 2007) comprises 12 items rated on a 5-point Likert scale. It provides a total score and two subscales (baby's rewards and stressors), with higher scores showing a higher level of parental stress. The internal consistency was acceptable ($\alpha = 0.758$) for the total score and questionable and acceptable ($\alpha = 0.600$ and $\alpha = 0.778$) for the subscales.

Socio-family risk index (SFRI) is a composite measure with six social and family variables, based on previous studies (Jiménez-Luque et al., 2023; Sánchez-Sandoval and Verdugo, 2021; Yaari et al., 2019). The variables that constitute SFRI are: family structure (0 = biparental; 1 = separated parents, joint custody, or reconstituted family; 2 = single caregiver), maternal education level (0 = university; 1 = semi-qualified; 2 = formal), employment status of both caregivers (0 = employment; 1 = employment of one of the caregivers; 2 = unemployment/pension), family income (0 = more than 1,801 €; 1 = 901–1,800 €; 2 = less than 900 €), language spoken at home (0 = only Spanish; 1 = some Spanish; 2 = no Spanish), and maternal age at birth (0 = more than 21 years of age; 1 = 18–21 years old; 2 = less than 18 years of age). Depending on the risk, values from 0 to 2 were assigned to each variable, with a total index range from 0 to 12. Data were obtained from an *ad hoc* Socioeconomic Status Questionnaire (SES).

Neonatal medical risk index (NMRI; Jiménez-Luque et al., 2023) is a cumulative index that encompasses the presence of these perinatal conditions: confirmed necrotizing enterocolitis (Bell Stage II or higher), moderate-to-severe bronchopulmonary dysplasia (oxygen requirements at 36 weeks of postmenstrual age), significant patent ductus arteriosus (requiring surgical or pharmacological closure), severe retinopathy of prematurity (stage 3 or higher retinal vasculopathy), severe brain injury (grade 3 intraventricular hemorrhage, parenchymal hemorrhagic infarction and/or moderate to severe white matter injury) and late-onset sepsis (systemic signs of infection and isolation of a bacterial pathogen in blood culture after 5 days of life). The absence and presence of the disease were assigned a value of 0 and 1, respectively, with a total index range from 0 to 6. Perinatal data were obtained from medical records.

2.3 Procedure

Preterm children were recruited for the PRETERM Health and Development Follow-up Project, approved by the Bioethics Committee of the authors' university. In collaboration with the

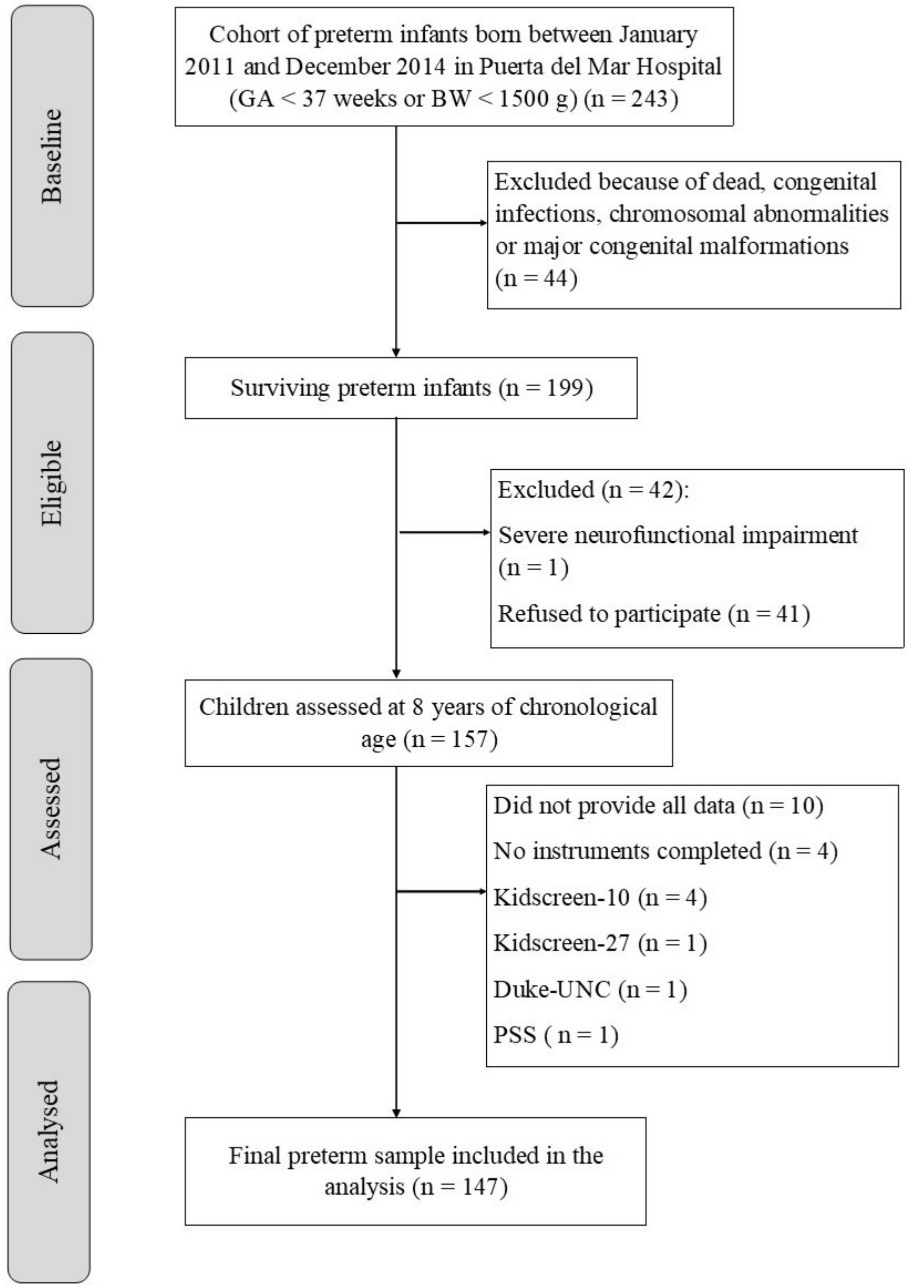

FIGURE 2
Flowchart of participants.

hospital, families were contacted to inform them about the research. A face-to-face meeting was arranged, where the parents filled and signed the informed consent. The researchers conduct an interview where the demographic data of family and children are collected. Subsequently, in separate rooms, one researcher with the child and one with the parent or parents administered the questionnaires and answered any questions that they had, while they completed the questionnaires on their own. The measure referred to children was completed by agreements between both parents or, in the case of absent father, only by the mother. All other questionnaires were completed individually, although only data collected from the mother are included here.

Regarding attrition, 26.13% of the surviving sample (n = 199) did not participate in the study. There were no significant differences concerning sex, GA and BW between participants and non-participants (see Table 2).

2.4 Data analysis

IBM SPSS Statistics v29, PROCESS macro (Hayes, 2022) for SPSS, and Jamovi software were used for statistical analyses.

According to the missing-value analysis, 25 (17%) participants had at least one missing value. In particular, KIDSCREEN-27 showed

TABLE 1 Demographic characteristics of the sample.

Demographic variable	Total sample
Children (n = 147)	
Gestational age, mean weeks (*SD*)	29.81 (2.16)
Birth weight, mean grams (*SD*)	1,288.41 (362.16)
Female, *n* (%)	70 (47.6)
SGA, *n* (%)	17 (11.6)
Multiple birth, *n* (%)	68 (46.3)
IVF, *n* (%)	37 (25.2)
Cesarean sections, *n* (%)	106 (72.1)
Apgar score 1 min, mean (*SD*)[a]	6.58 (1.74)
Apgar score 5 min, mean (*SD*)[a]	8.16 (1.30)
Necrotising enterocolitis, *n* (%)	0 (0.0)
Bronchopulmonary dysplasia, *n* (%)	5 (3.4)
Patent ductus arteriosus, *n* (%)	5 (3.4)
Grade 3+ retinopathy of prematurity, *n* (%)	3 (2.0)
Severe brain injury, *n* (%)	1 (0.7)
Late-onset sepsis, *n* (%)	24 (16.3)
Neonatal medical risk index, mean [range]	0.26 [0–3]
Higher neonatal medical risk index, *n* (%)	31 (21.1)
Age at the time of assessment, mean years (*SD*)	8.66 (0.96)
Mothers (n = 116)	
Family structure	
Biparental, *n* (%)	89 (76.7)
Separated parents, joint custody, or reconstituted family, *n* (%)	11 (9.5)
Single caregiver, *n* (%)	16 (13.8)
Education level	
University (>12 years), *n* (%)	38 (32.8)
Semi-qualified (11–12 years), *n* (%)	40 (34.5)
Formal (<11 years), *n* (%)	38 (32.8)
Employment status of both caregivers	
Employment, *n* (%)	68 (58.6)
Employment of one of the caregivers, *n* (%)	44 (37.9)
Unemployment/pension, *n* (%)	4 (3.4)
Family income	
≥1,801 €, *n* (%)	61 (52.6)
901–1,800 €, *n* (%)	42 (36.2)
<900 €, *n* (%)	13 (11.2)
Language spoken at home	
Only Spanish, *n* (%)	112 (96.6)
Some Spanish, *n* (%)	2 (1.7)
No Spanish, *n* (%)	2 (1.7)
Maternal age at child's birth, mean years (SD)	**32.98 (5.22)**
>21 years of age, *n* (%)	109 (94)
18–21 years of age, *n* (%)	5 (4.3)
<18 years of age, *n* (%)	2 (1.7)
Socio-family risk index, mean [range]	2.52 [0–9]
Age at the time of assessment, mean years (*SD*)	41.40 (5.22)

[a]Mean over 141 participants; SGA, small for gestational age; IVF, in vitro fertilization.

more missing data. We considered for the imputation the loss of 7% of the total items of the questionnaire and 5% of the loss of the item in the sample (Heymans and Twisk, 2022). A multiple imputation was conducted on the dataset. A missing value analysis was performed in IBM SPSS Statistics v29, estimating the loss by randomization with EM and recovering the data by regression for each set of items in each instrument. Little's MCAR test was used to assess whether missing values were missing due to chance. The assumption of missing at random (MAR) was confirmed for each measurement ($p > 0.05$). Specifically, four imputations were generated for KIDSCREEN-10, KIDSCREEN-27, Duke-UNC and PSS recovering 2, 16, 2, and 6 participants, respectively.

The attrition in the sample was analyzed. Differences between the participant and non-participant samples were studied with a chi-squared test (sex) and independent t-test for two samples (gestational age and birth weight) (Table 2). Descriptive data from demographic and HRQoL variables were presented as mean and *SD* or frequencies. For KIDSCREEN, *t*-values were used and compared with the normed sample ($M = 50$) with a one-sample *t*-test.

Pearson's correlations were performed between the variables. Multiple mediation analysis, described by Hayes (2022), was applied to investigate simultaneous mediation effects of maternal stress (*M1*) and functional social support (*M2*), between the NMRI (*X*), SFRI (*X*) and HRQoL (*Y*) shown in the hypothetical model (Figure 1). Other similar models considering other variables and all PedsQL subscales were also tested to find the best fit. Multiple mediation analysis is based on regressions, and effect values are unstandardized regression coefficients, measuring indirect effects rather than temporal mediation. The analysis provides a total effect of the model (*c*, including all the effects over *Y*), a direct effect (*c'*, considering only the effect of *X* over Y) and indirect effects (*axb* considering the effects of the mediators). The indirect effect is the product between the effects of *X* over the mediator/s (paths type *a*), and the effects of the mediators on *Y* or partial effects while controlling covariates in the model (paths type *b*). In this case, PROCESS model type 6 (two mediators) (Hayes, 2022) and 10,000 bootstrap simulations were used in the PROCESS macro for SPSS. Bootstrapping is the base for the calculation of the 95% confidence intervals for the indirect effects (lowest and highest results from the random samples). If confidence interval did not include zero, the effect was considered statistically significant.

3 Results

A total of 147 VLBW children were followed up until they reached 8 years of age. Table 3 presents descriptive results of KIDSCREEN-27 and KIDSCREEN-10 scores. The means of our sample were higher than the KIDSCREEN normed mean ($M = 50$, $p < 0.001$). Cohen's *d* ranged from 0.506 to 0.898, indicating medium-to-high effect sizes (see Table 3).

Correlations between the variables in the study are shown in Table 4. First of all, the scores of self-reported KIDSCREEN-10 showed positive correlations with the scores of parent-reported KIDSCREEN-27, being significant only with the psychological well-being and social support and peers subdimensions. Moreover, non-significant correlations were found between KIDSCREEN-10 and the other variables, except the negative correlation with maternal stress. NMRI did not correlate with KIDSCREEN-27 total scores,

TABLE 2 Distribution of sex, gestational age and birth weight in participants and non-participants.

	Participants	Non-participants	χ^2/t	*p*	Phi/ Cohen's *d*
Female	70 (47.62%)	28 (53.85%)	0.596	0.440	0.055
Male	77 (52.38%)	24 (46.15%)			
Gestational age	29.8 (2.2)	30.3 (1.9)	1.510	0.066	0.244
Birth weight	1,288 (362)	1,355 (328)	1.172	0.121	0.189

***$p < 0.001$; **$p < 0.01$; *$p < 0.05$.

TABLE 3 Mean self-and parent-reported KIDSCREEN scores and mean differences from the normed mean.

KIDSCREEN domains	Mean (*SD*)	Mean difference	*p*	Cohen's *d*
KIDSCREEN-10 (self-reported)	55.11 (10.10)	5.11	< 0.001	0.506
KIDSCREEN-27 (parent-reported)				
Physical well-being	57.94 (11.08)	7.94	< 0.001	0.717
Psychological well-being	60.87 (12.16)	10.87	< 0.001	0.894
Autonomy and parental relationship	56.94 (13.72)	6.94	< 0.001	0.506
Social support and peers	56.68 (9.72)	6.68	< 0.001	0.688
School environment	58.57 (10.60)	8.57	< 0.001	0.808
Total score	58.20 (9.13)	8.20	< 0.001	0.898

although it did correlate with its physical well-being subdimension. Total KIDSCREEN-27 score and the score of some of its subdimensions were also negatively correlated with SFRI and maternal stress. Maternal perceived support correlated negatively with KIDSCREEN-27. SFRI correlated significantly and negatively with functional social support.

Analyses of the initial theoretical model (Figure 1) did not show the expected results. Some relationships between variables were not significant, as was the total effect of the model ($F = 1.69$, $p > 0.05$, $R^2 = 0.12$). Based on these results, two partial models were tested with the two risk indexes. The first partial model (with the neonatal medical risk index) did not show significant direct neither indirect effects between most variables (NMRI with social support, $p = 0.70$; NMRI with maternal stress, $p = 0.61$, NMRI with HRQoL, $p = 0.08$ and social support with HRQoL, $p = 0.75$). The second partial model (with the socio-family risk index) was validated, and it is graphically presented in Figure 3.

Table 5 and Figure 3 show the results of the mediation analysis with the direct and indirect effects. It is shown in Figure 3 that there was a significant influence of SFRI and functional social support ($a_1 = -0.71$, $p = 0.018$). Maternal stress scores were explained by functional social support ($d = -0.31$, $p < 0.001$), but not by SFRI ($a_2 = -0.08$, $p = 0.762$). Furthermore, SFRI ($c' = -0.80$, $p = 0.036$) and maternal stress ($b_2 = -0.39$, $p = 0.001$) exerted a statistically significant influence on the dependent variable of this model (parent-reported HRQoL). However, this result was not significant for functional social support ($b_1 = 0.04$, $p = 0.733$). Finally, regarding the total model effect, there was a significant influence of SFRI on HRQoL ($c = -0.88$, $p = 0.023$).

Three possible indirect effects were established in this model (Table 5). The first indirect effect did not explain the relationship between SFRI and HRQoL through social support. The results of the second indirect effect were also non-significant, thus SFRI had no effect on HRQoL through maternal stress. Only the third indirect effect was significant, in which SFRI was related to HRQoL through the indirect effects of the two mediating variables: functional social support and maternal stress.

4 Discussion

This study aimed to examine the HRQoL of children born preterm with VLBW at 8 years of age and to explore the mediation effects of maternal variables on the relationship between NMRI, SFRI, and HRQoL. This study adds evidence to the existing results in the preterm child population and illustrates relationships between variables that affect children born preterm and their families.

Contrary to our first hypothesis, we found that self-and parent-reported HRQoL of school-aged VLBW children was better than that of the population norm of KIDSCREEN (Ravens-Sieberer et al., 2007). These findings are in disagreement with those of previous studies; however, few works have examined HRQoL in school-aged VLBW children (Peart et al., 2021; Stahlmann et al., 2009; Vederhus et al., 2010). Huhtala et al. (2016) found that healthy VLBW children at 8 years of age did not differ significantly in HRQoL from a control group. Moreover, Hack et al. (2011) found that self-reported health results ELBW children were comparable to those of normal birth weight children. To explain this result, possible hypotheses to be tested in the future would be the existence of greater family involvement from the beginning due to the condition of their children or the fact that they were attending the early care service (greater professional intervention from the beginning). In fact, a large proportion of the participants in this study received care in early intervention services (physiotherapy, psychology and speech therapy), with two thirds of the sample being discharged between the ages of 0 and 3 years old (Lacalle et al., 2023). It has been found that the higher maternal sensitivity is explained by being in early childhood care (Sánchez-Sandoval and Jiménez-Luque, 2023).

The second hypothesis, related to the negative association of NMRI and SFRI with HRQoL, was only partially confirmed. The

TABLE 4 Correlations between KIDSCREEN scores, gestational age, birth weight, socio-family risk index, neonatal medical risk index, functional social support and maternal stress.

	KC10	KP27 T	KP27 Ph	KP27 PW	KP27 Pa	KP27 Pe	KP27 Sc	GA	BW	SRI	NMRI	FSS	MS
KC10													
KP27 T	0.126												
KP27 Ph	0.077	0.770**											
KP27 PW	0.187*	0.846**	0.642**										
KP27 Pa	−0.006	0.793**	0.427**	0.567**									
KP27 Pe	0.162*	0.763**	0.517**	0.511**	0.522**								
KP27 Sc	0.106	0.805**	0.505**	0.621**	0.545**	0.567**							
GA	−0.039	−0.001	0.110	−0.062	−0.150	−0.075	0.077						
BW	−0.105	−0.010	0.022	−0.030	−0.149	0.088	0.081	0.688**					
SRI	−0.103	−0.187*	−0.164*	−0.179*	−0.103	−0.112	−0.195*	0.033	−0.078				
NMRI	−0.082	0.153	0.193*	0.025	0.165*	0.064	0.078	−0.120	−0.275**	−0.011			
FSS	0.133	0.157	0.212*	0.183*	−0.035	0.168*	0.136	−0.075	−0.006	−0.195*	0.685		
MS	−0.240**	−0.293**	−0.182*	−0.290**	−0.159	−0.193*	−0.357**	0.056	0.179*	0.044	−0.051	−0.344**	

KC10, KIDSCREEN-10 children; KP27 T, KIDSCREEN-27 parents, total score; KP27 Ph, KIDSCREEN-27 parents, physical well-being; KP27 PW, KIDSCREEN-27 parents, psychological well-being; KP27 Pa, KIDSCREEN-27 parents, autonomy and parent relationship; KP27 Pe, KIDSCREEN-27 parents, social support & peers; KP27 Sc, KIDSCREEN-27 parents, school environment; GA, gestational age; BW, birth weight; SRI, socio-family risk index; NMRI, neonatal medical risk index; FSS, functional social support; MS, maternal stress.
$^{**}p < 0.01$; $^{*}p < 0.05$.

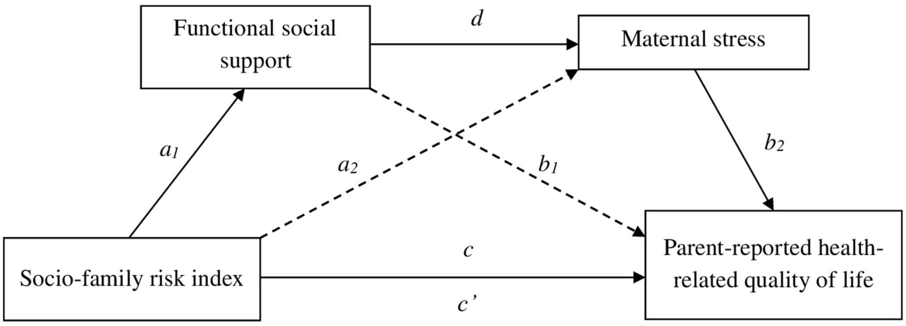

FIGURE 3
Mediating effect of functional social support and maternal stress in the relationship between socio-family risk and parent-reported health-related quality of life.

correlations between variables indicated that they were related to each other before proposing the predictive models. Regarding children's self-perception, this was barely associated with SFRI and NMRI, but association was significant in the case of parents' perception. Thus, the predictive models were carried out on parent-reported HRQoL. Although the use of the SFRI and NMRI is limited in previous literature, some studies yield results that align with those obtained in this work. For example, the systematic review by Jardine et al. (2014) shows that the self-perceptions of children with various medical conditions (including some considered in the construction of the NMRI) are similar to those of their reference group. In contrast, from the families' perspective, the health-related quality of life of these children tends to be rated lower (Cremeens et al., 2006; Jardine et al., 2014). According to these authors, those differences may be related to many variables, including family-related factors.

With regard to perinatal variables, in contrast to other studies (Vederhus et al., 2010), our preliminary correlation analysis showed that GA did not correlate with HRQoL outcomes. Birth weight did not correlate either, but inconclusive results were found in Vieira and Linhares' (2016) systematic review, where some studies found correlations and others did not. Finally, the cumulative NMRI did not correlate with the total HRQoL score, only weakly with the subdimension of physical well-being at school age. This is consistent with results found in another study, where VLBW children's neonatal morbidity was mostly unrelated to HRQoL (Vederhus et al., 2010).

On the other hand, this study confirmed that higher socio-family risk correlates with lower HRQoL, both in their total score and in the physical, psychological, and school well-being subdimensions. Other studies have also shown that different variables included in our SFRI (parental education status, higher socioeconomic deprivation) were negatively associated with children's HRQoL (Berbis et al., 2012; Chien et al., 2006; Liu, Harding, and for the PIANO Study Team, 2021). The final model demonstrated a direct and negative effect of SFRI on HRQoL. The impact of negative social circumstances on

TABLE 5 Mediation effects of socio-family risk index on parent-reported health-related quality of life through functional social support and maternal stress.

	β	*SE*	Bootstrap 95% CI	*p*
Socio-family risk index → functional social support (a_1)	−0.71	0.30	−1.30, −0.12	0.018
Socio-family risk index → maternal stress (a_2)	−0.08	0.26	−0.60, 0.44	0.761
Functional social support → HRQoL parents report (b_1)	0.04	0.11	−0.18, 0.25	0.733
Maternal stress → HRQoL parents report (b_2)	−0.39	0.12	−0.63, −0.16	0.001
Total effect of socio-family risk index on HRQoL (*c*)	−0.80	0.38	−1.55, −0.05	0.036
Direct effect (*c'*)	−0.88	0.38	−1.64, −0.12	0.023
Functional social support → maternal stress (*d*)	−0.31	0.07	−0.45, −0.17	< 0.001
Total indirect effect of socio-family risk index on HRQoL	−0.08	0.13	−0.35, 0.18	
Indirect effect 1: socio-family risk index → functional social support → HRQoL parents report	−0.03	0.10	−0.23, 0.18	
Indirect effect 2: socio-family risk index → maternal stress → HRQoL parent-reported	0.03	0.12	−0.21, 0.26	
Indirect effect 3: socio-family risk index → functional social support → maternal stress → HRQoL parent-reported	−0.09	0.14	−0.21, −0.01	

This was carried out using Model 6 (two mediators) and 10,000 bootstrap simulations. HRQoL, health-related quality of life; SE, standard error; CI, confidence interval.

children's quality of life has also been highlighted in studies of children born at term (Kim et al., 2018; Von Rueden et al., 2006).

The third hypothesis stated that two maternal variables, i.e., maternal stress and perceived social support, could influence the relationship between these risk factors and HRQoL. Maternal stress and social support, which are considered risk and protective factors, respectively, did correlate with different dimensions of children's HRQoL. Treyvaud (2014) emphasized the importance of social and parental factors in influencing child development. The focus on parental role stress was based on research suggesting a negative impact of high parenting stress on VLBW child outcomes (Huhtala et al., 2012). Although the initially proposed model could not be fully validated, a partial model could be confirmed.

The results showed evidence of the mediating effects of functional social support and maternal stress. A higher SFRI was related to lower scores in functional social support, low perceived social support was associated with higher levels of maternal stress, and finally, high levels of maternal stress involve lower perception of HRQoL in their children. Parents' social support did not find a significant direct association with HRQoL, as was the case of SFRI with parental stress. The effect of social support on HRQoL is mediated by maternal stress. In a study by Howe et al. (2014), mothers reported high levels of stress, as well as high levels of social isolation and little support from their partners.

It should be noted that the variables included in this study did not correlate with the variables most closely related to preterm births (gestational age and birth weight), and that no statistically significant partial model was found for NMRI. This suggests that, the older the children born preterm, the lower the impact of NMRI on quality of life, and the more important SFRI becomes. These mediating effects need to be studied further, in larger populations and at different ages, to confirm this new hypothesis and establish it with certainty. Vieira and Linhares (2016) suggested in their systematic review that there was a need to identify predictive models that assess mediating and moderating effects on HRQoL outcomes with more challenging statistical analyses in people born preterm. Kim et al. (2023) confirmed evidence of neonatal morbidity effects, although they stated that mediation analyses are limited and only considered two types of morbidities. To the best of our knowledge, there are studies investigating risk and protective factors in children born preterm and their relationship with children's developmental outcomes, but not the mediating effects of family variables on HRQoL outcomes.

This study provides evidence of how some of these family variables mediate the HRQoL of VLBW children. Even though the children in our sample reported, on average, good HRQoL, the results may be important for targeting interventions to improve the quality of life of preterm children scoring below average. It is difficult to intervene in variables intrinsic to the individual (gestational age, birth weight, medical variables, or socio-family factors) or in the quality of life directly. On the other hand, achieving good practice in intervention on mediating variables that positively or negatively affect children's HRQoL, such as parental stress (Martínez-Shaw and Sánchez-Sandoval, 2023) or social support (Guralnick, 2012), would significantly improve the lives of these children and their family context.

One of the strengths of this study include both self-and parent-reports of HRQoL. Systematic reviews by Eiser and Morse (2001) and Zwicker and Harris (2008) highlight the importance of obtaining information on HRQoL from various sources whenever possible. This work follows these recommendations, having assessed the HRQoL from both perspectives (children and parents). Another strength is the opportunity to shed light on poorly studied variables in the VLBW population and their relationship with family variables. Risk and protective factors for the adequate development of these children have been studied, but not as much as the influence or weight of certain variables on HRQoL. Greater knowledge about medical, psychological, and family variables and their relationship and influence on quality of life will allow developing better intervention programs by combining efforts on what is important.

The limitations include the small sample size, which may have reduced our statistical power. However, it is close to the recommendations made by (Sim et al., 2022) ($n = 160$). The neonatal medical risk index is based on a composite score and does not take into account the impact of each chronic condition on HRQoL, and these results should be interpreted with caution. The effect of bronchopulmonary dysplasia (Kim et al., 2023) is being studied, but would need to be studied with each of the medical conditions of prematurity. The measures used in this study were self-reported. The use of these type of measures could introduce different sources of bias in the results, such as social desirability, although these instruments have been widely used in research. One reason for the loss of some items could be the size and duration of the global questionnaire for parents. Although the children in this sample were, on average, 8 years old and sufficiently able to express their thoughts and emotions (Kim et al., 2023), some may have found it difficult to understand some items due to their conditions. This is the reason why different versions of the KIDSCREEN were chosen to minimize participant fatigue. This made comparisons between them statistically unfeasible. This study used a prospective two-wave design. Longitudinal designs with only two data collection points may overlook certain temporal changes, whereas multi-wave longitudinal studies with at least three data points provide a more robust approach to capturing changes over time. With only two data points, this mediation analysis cannot confirm temporal order or account for potential confounding variables that may influence outcomes between these two time points, reducing its robustness for a full temporal mediation. Data collection was conducted during the COVID-19 pandemic, which made it difficult to access participants and some families refused to participate. Demographic characteristics of non-participating families are not available, so comparisons with participating families could not be studied. Furthermore, loss to follow-up at 8 years may limit the generalizability of the results, although the distribution of sex, gestational age and birth weight did not differ between participants and non-participants. Moreover, it would be interesting to include participants from other hospitals in Spain and even make comparisons with preterm children and their families from other countries.

It would have been valuable to have a control group of full-term children. Our results may be due to the bias introduced by not having said control group. It should be considered that test norms may be outdated (Wolke and Sohne, 1997), thus the quality of life of these preterm children may be overestimated if there is no contemporary comparison group. This would increase the risk of misidentifying fewer children and families in need of support. Therefore, the argument that a control group in the same geographical area would be needed is reinforced for a future line of research.

This study provides evidence on the HRQoL of VLBW preterm school-aged children, which has been understudied in the literature. Although prematurity is often presented as a major risk factor for child development, this study shows a favorable picture for these children during middle childhood. On average, these children and their parents reported better HRQoL than the mean reference value of the KIDSCREEN scales. Probably, medical advances, as well as the involvement of parents and professionals during the first years of life of these children, have been fundamental in overcoming some initial difficulties. In fact, the possible variability in HRQoL is not explained by variables related to extreme prematurity (gestational age, birth weight) or increased neonatal medical risk. Other circumstances common to other families come into play, such as socio-familial factors and the role of the mothers. Our analyses corroborate that when socio-familial circumstances are more adverse, quality of life in childhood suffers. In addition to this direct effect, the socio-familial circumstances of risk weaken the social support that mothers perceive, thereby escalating the stress with which they face their motherhood, also negatively affecting the quality of life of their children in this way. These findings underline the need to implement social policies that support parenthood, especially in adverse social circumstances; and in families with children with higher medical needs where maternal stress has been found to be higher.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Comité de Ética de la Investigación de Cádiz. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

MM-S: Conceptualization, Formal analysis, Investigation, Methodology, Supervision, Visualization, Writing – original draft, Writing – review & editing. KE: Conceptualization, Methodology, Writing – review & editing. SM: Formal analysis, Methodology, Writing – review & editing. YS-S: Conceptualization, Methodology, Writing – review & editing, Formal analysis, Funding acquisition, Investigation, Project administration, Supervision, Visualization, Writing – original draft.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyg.2024.1463804/full#supplementary-material

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EDITED BY
Livio Provenzi,
University of Pavia, Italy

REVIEWED BY
Yuzhu Teng,
Anhui Medical University, China
Artur C. Jaschke,
University of Cambridge, United Kingdom

*CORRESPONDENCE
Samantha J. Lee
✉ Samantha.lee@canterbury.ac.nz

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Executive functioning challenges of adolescents born extremely and very preterm

Samantha J. Lee[1]*, Lianne J. Woodward[1], Stephanie Moor[2] and Nicola C. Austin[3,4]

[1]School of Health Sciences and Canterbury Child Development Research Group, University of Canterbury, Christchurch, New Zealand, [2]Older Person's Mental Health, Burwood Hospital, Christchurch, New Zealand, [3]Department of Paediatrics, University of Otago Christchurch, Christchurch, New Zealand, [4]Neonatal Unit, Christchurch Women's Hospital, Christchurch, New Zealand

Background: Children born very preterm (VPT; <32 weeks) are at increased risk of executive functioning (EF) difficulties. But less is known about the nature and extent of these executive difficulties during late adolescence, particularly across multiple EF domains and in response to varying degrees of executive demand.

Methods: Using data from a prospective longitudinal study, this paper describes the EF profiles of 92 VPT and 68 full-term (FT) adolescents at age 17 years. Relations between gestational age (GA) and later EF performance, in addition to neonatal predictors, were examined.

Results: VPT-born adolescents performed less well than FT adolescents across the domains of working memory, planning, and cognitive flexibility, with the largest differences observed for those born <28 weeks GA (effect sizes −0.6 to −1.0 SD), and when task demands were high. The effects of GA on EF outcome were fully mediated by neonatal medical complexity ($b = 0.169$, $t = -1.73$) and term equivalent white matter abnormalities ($b = 0.107$, $t = -3.33$).

Conclusion: Findings support the need for long-term cognitive support for individuals born very preterm, particularly those exposed to high levels of medical and neurological risk, with these factors largely explaining associations between GA and EF outcome.

KEYWORDS

very preterm birth, neonatal risk, medical complexity, executive function, neurodevelopmental outcome, adolescence

1 Introduction

Advances in neonatal care have significantly improved survival for children born very preterm (VPT; <32 weeks), with the most dramatic gains seen amongst those born at the lower limits of viability (Higgins et al., 2024; Morgan et al., 2022). But despite these gains, rates of adverse neurodevelopmental outcomes for VPT infants remain stable (Cheong et al., 2017). These include cerebral palsy, developmental co-ordination disorder, blindness, deafness, attention deficit-hyperactivity disorder, autism spectrum disorder, and educational underachievement (Broring et al., 2018; Cheong et al., 2017; Doyle et al., 2021; Jois, 2019; Pierrat et al., 2021).

By far, the most common adverse neurodevelopmental outcome is cognitive impairment. Meta-analyses indicate that children and adolescents between the ages of 4 and 20 years consistently obtain IQ scores that are more than 0.8 SDs below their full-term (FT) peers

(Brydges et al., 2018; Twilhaar et al., 2018), with between 40 and 50% experiencing mild to severe cognitive impairment (Doyle et al., 2021; Erdei et al., 2020; Pierrat et al., 2021). Executive functioning (EF) difficulties are also common during early and middle childhood. Executive functions consist of a range of interrelated top-down cognitive skills that enable an individual to achieve a desired goal. Key domains include inhibitory control, working memory, planning, and cognitive flexibility (Nigg, 2017). Findings suggest that between the ages of 4 and 14 years, mean score differences between VPT and FT-born children range from 0.39 to 0.52 SDs across different EF-related tasks (van Houdt et al., 2019).

Less is known about the EF performance of VPT children during late adolescence. Yet, adolescence is a critical period of brain development marked by dramatic neurological changes alongside rapid increases in learning, independence, and social change (Blakemore and Choudhury, 2006; Steinberg, 2005). It is also a time when executive difficulties may have pervasive impacts on daily functioning and life course opportunities (Larsen and Luna, 2018). Data generally suggest that during this developmental stage, individuals born VPT tend to perform less well than FT controls across multiple EF measures, but with varying magnitudes of performance detriment (Burnett et al., 2015; Lundequist et al., 2015; Luu et al., 2011; Stalnacke et al., 2019; Taylor et al., 2004). However, there is considerable variability across existing studies on the conceptualization and measurement of EF, with some studies utilizing a single measure to assess one EF skill and comparatively few employing multiple measures across different EF domains. Further, the effects of varying degrees of task difficulty on EF performance at this age are unclear. Adolescents born VPT are more likely to experience educational and social challenges (Twilhaar et al., 2019; Wolke et al., 2013), which may reflect difficulty coping with the increased EF demand. Thus, a detailed assessment of how changing task demands may impact neurocognitive performance could help further our understanding of the nature of the difficulties some individuals may experience, and potentially the conditions under which risks may be greatest and the various ways these problems may manifest.

In the current study, we used the unity/diversity (Miyake and Friedman, 2012) and executive control system frameworks (Anderson, 2002) to inform our operationalization and measurement selection to characterize the EF profile of 17-year-old adolescents who were born VPT. Three core executive domains shown to have different developmental trajectories from early childhood to adolescence were assessed, spanning working memory, planning, and cognitive flexibility (Diamond, 2013). We examine these domains at age 17 since this age marks an important transition point between adolescence and young adulthood that is associated with increasing autonomy. For those with developmental challenges, it can be a particularly complex stage given the range and level of cognitive skills involved in making a successful transition to adult roles and responsibilities (Leebens and Williamson, 2017). Finally, EF measures were also selected to allow an examination of the extent to which EF performance varied with increasing task difficulty or cognitive demand and to minimize possible floor or ceiling effects.

A further issue of interest is the early identification of those VPT born infants that may be at greatest risk of EF challenges, since timely intervention is critical to mitigate long-term impacts. The varying degrees of executive dysfunction observed across previous cohorts suggests that later EF challenges were more pronounced for adolescents born extremely preterm (EPT; <28 weeks) (Burnett et al., 2015; Farooqi et al., 2016; Lundequist et al., 2015; Taylor et al., 2004). However, the extent to which these elevated risks are explained by infant neonatal medical and postnatal factors has been less well studied. Most studies to date have separately examined a range of individual medical factors, with findings inconsistent across studies and results varying depending on the outcome measures used. Medical factors linked with lower EF performance include ventilation requirement, chronic lung disease, inflammation/infection, and abnormal EEG or cranial ultrasound results (Leviton et al., 2018; Luu et al., 2011; Saavalainen et al., 2007; Taylor et al., 2004). Yet, in reality, many neonatal medical risk factors are highly comorbid. They are also likely to have potentially cumulative impacts on child outcomes, with later risks increasing with higher levels of neonatal medical risk (Barnett et al., 2018). Thus, a cumulative medical risk index may be a better approach in terms of studying the impacts of neonatal medical adversity when identifying individuals at later EF risk.

Furthermore, few adolescent EF studies have included measures of early neurological risk. A strong association between the extent of white matter abnormalities and preschool and school-age neurocognitive outcomes was found in the current cohort (Woodward et al., 2012; Woodward et al., 2011), and other VPT samples (Anderson et al., 2017; Iwata et al., 2012). The presence of neonatal white matter abnormalities is, therefore, considered as another potentially useful predictor of EF problems that persist into adolescence.

Taken together, the specific study aims were as follows:

1. To compare the EF performance of EPT (23–27 weeks), VPT (28–32 weeks) and FT comparison adolescents at age 17 years across three domains including working memory, planning, and cognitive flexibility. Also of interest was the extent to which increasing cognitive demand might impact EF performance for each group, and whether between-group differences might also be explained by family social background factors correlated with very preterm birth.
2. To examine the extent to which neonatal medical complexity and the presence of white matter abnormalities by term equivalent might mediate associations between gestational age (GA) and EF performance at age 17 years. Hypothesized pathways between these variables of interest are shown in Figure 1.

2 Materials and methods

2.1 Participants

Participants included two groups of adolescents drawn from a prospective longitudinal study in Christchurch, New Zealand. The first group was a regional cohort of 110 children born ≤33 weeks gestation and/or ≤ 1,500 g who were consecutively admitted to a level III neonatal intensive care unit at Christchurch Women's Hospital from November 1998 to December 2000 (92% recruitment). Children with congenital abnormalities and non-English speaking parents were excluded. Follow-up assessments were conducted at corrected age 2, 4, 6, 9, and 12 years. Excluding deaths ($n = 3$), 86% ($N = 92$) of these participants completed the 17-year follow-up assessment. Reasons for non-participation included declined ($n = 12$), and ineligible (did not meet original study criteria, $n = 3$). There was no significant difference

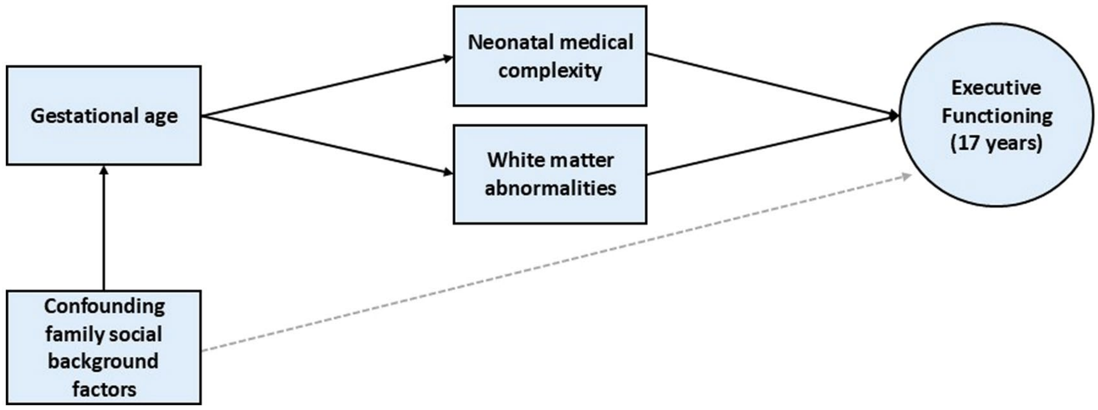

FIGURE 1
Hypothesized pathways from gestational age to executive functioning outcome at age 17 years.

in the mean GA or family socioeconomic status (SES) between participants and non-participants. For the current analysis, the VPT group was further stratified into those born EPT (23–27 weeks) and VPT (28–32 weeks).

The second group comprised 113 full-term born (38–41 weeks gestation) adolescents who were recruited at age 2 years (62% recruitment), and then assessed alongside the VPT group. These full-term control group participants were identified from hospital birth records by selecting a same-sex child born two births before or two births after the delivery of each VPT participant. Exclusion criteria were congenital abnormalities, foetal alcohol effects, birth complications such as growth restriction, and non-English speaking parents. A comparison of the socioeconomic profile of this group with regional census data showed that it was highly representative of the recruitment region. A total of 68 full-term controls were seen at the 17-year follow-up (60% retention). Reasons for attrition included declined participation ($n = 27$), withdrawal (atypical development precluded further participation, $n = 4$), ineligible (did not meet original study criteria, $n = 1$), relocation, with funding restrictions preventing invitation to participate ($n = 15$), and severe illness ($n = 1$). There was no significant difference in family SES between participants and non-participants.

2.2 17-year procedure

All procedures and measures were approved by the Southern Health and Disability Ethics Committee (ref: 14/STH/208), and all adolescent participants and their parents/caregivers provided written informed consent. At age 17, participants underwent neuropsychological testing as part of a larger multidisciplinary one-day follow-up assessment, including an extensive battery of EF measures. One clinical psychologist blinded to the participant's group status administered the test battery in the same predetermined order.

2.3 17-year EF measures

Four EF tasks from the Cambridge Neuropsychological Test Automated Battery (CANTAB) (Cambridge Cognition, 2013) were administered on a 10.1-inch touchscreen tablet. Working memory was assessed with the Spatial Span (SSP) and Spatial Working Memory (SWM) tasks, planning abilities were assessed with the Stockings of Cambridge (SOC) task, and cognitive flexibility was assessed with the Intra-Extra Dimensional Set Shift (IED) task. The Comprehensive Trail-Making Test (CTMT) (Reynolds, 2002) was administered as an additional measure of cognitive flexibility. Further description of each of these tasks and the outcome measures used in the analysis are provided in Table 1.

2.4 Infant clinical characteristics

Infant clinical data, including GA, sex and medical information were gathered from hospital records. A continuous neonatal medical complexity index was also created by identifying six major infant medical exposures that were experienced during the NICU stay. These included: level of respiratory support; time to full enteral feeds; severe retinopathy of prematurity; neonatal sepsis including necrotizing enterocolitis (NEC): intraventricular haemorrhage/periventricular leukomalacia (IVH/PVL); and any major surgery. Scores from 0 to 2 were assigned to each medical exposure based on severity, with scores summed to provide an overall neonatal medical complexity score (see Supplementary Table S1 for further details).

2.5 Neonatal white matter abnormality

All EPT and VPT infants underwent structural MR imaging at term equivalent age (39–41 weeks gestation), using a 1.5-tesla General Electric Signa System. MRI at term equivalent was used given its predictive accuracy in identifying high-risk children who may benefit from surveillance and targeted early intervention. Each infant's scan was scored by a blinded pediatric neuroradiologist and independently reviewed by a pediatric neurologist (95% inter-rater agreement) on the following scales: the presence and severity of periventricular white matter volume loss, white matter signal abnormality, the presence of cystic abnormalities, ventricular dilation, and thinning of the corpus callosum and reduced myelination (See Woodward et al. (2006) for further details). Based on their total white matter abnormality scores, children were classified as follows: (1) no abnormalities (score of 5 to

TABLE 1 Description of executive function measures and key variables.

Test name	Test description	Key dependent variables
Working memory		
CANTAB Spatial span (SSP)	Adapted Corsi Blocks task. Participant is required to recall a sequence of boxes that change color one by one. Trials begin at 2-box sequences and continue up to 9-box sequences. In the backward variant, boxes must be selected in the reverse order that they were displayed.	(1) Span length: the max. Sequence recalled (higher score = better spatial span)
CANTAB Spatial working memory (SWM)	Adapted self-ordered search task. Participants search a number of boxes to uncover a hidden "token." Trial continues until all tokens are found. Four trials each consisting of 4-, 6-, and 8-boxes to search under are assessed, for a total of 12 trials.	(1) Total revisit errors: times a box already found containing a token was selected (lower scores = fewer errors)
Planning		
CANTAB Stockings of Cambridge (SOC)	Adapted Tower of London task. Participants must move balls to recreate a target display in a specified number of moves. There are two trials each for the 2- and 3-move levels, and four trials each for the 4- and 5-move levels. Trials are terminated if unsolved after more than double the minimum moves have been executed.	(1) % of problems solved in the specified number of moves or "perfect solutions" (higher = more problems solved) (2) planning time before moving first ball (longer = greater planning time)
Cognitive flexibility		
CANTAB Intra-extra dimensional set shift (IED)	Adapted Wisconsin Card Sorting task. A forced-choice discrimination test of rule acquisition and reversal. Participants select an image and, through trial and error, discover the rule that determines which image is correct. Following six consecutive correct choices, the rule then changes without notice. Rule shifts in the initial stages are intra-dimensional stimulus shifts and in the later stages are extra-dimensional shifts.	(1) Total number of errors made, adjusted for total stages completed (2) Intra-dimensional shift errors (3) Extra-dimensional shift errors (lower scores = fewer errors made)
Comprehensive trail-making test (CTMT)	A pen and paper test comprised of five visual search and sequencing trails. Participants must connect a series of stimuli in a predetermined order as quickly as possible. The trails become increasingly difficult by including distractor stimuli, and incorporating different stimuli into the sequence.	(1) Total time taken to complete the sequence (faster = better) (2) Composite Index T score (higher score = better overall performance)

6); (2) mild abnormalities (score of 7 to 9); (3) moderate abnormalities (score of 10 to 12); or (4) severe abnormalities (score > 12).

2.6 Covariate measures

Additional measures were selected based on previous research linking the covariate with neurocognitive outcomes. These included family socioeconomic status and maternal education at birth, given consistent evidence showing that these factors are correlated with child executive functioning ability (Linsell et al., 2015; Stalnacke et al., 2019; Rhoades et al., 2011; Luu et al., 2011; Hackman et al., 2015; Murtha et al., 2023). Several other family social background factors were also explored, including maternal age and marital status. However, these were not included as covariates because they did not correlate significantly with GA group status.

Family socioeconomic status (SES) was assessed using the Elley-Irving index when participants were corrected age 2 years (Elley and Irving, 2003). This measure classified families based on the highest parental occupation, into three groups: codes 1–2 = professional/managerial roles, 3–4 = technical/skilled work, 5–6 = semi- and unskilled work and unemployed. Low-family SES was defined as semi-skilled, unskilled roles and unemployed. Parental education was also recorded based on each parent's highest qualification, ranging from 1 (did not finish high school) to 5 (university degree).

In addition, processing speed was also considered a potential covariate given findings showing that it influences how efficiently an individual can complete speeded executive tasks (Anderson, 2002; Mulder et al., 2011; Rose et al., 2011). This was measured using the Symbol Digit Modalities Test (Smith, 1973) at age 17 years. Participants used a reference key to match as many numbers with geometric figures as they could in 90 s, with the total score reflecting the correct number of substitutions made.

2.7 Statistical analyses

Data analysis was conducted in four steps using SPSS version 29: (1) examine the unadjusted EF scores for EPT, VPT and FT adolescents, (2) examine the impact of cognitive load on EF

TABLE 2 Sample characteristics.

Measure	Gestational age group			F/χ^2	p
	EPT *N* = 36	VPT *N* = 51	FT *N* = 68		
Infant Clinical Characteristics					
M (SD) Gestational age, weeks	26.06 (1.35)	29.76 (1.17)	39.50 (1.28)	1612.58	<0.001
M (SD) Birth weight, grams	795 (233)	1,237 (235)	3,522 (428)	1060.97	<0.001
% IUGR	19.4	5.9	1.5	11.70	0.003
% Male	58.3	47.1	50.0	1.12	0.57
% Twin	27.8	41.2	5.9	21.49	<001
M (SD) neonatal medical complexity score[a]	3.7 (2.5)	0.9 (1.6)	–	41.23	<0.001
White matter abnormality: % none	11.4	31.4	–	5.59	0.13
% mild	71.4	54.9	–		
% moderate	17.1	11.8	–		
% severe	0.0	2.0	–		
Family background characteristics					
% Mother NZ/Other European ethnicity	80.6	90.2	88.2	1.89	0.39
M (SD) Maternal age	30.97 (5.76)	30.47 (4.70)	31.37 (4.14)	11.73	0.59
% Young mother <21 years	5.6	2.0	1.5	1.68	0.43
% Single mother	22.2	15.7	10.3	2.69	0.26
% Low family SES	27.8	29.4	10.3	7.96	0.02
% Mother left school <16 years	33.3	39.2	16.2	8.45	0.02
% Father left school <16 years	34.3	32.7	23.9	1.64	0.44
17-year characteristics					
M (SD) Full Scale IQ	103.7 (9.6)	105.3 (13.8)	114 (10.9)	12.48	<0.001
M (SD) Processing speed score	45.2 (9.5)	49.4 (11.8)	53.7 (10.1)	7.78	<0.001

[a]A summative index including presence and severity of need for respiratory support, time taken to reach full enteral feeding, retinopathy of prematurity, neonatal sepsis, intraventricular haemorrhage/periventricular leukomalacia (IVH/PVL) and any major surgery.

performance for each group, (3) examine whether expected group differences in overall EF persisted after adjusting for family social background and processing speed, and (4) examine the extent to which neonatal medical complexity and white matter abnormalities might mediate the relationship between GA and EF performance.

First, between-group differences in EF performance were examined using ANOVA, and rates of impairment were compared using chi-square tests of independence. Second, mixed ANOVAs were run with GA group as the between-subjects factor, and task level as the within-subjects factor, to examine how the different groups performed at different demand levels of each task. Third, principal components analysis and confirmatory factor analysis were conducted to assess the suitability of a single-factor model of EF for further analysis. This overall EF factor was subject to ANOVA and chi-square tests of independence as per step one, as well as ANCOVAs to control for SES, maternal education, and processing speed, and a two-way ANOVA to explore a sex by GA interaction. Finally, path analysis was conducted using the Hayes PROCESS macro to examine the extent to which associations between continuous measures of GA and overall EF performance at age 17 years might be mediated by infant neonatal medical risk over the NICU stay and/or cerebral white matter abnormalities on term MRI.

3 Results

3.1 Characteristics of the sample

Executive functioning task data were available for 36 EPT participants (missing data due to blindness, $n = 1$; severe neurodevelopmental impairment, $n = 2$, time constraints, $n = 1$, excluded due to severely impaired performance, $n = 1$), 51 VPT participants (missing data due to Cortical Visual Impairment, $n = 1$, time constraints $n = 3$), and 68 FT participants. The infant clinical and family background characteristics of the sample are presented in Table 2, with infant medical risk exposures for the EPT and VPT groups described in more detail in Supplementary Table S1. The table shows that there were expected differences in the infant clinical characteristics between the three groups (GA, birth weight, growth restriction, and plurality), but similar proportions of participants born male. The EPT group had a significantly higher neonatal medical complexity score than the VPT group ($p < 0.001$). While the EPT group had higher rates of mild to moderate white matter abnormalities than the VPT group, this trend was not statistically significant. The three groups had similar proportions of mothers who identified as

New Zealand/other European, mothers who were under 21 years of age at their child's birth, single mothers, and fathers who did not complete high school. Adolescents in the EPT and VPT groups were more likely to have been born into low SES families and to mothers who had not completed high school than FT adolescents ($p = 0.02$). EPT and VPT adolescents also had lower mean IQ and processing speed scores than their FT peers at 17 years ($p < 0.001$).

3.2 Between-group differences in executive functioning task performance at age 17

The performance of EPT, VPT, and FT adolescents across the EF tasks is described in Table 3. As shown, there were significant linear effects of GA group on all key EF variables, with the exception of overall SOC planning time. *Post hoc* analyses showed that there were significant sub-group differences, with the EPT group performing consistently below the FT group with moderate to large effect sizes (Cohen's *d* range: 0.58–1.03). The results also showed that the VPT group was characterized by impaired EF task performance relative to the FT group across most measures, with effect sizes predominantly in the moderate range (Cohen's *d* range: 0.51–0.75). Although adolescents in the EPT group consistently performed less well than adolescents in the VPT group across all EF outcome measures, these between-group differences did not reach statistical significance, with the exception of the SWM task (Cohen's $d = 0.50$ for the total errors score).

Table 4 describes the rates of EF impairment for each study group, based on the lowest 10% of the comparison group score distribution for the key variables from each EF domain. As shown, EPT-born adolescents were at greatest risk for EF impairment across all domains compared to the FT group, with relative risks ranging from 1.4 to 3.7. The VPT-born adolescent group was also at increased risk for EF impairment compared to the FT group, with relative risks ranging from 1.2 to 3.1 across domains.

3.3 Impact of increasing cognitive demand on EF task performance

We next examined the impact of increasing cognitive demand on EF performance for those tasks with trials of varying levels of difficulty (SWM, SOC, IED, CTMT). On the SWM task (Figure 2A), an interaction was observed between GA group and demand level that approached significance, $F(2.77, 210.83) = 2.43$, $p = 0.071$, partial $\eta^2 = 0.031$, $\varepsilon = 0.694$. Follow-up analyses revealed that the EPT group made significantly more errors than the VPT and FT groups on the 6-box trials and significantly more errors than the FT group on the 8-box trials (see Table 3).

On the SOC task, there was a significant interaction between GA group and demand level for the percentage of trials solved in the minimum number of moves (Figure 2B), $F(5.41, 411.34) = 4.70$, $p = 0.001$, $\eta^2 = 0.058$, $\varepsilon = 0.902$. Follow-up analyses revealed a clear between-group difference across the 3-, 4-, and 5-move trials, with both the EPT and VPT groups solving significantly fewer problems than the FT group (see Table 3). An interaction was also found for GA group and demand level on initial planning time (Figure 2C), $F(4.26, 323.59) = 2.90$, $p = 0.02$, $\eta^2 = 0.037$, $\varepsilon = 0.710$, with follow-up analyses revealing that, compared to the FT group, the EPT group spent significantly less time planning on trials at the highest difficulty level (5 moves; see Table 3).

On the IED task, there was no interaction between GA group and task demand level (Figure 2D), $F(2, 152) = 0.10$, $p = 0.91$, $\eta^2 = 0.001$. Finally, on the CTMT task, there was a significant interaction between GA group and CTMT trail on completion time (Figure 2E), $F(5.89, 436.25) = 2.75$, $p = 0.01$, partial $\eta^2 = 0.036$, $\varepsilon = 0.737$. Follow-up analyses showed that EPT and VPT adolescents were significantly slower to complete each of the trails than the FT group (see Table 3).

3.4 Overall EF outcome

Given the generally consistent pattern of results across EF outcome measures, we assessed the possibility of creating a composite measure of adolescent EF to allow an examination of the extent to which later EF performance might be predicted by neonatal factors. This approach was chosen for several reasons, including that (1) empirical research with this cohort supported an underlying common EF factor at earlier ages, (2) generally consistent between-group differences were evident across all EF domains, and (3) the modest sample size precluded the inclusion of multiple latent factors. As noted in the Methods, Principal Components Analysis and Confirmatory Factor Analysis further supported the use of a single EF factor (see Supplementary material 2 for a summary of these results). Thus, a composite measure of EF was computed by summing z-scores (based on the comparison group results) from each of the key task variables. These key variables were (1) SSP forwards span, (2) SSP backwards span, (3) SWM total revisit errors, (4) SOC percent of perfect solutions, (5) IED total adjusted errors, and (6) CTMT composite index T score. Summed z-scores were then standardized ($M = 10$, SD = 2).

Before examining the role of neonatal factors in overall EF performance, we examined group differences on this overall composite, adjusting for additional covariates and known risk factors. As shown in Table 3, adolescents born EPT and VPT had significantly lower EF composite scores than the FT group, and the overall between-group difference remained following adjustment for family SES, maternal education, and processing speed ($p = 0.002$, partial $\eta^2 = 0.081$). We also examined the role of sex at birth and found no sex by GA group interaction for this EF composite score, $F(2, 149) = 1.56$, $p = 0.213$, partial $\eta^2 = 0.021$. Scores also did not differ by participant sex, $F(1, 149) = 1.04$, $p = 0.310$, partial $\eta^2 = 0.007$. As shown in Table 4, EPT-born adolescents had relative risks of later overall EF impairment that were 4.9 times, and VPT-born adolescents 2.9 times, higher than FT adolescents.

3.5 The role of neonatal medical complexity and neonatal white matter abnormalities in executive function outcome

An unadjusted linear regression analysis showed that GA significantly predicted overall EF performance at age 17 years within the EPT and VPT groups ($\beta = 0.25$. $p = .02$). To examine the role of

TABLE 3 Executive function performance for extremely preterm, very preterm and full term born adolescents at age 17 Years.

		Gestational age group			ANOVA *F*	*Post hoc* tests	
EF measure		I: EPT *N* = 36	II: VPT *N* = 51	III: FT *N* = 68		Sub-group differences	Cohens *d* (95% CI)
Working memory							
SSP	Forwards span	6.47 (1.30)	6.76 (1.51)	7.51 (1.20)	15.38****[a]	I & III*** II & III**	0.84 (0.42–1.26) 0.56 (0.19–0.93)
	Backwards span	5.72 (1.21)	5.92 (1.32)	6.63 (1.34)	13.33****[a]	I & III** II & III*	0.70 (0.29–1.12) 0.53 (0.16–0.90)
SWM	Total revisit errors	27.42 (17.94)	18.88 (16.76)	17.87 (15.62)	6.78**[a]	I & II* I & III*	0.50 (0.06–0.93) 0.58 (0.17–0.99)
	4-boxes	0.64 (1.50)	0.39 (1.15)	0.62 (2.20)	0.30	–	–
	6-boxes	7.72 (7.71)	4.29 (5.36)	3.99 (5.28)	5.11**	I & II** I & III***	0.53 (0.10–0.97) 0.60 (0.19–1.01)
	8-boxes	19.06 (12.20)	14.20 (12.00)	13.26 (11.38)	2.99*	I & III*	0.50 (0.09–0.91)
Planning							
SOC	Percent of perfect solutions	68.98 (17.44)	73.86 (15.99)	81.50 (14.17)	16.48****[a]	I & III*** II & III*	0.81 (0.39–1.23) 0.51 (0.14–0.88)
	2-moves	97.22 (11.61)	100.00 (00.00)	98.53 (8.51)	1.32	–	–
	3-moves	75.00 (18.36)	92.16 (18.36)	96.32 (13.15)	12.74***	I & II*** I &III***	0.68 (2.34–1.12) 0.97 (0.55–1.40)
	4-moves	66.67 (23.15)	62.25 (25.68)	73.90 (23.03)	3.56*	II & III*	0.48 (0.11–0.85)
	5-moves	54.17 (27.71)	63.24 (27.09)	73.16 (24.93)	6.41**	I & III*** II & III*	0.73 (0.32–1.15) 0.38 (0.02–0.08)
	Planning time	5443.56 (3635.87)	6318.74 (3907.61)	6518.91 (4139.95)	1.57[a]	–	–
	2-moves	2069.68 (1517.51)	2235.15 (1271.17)	2130.41 (2455.49)	0.08	–	–
	3-moves	5335.81 (3315.48)	4946.68 (3306.97)	4564.05 (3568.41)	0.54	–	–
	4-moves	7862.17 (7544.23)	8039.77 (5448.06)	8927.75 (6198.11)	0.45	–	–
	5-moves	6506.60 (5044.31)	10053.34 (10019.69)	10453.43 (7738.15)	3.05*	I & III*	0.57 (0.16–0.92)
Cognitive flexibility							
IED	Total adjusted errors[b]	23.25 (16.50)	25.06 (18.68)	18.50 (15.56)	4.18*[a]	–	–
	Intra-dimensional shift errors	7.17 (5.50)	6.10 (2.19)	6.00 (2.05)	0.41	–	–
	Extra-dimensional shift errors	10.56 (9.32)	11.36 (9.54)	8.51 (9.08)	2.72	–	–

(Continued)

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TABLE 3 (Continued)

EF measure		Gestational age group			ANOVA *F*	*Post hoc* tests	
		I: EPT *N* = 36	II: VPT *N* = 51	III: FT *N* = 68		Sub-group differences	Cohens *d* (95% CI)
	Composite Index T score	35.65 (9.79)	37.96 (11.10)	47.00 (11.80)	28.14***[a]	I & III*** II & III***	1.03 (0.60–1.45) 0.75 (0.37 1.13)
CTMT	Trail 1, ms	41.06 (12.64)	40.60 (16.28)	33.22 (12.96)	5.44**	I & III* II & III*	0.61 (0.19–1.02) 0.51 (0.13–0.89)
	Trail 2, ms	44.08 (15.15)	43.92 (21.56)	34.27 (11.93)	6.63**	I & III* II & III**	0.75 (0.33–1.16) 0.58 (0.20 - 0.96)
	Trail 3, ms	50.39 (13.68)	50.13 (18.72)	38.54 (13.56)	10.74***	I & III*** II & III***	0.87 (0.45–0.29) 0.73 (0.34–1.11)
	Trail 4, ms	37.44 (12.31)	36.94 (15.23)	29.22 (10.10)	7.44**	I & III** II & III**	0.75 (0.33–1.17) 0.61 (0.23–0.99)
	Trail 5, ms	67.03 (23.88)	61.44 (22.66)	48.31 (18.31)	10.76***	I & III*** II & III**	0.92 (0.419–1.34) 0.65 (0.27–1.03)
Executive function composite score		7.76 (2.02)	8.51 (2.30)	9.99 (2.00)	29.27***[a]	I & III*** II & III***	1.11 (0.68–1.54) 0.70 (0.32–1.07)

All data presented are Mean (SD). SSP, Spatial Span; SWM, Spatial Working Memory; SOC, Stockings of Cambridge; IED, Intra-Extra Dimensional Set Shift; CTMT, Comprehensive Trail-Making Test. * ≤ 0.05, ** ≤ 0.01, *** < 0.001.
[a]ANOVA test of linearity used.
[b]Results analysed using log transformed variable.

neonatal medical complexity and white matter abnormality in potentially explaining the relationship between continuous GA and overall EF, we ran a multiple mediation model. These results are summarized in Table 5. Findings revealed a significant indirect effect of GA on EF performance through medical complexity ($b = 0.169$, $t = -1.73$) and a significant indirect effect of GA on EF performance through neonatal white matter abnormality ($b = 0.107$, $t = -3.33$). Furthermore, the direct effect of GA on EF performance in the presence of these mediators was no longer significant ($b = -0.05$, $t = 0.38$), suggesting full mediation. An examination of the individual risks included in the medical complexity score showed that the indirect relationship between GA and EF through medical complexity was driven mainly by the degree of neonatal sepsis, and including sepsis in the model in place of medical complexity revealed similar results.

4 Discussion

In this regionally representative sample of adolescents born VPT, we found that adolescents born very and extremely preterm are at increased risk of experiencing EF challenges that span working memory, planning, and cognitive flexibility domains. Consistent with existing research, the degree of prematurity significantly impacted 17-year EF performance (Lundequist et al., 2015; Taylor et al., 2004). Specifically, the EPT group performed most poorly, obtaining scores that were 0.6 to 1.0 SDs below the FT group across the individual EF measures, and 1.1 SDs below the FT group on the EF composite measure. As a result, EF impairment was relatively common, with 50% meeting criteria on our composite measure. Nonetheless, adolescents in the VPT group also showed compromised EF performance, with scores 0.5 to 0.75 SDs below the FT group across individual EF measures and the EF composite, and 29% demonstrating overall EF impairment. Between-group differences in overall EF remained unchanged following adjustment for potential confounders including family SES and maternal education.

Despite seemingly pervasive EF difficulties, between-group differences varied in magnitude across measures. Specifically, there were no differences between the VPT and FT groups on the SWM task, in contrast to previous studies of younger adolescents (Curtis et al., 2002; Fitzpatrick et al., 2016; Litt et al., 2012). However, the VPT group performed worse than the FT group on the SSP, another working memory task. This finding highlights the importance of employing multiple indicator measures for each construct of interest to avoid measurement-specific findings that might underestimate the cognitive challenges of those born VPT. This could be addressed by including multiple tasks that tap the same construct or utilizing tasks with even greater progressive difficulty.

Using the latter approach, we found that in general, VPT and EPT adolescents were characterized by progressively deteriorating performance on EF tasks with increasing cognitive demand, extending previous research conducted in childhood and early adolescence (Jaekel et al., 2013; Wehrle et al., 2016; Woodward et al., 2022). This effect was most marked for the EPT group, whose performance deviated significantly from the FT comparison group when task demands were highest. This is likely to be reflected in widening discrepancies in academic achievement in response to the increasing EF demands of secondary school (Zelazo and Carlson, 2020).

TABLE 4 Rates of impairment on executive function measures for EPT, VPT, and FT born adolescents at age 17 Years.

EF measure	EPT *N* = 36	VPT *N* = 51	FT *N* = 68	X^2	*p*
Working memory					
SSP Forwards	22.2	23.5	8.8	5.51	0.06
SSP Backwards	47.2	41.2	22.1	8.27	0.02
SWM total revisit errors	16.7	13.7	11.8	0.49	0.79
Planning					
SOC percent of perfect solutions	33.3	17.6	8.8	9.83	0.007
Cognitive flexibility					
IED total adjusted errors	22.2	25.5	11.8	3.99	0.14
CTMT composite index	38.9	37.5	11.9	13.11	0.001
Executive function composite score	50.0	29.4	10.3	19.90	<0.001

All data are presented as %. SSP, Spatial Span; SWM, Spatial Working Memory; SOC, Stockings of Cambridge; IED, Intra-Extra Dimensional Set Shift; CTMT, Comprehensive Trail-Making Test.

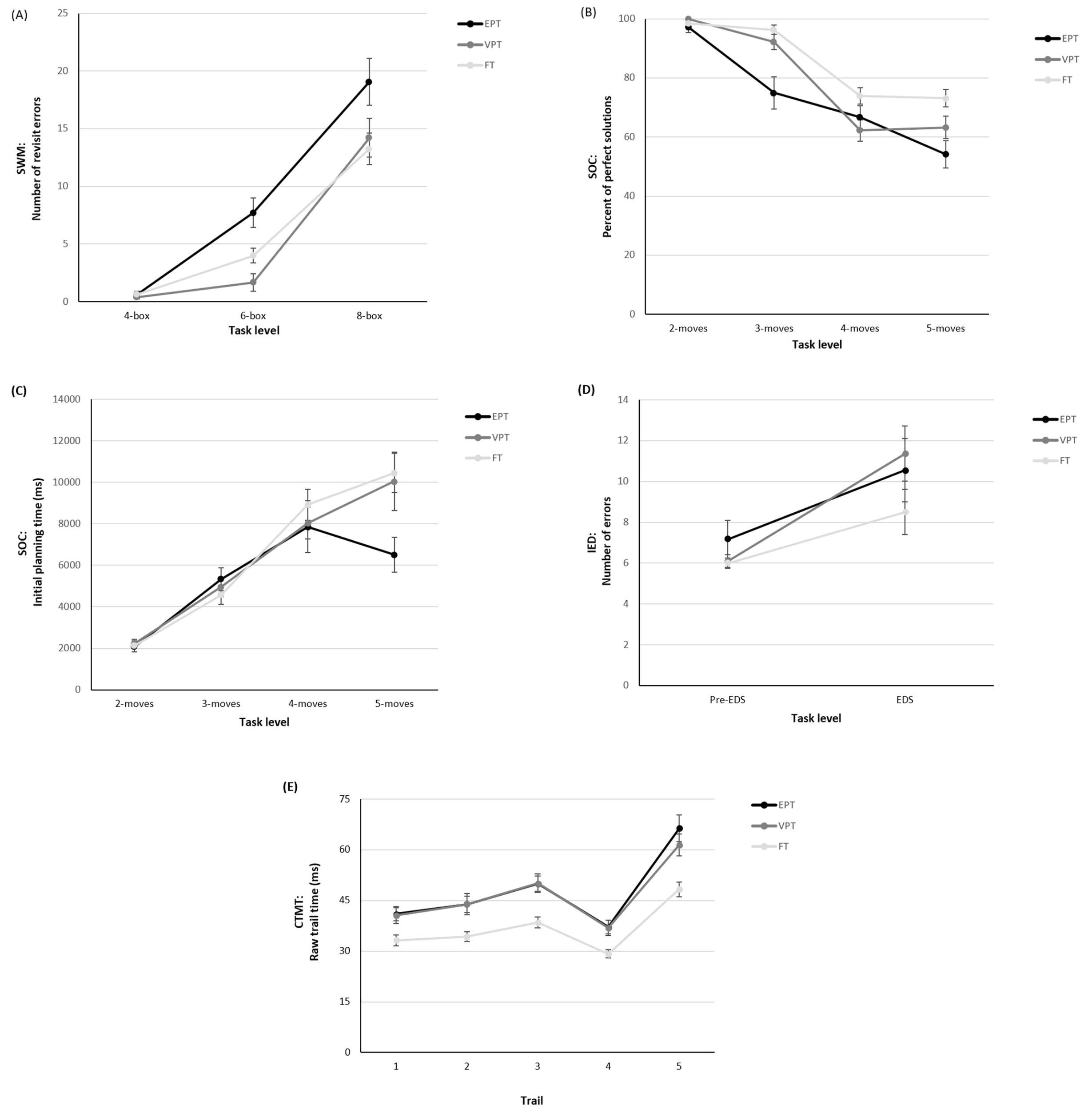

FIGURE 2
EF task performance by gestational age group and cognitive load. **(A)** SWM total revisit errors; **(B)** SOC percent of perfect solutions; **(C)** SOC initial planning time; **(D)** IED total adjusted number of errors; and **(E)** CTMT raw trail completion time across task levels.

TABLE 5 Mediation analysis summary.

Total effect (GA - > EF performance)	Direct effect (GA - > EF performance)	Relationship	Indirect effect	Confidence interval		*t*	Conclusion
				Lower	Upper		
0.223 ($p = 0.04$)	−0.054 ($p = 0.70$)	GA → medical complexity score → EF performance	0.169	0.152	0.370	−1.73	Full mediation
		GA → white matter class → EF performance	0.107	0.025	0.219	−3.33	Full mediation

Alongside school success, autonomy is central to late adolescence, and several salient and complex facets of adolescent life, such as navigating peer social relationships, gaining employment, and learning to drive, require high cognitive resources. Therefore, executive deficits that impact planning, problem-solving, and flexible thinking will present significant challenges during this developmental transition (Ben-Asher et al., 2023; Ghawami et al., 2022; Holmes et al., 2016; Pope et al., 2016).

Regarding early life predictors of the late adolescent EF abilities of those born very preterm, neonatal medical complexity and neonatal white matter abnormality class mediated the association between GA and overall EF performance at age 17 years. Concerning medical complexity, we found that a lower GA was associated with a higher medical complexity score, which, in turn, was associated with a lower overall EF score at 17 years. A similar approach to examining the additive impacts of neonatal risk factors was taken by Curtis et al. (2002), who found that a higher cumulative risk score predicted poorer spatial working memory in early adolescence. Stalnacke et al. (2019) also found an indirect relationship between cumulative risk and cognitive flexibility at 18 years.

In a secondary exploratory analysis, we found that the only individual risk factor significantly associated with later EF performance was the degree of neonatal infection. Sepsis has been shown to be an independent risk factor associated with neurodevelopmental outcomes in infancy and toddlerhood (Fibbiani et al., 2019; Rallis et al., 2019) and to middle childhood (Rand et al., 2016), yet its longer-term cognitive effects have not yet been examined. Other studies have linked individual medical factors such as oxygen requirement (Saavalainen et al., 2007; Taylor et al., 2004), and abnormal neonatal brain EEG or ultrasound (Luu et al., 2011; Saavalainen et al., 2007) with poorer EF performance in adolescence, suggesting dramatic long-term effects of inflammation, reduced cerebral blood flow and ischaemic injury on the developing brain.

In our study, sepsis was also strongly associated with the presence of the other medical risks included in the composite, meaning those individuals with sepsis also had high medical complexity scores. Further, there were relatively high rates of sepsis in the cohort compared to some of the other independent risk factors, allowing for greater statistical power to predict our EF outcome. With smaller cohorts, the ability to detect the effects of individual risk factors on later cognitive outcomes is limited, so comparing the impacts of sepsis and related individual neonatal outcomes on longer-term EF development requires further exploration.

White matter abnormalities at term equivalent also mediated the relationship between GA and 17-year EF performance. Specifically, a lower GA predicted more severe white matter pathology. In turn, more severe white matter abnormalities predicted poorer overall EF performance. Previously, white matter abnormalities were shown to predict global EF impairment at age 4 years (Woodward et al., 2011) and poorer performance across various neurocognitive domains at ages 4 and 6 years in the current cohort (Woodward et al., 2012). Similarly, others have reported an association between white matter abnormalities and cognitive ability up to age 9 years (Anderson et al., 2017; Iwata et al., 2012). There is growing evidence to suggest that early cerebral abnormalities have both primary and secondary longer-term impacts on brain development. Early diffuse white matter injury and structural changes impact subsequent gray and white matter development (Back, 2017; Boardman et al., 2006; Hüppi et al., 2001; Thompson et al., 2022), including altering functional connectivity networks, which are important for higher-order cognitive functions (Cheong et al., 2009; He and Parikh, 2015). Several studies have also shown that persisting white matter alterations present in adolescents and young adults born VPT, such as reduced fractional anisotropy in several white matter tracts and reduced white matter volume, are associated with poorer cognitive performance (Narberhaus et al., 2008; Nosarti et al., 2008; Skranes et al., 2007; Vollmer et al., 2017; Thompson et al., 2022). The current study further supports the neonatal importance of early white matter abnormalities for later neurocognitive risk, showing that the impacts extend well into adolescence.

This study had numerous strengths, including its prospective longitudinal design and a representative cohort of individuals born VPT with high retention over 17 years. In addition, we included a comprehensive battery of tasks assessing our key EF constructs of interest. Despite these strengths, several limitations are worth noting. First, we experienced quite high attrition (45%) at age 17 years in the FT comparison group. This was predominantly due to cohort members living outside the region and funding constraints. Despite this, systematic bias was unlikely given that assessed and not assessed FT study participants did not differ on social background measures at age 17.

Second, despite good retention and representativeness in the very preterm group, we were limited in the number of variables included in the statistical analysis because of the modest sample size. A key focus of this paper was the neonatal predictors of later EF risk. Given that these neonatal factors were found to fully mediate the effects of GA at birth on later EF, other postnatal factors, such as parenting and family functioning factors, were not included in the mediation model. We also did not include postnatal brain MRI measures since the model was fully mediated by neonatal factors. However, future research should examine how aspects of parenting and/or early or school-based intervention might help improve EF skills following VPT birth in this older age group.

In conclusion, findings indicate that adolescents born VPT and EPT were more likely to experience EF difficulties across working memory, planning and cognitive flexibility domains, especially when task demands were high. Associations between GA and EF outcome were fully mediated by neonatal medical complexity (predominantly neonatal infection) during the NICU stay and the presence/severity of cerebral white matter abnormalities at term equivalent. This supports the importance of post-discharge monitoring and early intervention at least to school age for very preterm infants subject to a complex medical course, so as to ensure likely longer-term challenges with EF can be detected and addressed to optimize longer-term outcomes. In addition, screening for white matter abnormalities at term may assist with identifying individuals born very preterm who are at risk of persistent neurocognitive difficulties and aid, or at least help justify, longer-term surveillance and support.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Southern Health and Disability Ethics Committee (14/STH/208). The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

SL: Conceptualization, Formal analysis, Visualization, Writing – original draft, Writing – review & editing. LW: Conceptualization, Methodology, Supervision, Writing – review & editing. SM: Conceptualization, Funding acquisition, Methodology, Resources, Supervision, Writing – review & editing. NA: Conceptualization, Funding acquisition, Methodology, Resources, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyg.2024.1487908/full#supplementary-material

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Children's Health Ireland, Ireland
Theano Kokkinaki,
University of Crete, Greece

*CORRESPONDENCE
Robert J. Ludwig
robertjludwig@gmail.com

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Six weeks that changed the preterm infant brain: lessons learned from the Family Nurture Intervention randomized controlled trials

Robert J. Ludwig[1,2]*, Michael M. Myers[1,2] and Martha G. Welch[1,2]

[1]Department of Pediatrics, Columbia University Medical Center, New York, NY, United States, [2]Martha G Welch Center, New York, NY, United States

Aim: We review extensive results from two randomized controlled trials conducted over 9 years, comparing standard care (SC) in level-4 neonatal intensive care units (NICUs) with SC plus Family Nurture Intervention (FNI).

Methods: FNI included ~six weeks of facilitated mother-infant interactions aimed at achieving mother-infant 'autonomic emotional connection', a novel construct that describes the emotional mother-baby relationship at the level of the autonomic nervous system.

Results and conclusion: Thus far, 18 peer-reviewed publications documented significant positive short-and long-term effects of FNI on infant neurobehavioral functioning, developmental trajectories and both mother and child autonomic health through five years. The observed profound effects of FNI on central and autonomic nervous system function following a relatively short intervention support a novel *autonomic theory of emotions*. We discuss the theoretical and clinical advances that grew out of the trials and speculate on how FNI changes the mother-infant relationship from 'dysregulation' to autonomic emotional co-regulation. We review new constructs and tools that can be used to view and measure the mother-infant autonomic emotional relationship. We present a simple blueprint to improve preterm birth outcomes. Finally, we discuss the significance of our findings and possible impact on the future of preterm infant care worldwide.

KEYWORDS

attachment, NICU intervention, brainstem, autonomic theory of emotions, emotional connection, instinct, mother-infant, skin-to-skin care

Introduction

Together with her team, author Welch designed the Family Nurture Intervention for the Neonatal Intensive Care Unit (FNI-NICU) based on a mother–child intervention she developed during her 30-year private clinical practice from 1970 to 2000, which is described in her 1988 book, Holding Time (Welch, 1988). The therapeutic intervention proved suitable for mothers and children with a wide range of behavioral problems (Welch, 1987; Welch and Chaput, 1988; Welch et al., 2006). The description and terminology of FNI-NICU differs from Welch's past work. However, the key mother-infant emotional exchange activity encouraged during FNI-NICU and the intervention objectives are the same.

Between 2008 and 2012, our group tested the efficacy of FNI-NICU in a single site randomized controlled trial (RCT) in a level-4 NICU. Between 2016 and 2019 we conducted a multisite replication RCT of FNI-NICU in two level-4 NICUs serving disparate populations in two different states. FNI promoted biobehavioral activities that enhanced the mother's and infant's sensory experiences of each other via mutual scent exchange, face-to-face contact, vocal communication, and skin-to-skin care. We expanded preterm infant neurodevelopment testing beyond that of previous research to include outcomes related specifically to the mother-infant autonomic emotional relationship and mother-infant autonomic physiology (Welch et al., 2012) and novel analyses of infant brain activity and development (Yrjola et al., 2022). Our primary objective across both studies was to determine whether repeated mother-infant emotional engagement improved the infant's developmental trajectory with respect to multiple outcomes—physiological, neurological and behavioral.

To date, we have published over 18 papers comparing groups receiving Standard Care (SC) with groups receiving Standard Care plus FNI (see Figure 1). Compared to controls, analyses showed that FNI infants had significantly improved neurobehavioral and autonomic function, FNI mothers showed significant improvement in depressive symptoms and the FNI-NICU dyads scored higher on relational health measures at key assessment points through age five.

Key short-term findings between the start of the intervention in the NICU stay to immediately following discharge included improved maternal caregiving behavior (Hane et al., 2015), a lower HR over the course of the NICU stay (Ludwig et al., 2021) and better infant autonomic regulation at term age (Porges et al., 2019).

The centerpiece of FNI infant brain function studies were comparisons of electroencephalographic (EEG) recordings collected at ~35 weeks gestational age and ~ six weeks later at ~term age (Figure 2). Seven publications documented dramatic changes in the brain function of FNI infants, including: Increased forebrain activity (Welch et al., 2014), Increased cortical EEG activity independent of regional power trajectories (Welch et al., 2017), altered EEG delta brush characteristics (Welch et al., 2020b), more mature cortical functional connectivity (Myers et al., 2015), advanced brain maturation & consciousness (Isler et al., 2018), increased forebrain EEG activity which was replicated in our multicenter RCT (Welch et al., 2022), and cortical EEG networks that were similar to full term networks and which predicted better 18-month outcomes (Yrjola et al., 2022).

Longitudinal findings included better infant autonomic regulation following a mother-infant social stress paradigm (Hane et al., 2019), better dyadic autonomic reflex behaviors at 4-month follow-up (Hane et al., 2019), better mother-infant face-to-face engagement (Beebe et al., 2018), and decreased maternal depressive symptoms and anxiety at 4-month follow-up (Welch et al., 2016), better child social relatedness, language, cognition, attention and a lower risk for autism at 18-month follow-up (Welch et al., 2015), and better empathic understanding (Firestein et al., 2022), and better autonomic regulation at 4–5 year follow-up (see Figure 1; Welch et al., 2020a). FNI-NICU documented the effects of the intervention on mother and child across multiple domains over a five-year period (See Figure 2).

Additional analyses are ongoing, with several additional manuscripts still in preparation. However, at this point in the follow-up of FNI trial cohorts, we can say with confidence that the infants and mothers in the intervention group experienced significant short and long term benefits from the intervention. Additionally, the longitudinal effects through age five suggest the intervention significantly reduced neurobehavioral risks and improved developmental *trajectories*.

The significant findings from the FNI trial, together with the novelty and relatively low dose of the intervention, led us to examine the key factors that might have accounted for the results. Important questions we considered were:

- What key elements of the intervention led to the changes?
- What behavioral and physiological biomarkers were associated with the change?

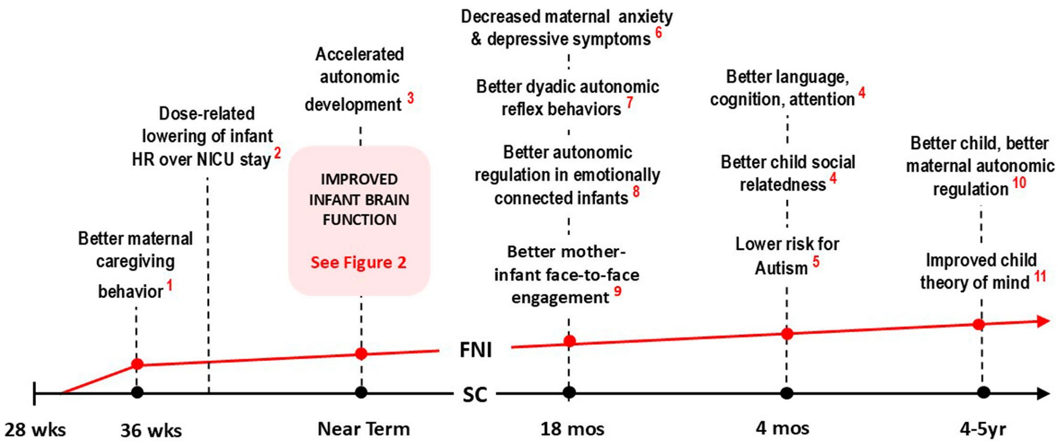

FIGURE 1
Timeline trajectory of FNI-NIU trial showing major effects of intervention at crucial stages of development. Note that at each stage, behavior and physiology were, on average, significantly better in the FNI group (indicated graphically by the red line), compared to the SC group (black line). Collectively, the results indicate that that infants in the FNI group were on a significantly better developmental trajectory following a relatively short intervention in the NICU (References: 1. Hane et al., 2015; 2. Ludwig et al., 2021; 3. Porges et al., 2019; 4. Welch et al., 2016; 5. Hane et al., 2019; 6. Beebe et al., 2018; 7. Welch et al., 2015; 8. Welch et al., 2020a; 9. Firestein et al., 2022).

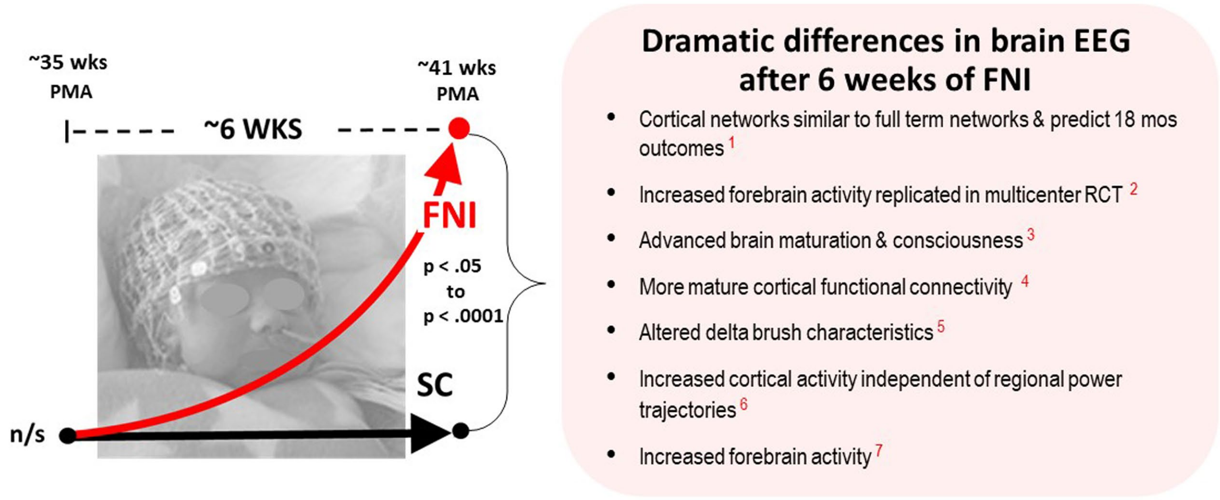

FIGURE 2
Schematic showing the dramatic changes in brain EEG following an average of six weeks intervention. Recorded at ~35 wks and ~ 41 postmenstrual age (PMA) using high density 128-lead nets. The richness of the data set and volume of EEG technical analyses, along with the p values and effect sizes, provide highly significant evidence that FNI had a very large beneficial impact on infant brain development—prompting the questions: *What exactly is the intervention?*, and *What mechanisms could explain these changes?* (Published EEG results referenced are in red: 1. Yrjola et al., 2022; 2. Welch et al., 2022; 3. Isler et al., 2018; 4. Myers et al., 2015; 5. Welch et al., 2020b; 6. Welch et al., 2017; 7. Welch et al., 2014) (Published results referenced are in red).

- What biological mechanisms might have accounted for the change?
- Is the intervention scalable?

Key elements of family nurture intervention

Mothers assigned to the FNI group agreed to attend at least four 1-h intervention 'calming sessions' per week while in the NICU. The average amount of time the mothers engaged with their babies in calming sessions was about the minimum we had required—between 24 to 36 h over an average six week stay. We encouraged other family members, including the father and grandparents to engage with the baby, especially when the mother could not be with the baby. However, all family members learned that their primary role was to support the disrupted emotional connection between mother and baby.

'Calming sessions' between mother and infant included skin-to-skin contact, mutual scent exchange, eye contact and oral communication. Skin-to-skin holding was encouraged as soon as possible but reassuring sustained touch of the infant's torso to mimic holding was initiated while the baby was in the isolette. These activities facilitated by FNI-NICU are used in other NICU interventions, with the goal of improving infant and maternal outcomes. However, the key singular activity that is encouraged during the 1-to 1.5-h FNI 'calming sessions', one that is unique to FNI is '*autonomic emotional expression*' between mother and baby. To our knowledge, FNI is the only intervention that focuses narrowly on autonomic emotional *expression* as the critical factor in changing the mother/baby autonomic emotional *relationship*.

The central mother-infant interaction of FNI was referred to as a 'calming cycle' (Figure 3 below). The basic phenomenon was first described in Holding Time (Welch, 1988), as schematically represented in Figure 4. The insight for the intervention came from Welch's clinical observations early in her career. She noted in the intervention that the mother/child emotional relationship cycled through upset, protest/conflict and resolution/calm. Sometimes the cycle occurred daily, sometimes multiple times (e.g., bedtime, drop off at day care, phone call interruptions). Welch noted that the upsets were usually related to separation, or the fear of separation. In her intervention, she discovered that if the mother and child processed the upset or fear by holding and communicating with one another until the upset was resolved—and if the two repeated this process each time upset occurred—the communication between the two improved, and the upsets and symptomatic behavior occurred less often, and the pair's emotional relationship and child behavior and development improved.

Welch designed a study to test her intervention in the neonatal intensive care unit (NICU), which came to known as Family Nurture Intervention (FNI-NICU). The main activity in the trials came to be known as a 'calming cycle', where the mother was encouraged to convey her heart-felt emotional communication directly to the infant. The central hypothesis for her studies was that repeated calming sessions would lead to observable positive physiological and behavioral changes in the infant and mother.

FNI-NICU focused on enabling mothers to engage in specified mother-infant emotional interactions as early as possible after birth, within the constraints of the NICU environment. Of necessity, these interactions began while the infant was confined to the isolette. Later, sessions occurred during skin-to-skin or clothed holding and near discharge during family sessions, when strategies were developed for the family members to support the mother and infant as they continued calming interactions at home. The maternal interactions principally included deeply felt *emotional expression* and firm sustained touch, vocal soothing and eye contact during the sessions, and an odor-cloth exchange at the end of each session.

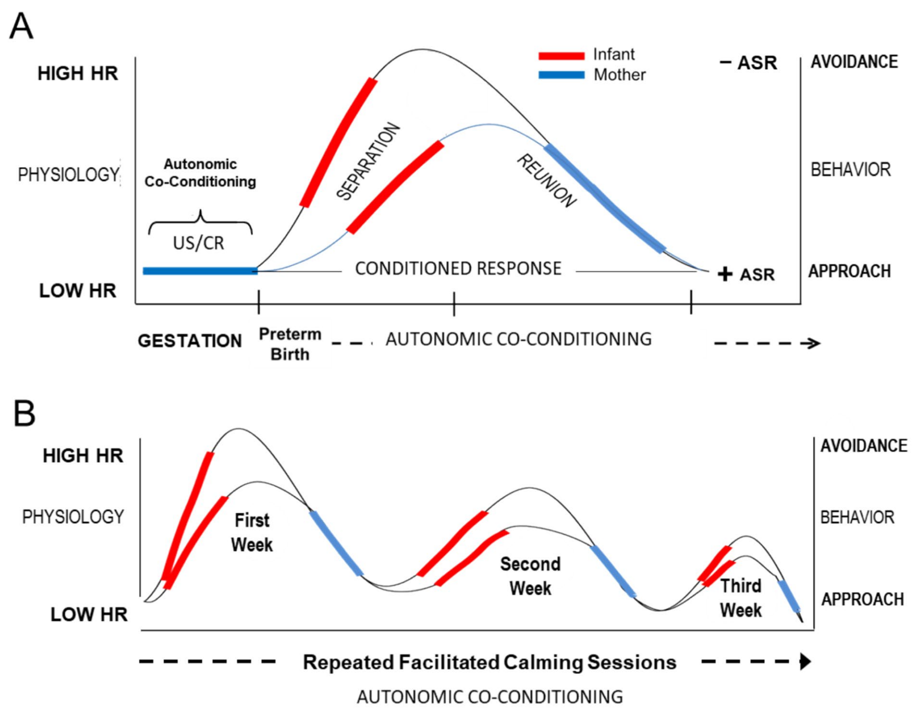

FIGURE 3
Conceptual diagram illustrating hypothesized autonomic conditioning of infant resting HR across the course of facilitated FNI calming sessions in the NICU. **(A)** Conditional autonomic reflexes (US/CRs) are formed between mother and fetus. The US/CRs are preserved transnatally in the form of *autonomic socioemotional reflexes* (ASR). Premature birth and NICU experience leads to autonomic dysregulation (e.g., increased resting HR and a negative avoidant ASR). Each facilitated calming session lowers resting HR and restores autonomic co-regulation. **(B)** Repeated facilitated calming sessions restore a positive ASR and lower resting HR, which promotes a healthy mother-infant relationship and adaptive growth and development.

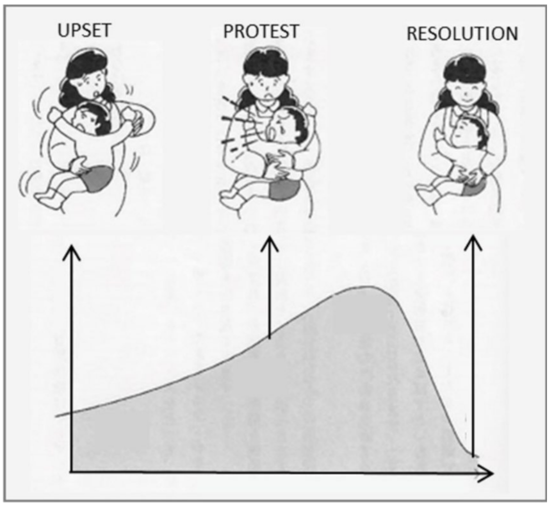

FIGURE 4
Schematic showing the hypothesized behavioral arc that results from the Welch Method.

Autonomic emotional expression

What is autonomic emotional expression? It is well documented that unexpected hospitalization, and the uncertain prognosis of pre-term infants often leads mothers to experience strong negative emotions, such as frustration, anger, anxiety, even guilt (Wang et al., 2021). In response, many strategies are now in place to support and help mothers cope with the NICU experience, such as Family Centered Care (Abukari and Schmollgruber, 2023), Skin-to-skin Care (Feldman and Eidelman, 2003; Durmaz et al., 2023), developmental care (Smith et al., 2023), Interpersonal therapy (Petersson et al., 2023), and telenursing (Maleki et al., 2022). Over the past 50 years, these interventions have greatly improved the quality of care of families of preterm infants. FNI shared the goals and methods of many of these strategies.

However, the central feature of the FNI-NICU method, one that distinguishes it from all prevailing strategies, was focusing on the release and expression by the mother of her deepest and strongest emotions directly to her infant during physical contact. Doing so can be very different from how she might express emotions and other social information in contexts that make up her everyday life, especially in the NICU (Barrett et al., 2019). To avoid confusion with other types of emotional expression by the mother, the FNI-NICU trials encouraged what we now term *Autonomic Emotional Expression* (*AEE*), i.e., strong emotion expression that triggers an autonomic response, such as crying during cuddling.

Nurture specialists (NS), in this case NICU nurses, facilitated mother/infant AEE during 1-to 2-h calming sessions. Rather than attempting to teach or educate the mother about autonomic emotional expression the NS prompted the mother to engage in sensory experiences of close physical contact and AEE. For instance, in the FNI trials the first calming session typically took place at the isolette about one week after birth. During the first session, the mother was prompted to express deep emotions and feelings directly to her baby while holding the baby's torso through the portals of the isolette. Such action typically led to eye contact and approach behaviors on the part of the baby.

Sometimes, the mother was emotionally blocked and had difficulty accessing her emotions with her baby. In these cases, the NS created privacy for the mother and baby and suggested things the mother could say directly to her baby. For instance, the NS said to the mother, tell your baby… '*the birth story*', or '*how you felt when you became pregnant*', or '*how you felt when you were told the baby was going to be premature*', etc.

Such prompting by clinical staff and therapists is often discouraged, based on the mistaken belief that it might cause psychological harm to the mother and infant in all cases. It is conventionally believed and widely accepted that prompting a mother to display or talk about past emotional disturbances may trigger unknown negative reactions. Consequently, NICU staff typically address clinical topics or keep conversations upbeat and positive. Mothers with a history of mental illness were excluded from our studies. However, almost all of the mothers were suffering from some degree of trauma and/or depression, even those who, at first, outwardly seemed to be happy, cheerful and totally unaffected by the preterm birth experience. And nearly every mother in the study who had a heart to heart talk employing AEE with her baby reported feeling better after the talk. These were documented in a study of FNI in preschool aged children (Markowitz et al., 2023). It was rare when the AEE prompts failed to evoke a mother's emotions, and as predicted the expression triggered a response from the baby.

FNI is trauma-informed. Approach behaviors of the infant overcome the shut-down and avoidance of the mother while the infant is hospitalized. Avoidance during hospitalization ranges from not visiting to lack of engagement even when present in the NICU or dissociative care. However, our research has shown that when mothers express deep emotions directly to the infant, the infant orients to mother, and often oxygen saturation increases (Markowitz et al., 2023). These are the markers of AEC beginning to occur. The feeling of 'guilt' over preterm birth in NICU mothers is often overlooked (Wang et al., 2021). One particularly effective prompt the NS used to help the mother release her emotions was to suggest to the mother that she tell her infant the story of the birth and to apologize to the baby and saying, '*I'm sorry for the separation and for the suffering you are going through*'. This invariably prompted an autonomic emotional response (e.g., release of tears) from the mother and the orienting response in the infant.

Crying is one of the deepest, most powerful and therapeutic emotions a mother and infant can experience together in the NICU (Craig et al., 2020; Twohig et al., 2016). It is common for the mother to hold back tears to appear stoic or "strong." Sometimes, the mother is told not to cry by friends and staff—'*Do not cry. Everything is going to be OK*'. Sometimes, the mother will release her emotions to the staff or family members, instead of to the baby. With FNI, crying in the presence of the infant was anticipated and welcomed. The NS told the mother to direct all her emotions to the baby and let herself cry while holding her baby, whenever and as often as she felt like it. The authentic expression of maternal emotion is a powerful initiator of connection between mother and infant and brings the dyad closer, which simultaneously stabilizes the baby's physiology, such as heart rate, oxygen saturation, etc.

As stated, the release of emotions by the mother while holding the baby typically elicits orienting behavior, which we define as a primary *social orienting reflex* on the part of the infant (Ludwig and Welch, 2022). Orienting includes turning toward the mother, opening their eyes to look at mother, and eventual direct sustained eye contact with her. When this happens, the mother typically feels an 'autonomic emotional' connection to her preterm baby for the first time, with mothers reporting that they feel they and baby are sharing their feelings directly with one another. The experience of AEC is accompanied by physiological changes in mother and infant, which NSs observed resulted in mutual states of calm and comfort. The NS encouraged the mother to engage in AEC whenever touching her baby in the isolette or holding her baby during skin-to-skin or clothed holding. The NS asked the mother not to use her cell phone during the brief time she had with her baby rather she was encouraged to direct her attention and emotional feelings directly to her baby.

When interacting with the hospitalized infant, FNI mothers were instructed to speak or sing to her baby in their 'native' tongue (i.e., the language spoken at home when she was a child), if she knew it. This is because the emotional content of expression between the mother and baby is conveyed in the primary language, sometimes referred to as 'motherese' (Welch and Ludwig, 2017a; Dave et al., 2018). NICU staff and NSs reported this had several benefits for mothers. At a time when privacy is difficult to establish, the dyad was drawn into an intense interpersonal communication that mentally blocked out external noises. It also reduced the feelings of isolation for the mothers who did not speak English. Finally, our research suggests that emotions are better communicated and more easily conveyed when expressed verbally in the pair's native language (Hane et al., 2024).

Clinical observations by the NSs and study staff confirm that once the mother released her deep emotions to the infant, the infant became emotionally available to the mother and responded behaviorally through eye contact and approach behaviors. This response from her baby prompted approach behaviors from the mother. This approach-seeking by FNI infants was evident in the NICU at 36-weeks and at 4-months with both mother and infants showing more approach-seeking behavior (Beebe et al., 2018; Hane et al., 2019).

We theorize that repeated AEE between the mother and infant over the course of the NICU stay changed the dyad's autonomic emotional relationship which, in turn, promoted positive changes in developmental trajectories of the infant's central and autonomic nervous system function, as well as the emotional well-being of the mother.

Physiological assessment of FNI

Electroencephalographic (EEG) biomarkers

During the NICU stay, the preterm infant cerebral cortex has begun to support early learning and assume critical sensory/motor functions. The prefrontal cortex is the location of our most advanced cognitive functions, including attention, motivation, and goal-directed behavior. Comparing the brain neuronal activity and development of infants receiving FNI in the NICU was the primary aim of the RCT.

A Columbia University team of EEG experts, led by author Myers, included Joseph Isler, Philip Grieve and Raymond I. "Buddy" Stark, with additional analyses performed by Sampsa Vanhatalo and his team in Finland. The EEG data was singular and groundbreaking for two reasons. At time of our first RCT, Columbia was a beta site for development of cutting-edge 128-lead (high density) EEG net technology. Therefore, the amount and quality of data collected on each infant was unprecedented. At the time, EEG was generally considered by clinicians to be a medical tool and not useful for evaluating interventions or in predicting neurodevelopmental outcomes. Indeed, Dr. Stark made a prediction at the very beginning—"*You will never show a difference in EEG after six weeks of intervention*." After our first report, he changed his mind and became one the team's strongest advocates.

Given the variety and quality of the EEG analyses and the metadata that accompany it, there can be little doubt the FNI EEG data will provide a rich resource for many future analyses. This was dramatically demonstrated when the Vanhatalo group performed novel network function analyses on the FNI EGG data and showed that the FNI infant EEG data was not significantly different from term-age birth network EEG data and that the FNI network function at term age predicted better 18-month neurodevelopmental outcomes (Yrjola et al., 2022). We are working to make the entire FNI EEG data set available for free download and analyses on a website.

Heart rate and vagal tone

As summarized above, FNI-NICU aims to facilitate the emotional connection between mother and infant and establish positive conditioning of the autonomic nervous system. Accordingly, we hypothesized that we should find changes in the infant and mother autonomic regulation associated with the repeated calming cycles experience of FNI. We focused on two physiological measures that might reflect these changes. First, we assessed measures of heart rate variability (i.e., respiratory sinus arrythmia (RSA), or vagal tone) that reflect ongoing effects of parasympathetic regulation of heart rate. In addition, we also measured heart rate itself, more specifically how heart rate changes over time in the NICU with exposure to calming sessions. Three outcome papers have been published thus far.

First, we found that from about 35 weeks to term age, vagal tone increased more rapidly in FNI infants, as did the effectiveness of vagal control on heart rate, or what has been termed vagal efficiency (Porges et al., 2019). In a second paper, we extracted hourly mean heart rates from a clinical monitoring system that acquired heart rate data 24/7 over the entire NICU stay. Results from this case-matched study showed that with time and 'dose' of calming sessions the heart rates of FNI infants decreased more rapidly than control infants (Ludwig et al., 2021). A successful replication of this finding is currently in preparation. Together, these two papers support our hypothesis that FNI-NICU enhances infant autonomic regulation and more rapid maturation of cardiac function.

Finally, in a paper assessing vagal tone data from a long-term follow-up study out to five years we found that children in the FNI group had significantly higher levels of RSA compared to the SC group (Welch et al., 2020a). In addition, RSA increased more rapidly in FNI children between infancy and the 4 to 5-year follow-up time point. Remarkably, we also found that mothers in the FNI group also had increased vagal tone at the 4–5 year follow-up. These results suggest that FNI-NICU leads to healthier long-term autonomic regulation in both mother and child.

These and previous findings strongly suggest that facilitating early nurturing interactions and emotional connection between preterm infants and their mothers is a practicable and effective means of optimizing postnatal development in preterm infants.

Theoretical advances

Many new theoretical concepts and constructs came out of the FNI-NICU trials. All of these involve the autonomic nervous system, which controls function of internal organs, including the heart. The theories and constructs describe the special neurobiological relationship between birth mother and newborn infant. Attachment theory, first developed by Bowlby (1988) and later systematized for scientific investigation by Mary Ainsworth (Bretherton, 1992; Ainsworth et al., 1971), emphasizes the central nervous system of the infant. The attachment model posits that the baby is born with a set of behaviors toward a *mother-figure*, which are motivated by self-interest and survival factors and which do not necessarily need to be learned or reinforced by the birth mother (Ettenberger et al., 2021; Guy-Evans, n.d.). As theorized, the mother is not substantially differentiated from other caregivers. In contrast, the autonomic model emphasizes the autonomic nervous systems of the infant and mother and holds that each baby is born with a singular dyadic *autonomic emotional relationship* to the birth mother, whether the birth is term or preterm, or whether the birth is single or multiple. Following birth, mutual autonomic learning, adaptation and reinforcement between the mother and baby plays a key role in determining the developmental trajectory of the infant.

The basics of the autonomic theory were articulated in the FNI study protocol (Welch et al., 2012), but subsequently the theory has been more fully explicated (Welch and Ludwig, 2017a; Ludwig and Welch, 2019; Welch and Ludwig, 2017b; Welch, 2016).

Biological mechanisms

Autonomic socioemotional reflex

Measuring the mother and infant relationship in terms of autonomic emotional connection (AEC) required rethinking the biological mechanisms mediating the phenomenon. Conventional constructs, such as attachment and bonding, focus on conscious and unconscious cortical learning mechanisms. In contrast, AEC theory posits that mother/infant emotions are controlled by highly conserved primitive learning mechanisms operating outside of consciousness. AEC theory proposes that specialized primary autonomic (i.e., cardiac) reflexes form between mother and fetus during gestation via autonomic learning or conditioning (Ludwig and Welch, 2020). Due

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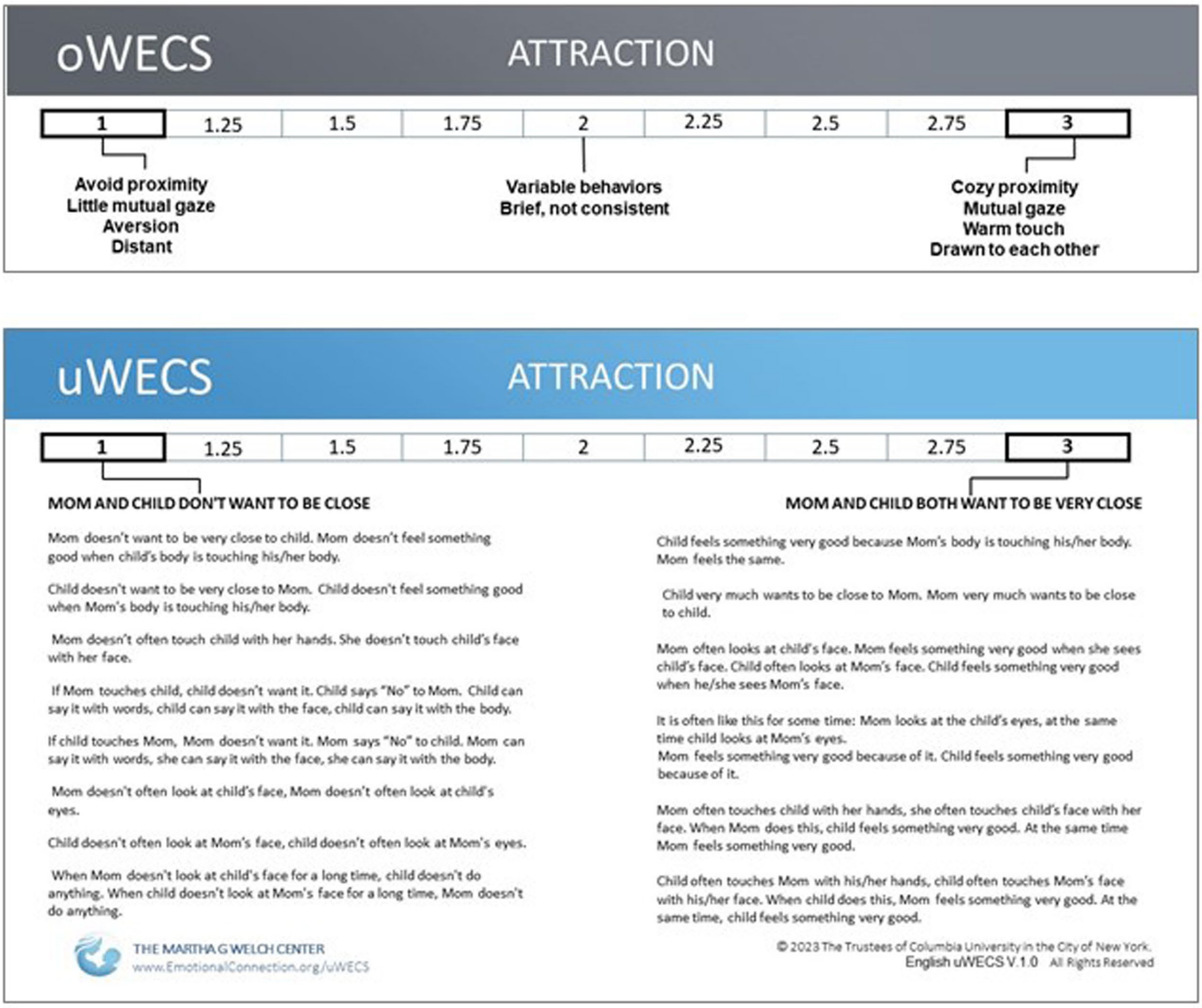

FIGURE 5
Comparison of the descriptors of *'Attraction'* on the **(A)** Original Welch Emotional Connection Screen (oWECS) and **(B)** the Universal Welch Emotional Connection Screen (uWECS). The descriptors on the oWECS turned out to be confusing to coders and difficult to translate into other languages. This led to the development of the uWECS. Note that while longer than the original descriptors, the uWECS only employs approximately 65 'universal' words common to all languages, making it easily accessible worldwide.

to their critical role in infant and child development, we have termed the mechanism the *autonomic socioemotional reflex (ASR)* (Ludwig and Welch, 2020). The ASR mechanism provides a biological explanation for mother-infant behaviors that are measured on the uWECS.

These ASR reflexes are 'conditional' in the sense that the behaviors associated with the ASR depend on environmental (in this case 'social') conditions. The ASRs account for subconscious so-called '*instinctive*' or *'innate'* mother-infant behaviors following birth. For instance, in a normal gestation and birth, gestational autonomic conditioning leads to adaptive social signaling between the mother and baby that assures 'approach' behavioral responses. In preterm birth, however, when the critical social signaling is disrupted between the two, the condition can result in adversely conditioned *'avoidant'* reflex behaviors (see Figure 6).

There is evidence that the ASR is common to other mammalian species. In fact, the idea was inspired by a phenomenon originally reported by Pavlov in 1925 when he described how the emotional relationship between a dog and trusted master profoundly impacted the dog's autonomic function and behavior (Gantt et al., 1991). Pavlov termed this phenomenon a conditional 'cardiac' or 'social' reflex (Gantt, 1964). The phenomenon was later shown by Pavlov's disciples to exist between many species, including humans (Gantt et al., 1991). We have extended this basic concept to the mother-infant relationship.

The ASR is a special case of the highly conserved *orienting reflex* (Ludwig and Welch, 2022). Dysfunctional orienting is highly correlated with socioemotional pathologies in infants and children, including social fear, anger, anxiety, depression and autism (Hedger et al., 2020). Orienting stems from activation of highly conserved autonomic defensive and appetitive motivational systems that evolved to sustain life (Boecker and Pauli, 2019), assuring the survival of species (Ludwig and Welch, 2022; Twilhaar et al., 2020). In this respect, the ASR orienting phenomenon in humans does not differ significantly from other species, from which it was conserved.

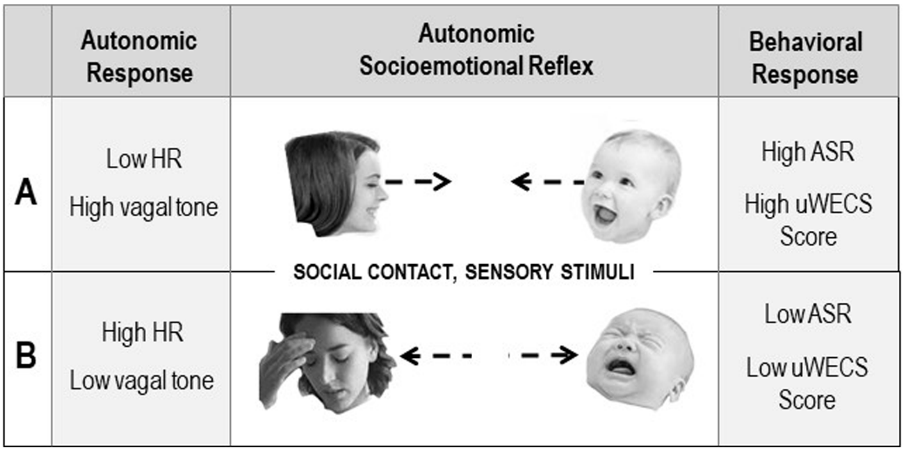

FIGURE 6
Diagram illustrating the Autonomic Socioemotional Reflex (ASR) and the hypothesized relationship between behaviors measured with the uWECS and autonomic physiology in two polar conditions. The central panels show opposite responses triggered by sensory stimuli resulting from close face to face social contact. Condition A shows a positive autonomic and behavioral response. Condition B shows a negative response. The left panels show the autonomic physiology in the two conditions, as measured by heart rate and vagal tone. The right panels show the Autonomic Socioemotional Reflex (ASR) behavioral response, as measured with the Universal Welch Emotional Connection Screen (uWECS).

Autonomic conditioning

Preterm birth is associated with cognitive learning difficulties, but the underlying mechanisms of these difficulties remain largely unclear (Twilhaar et al., 2020). The newborn infant's environment, including support of the mother, is well known to be crucial to the infant's survival. Yet how the environment influences behavior during this critical period remains unclear (Hunter et al., 2023). The FNI findings collectively suggest that focusing the interventional on subconscious 'autonomic' mother-infant co-conditioning offers a new way to optimize brain development and function, one that elevates the importance of relationship and co-regulation over many current efforts to develop self-regulation and independence.

Once the socioemotional signaling (i.e., social cueing) between the infant and mother is disrupted, as happens with premature birth, adverse autonomic conditioning of the dyad's primitive ASRs ensues. As a result, dyads display social behaviors described as 'avoidant' on the uWECS (e.g., autonomically dysregulated and emotionally disconnected). This is a common situation in the NICU. It was the case with both groups at the beginning of the FNI-NICU trials. We theorized that FNI overcame the maladaptive relationship between mother and infant, by facilitating adaptive '*autonomic conditioning*' of the ASRs during the mother-infant calming sessions. We theorize the mother's autonomic emotional expression (AEE) during calming sessions acted as important '*signaling cues*' and triggered the adaptive ASR orienting. In physiological terms, we can say that the maladaptive ASR produced by premature birth was '*counter-conditioned*' according to Pavlov's rules of autonomic conditioning (Gantt, 1964).

FNI-NICU focused on restoring the dysregulated autonomic states of mother and infant. Until recently, the consensus in neuroscience was that emotional behavior is controlled by the brain via top-down neuronal pathways and mainly conscious mechanisms (Krone et al., 2017). Over the past decade, however, evidence has emerged that suggests cognitive behavioral *states*, such as mood, motivation, attention, and arousal, are profoundly impacted by environmental signaling that involves integration of activity in the brainstem. Such behavioral states are modulated by the autonomic nervous system and the brainstem, which are activated in response to environmental challenges (Ludwig and Welch, 2022; Sara and Bouret, 2012).

Because of the fragility and medical condition of the preterm infant, it is common for the mother to feel helpless that her baby cannot respond to her. The opposite is true. By the third term of gestation, the autonomic neuronal wiring of the infant is fully in place to prompt cardiac orienting and attentional reflexes to the mother's autonomic emotional expression.

Human hearing develops progressively during the last trimester of gestation. Near-term fetuses can discriminate acoustic features and process complex auditory streams on communication (Granier-Deferre et al., 2011). Newborns prefer their mother's voice over other voices and perceive the emotional content of messages conveyed via intonation contours in maternal speech ("motherese") (Mampe et al., 2009). A study showed that three weeks of prenatal exposure to a specific melodic contour affects infants 'auditory processing' or perception, i.e., impacts the autonomic nervous system at least six weeks later, when infants are one month old (Granier-Deferre et al., 2011). A systematic review of studies between 1966 and 2013 showed that motherese functions developmentally to communicate affect, regulate infants' arousal and attention, and facilitate speech perception and language comprehension (Saint-Georges et al., 2013).

Autonomic co-regulation

We make the case that FNI_NICU changed the mother-infant relationship and changed the infant's and mother's autonomic regulation. Indeed, our findings support this claim (Porges et al., 2019; Welch et al., 2020a; Ludwig et al., 2021). The idea of a connection between autonomic physiology and social relationship is not new. Darwin and Pavlov studied it (Ludwig and Welch, 2019). More recently it has become a focus of parent-infant and parent–child biobehavioral research (Palumbo et al., 2017). Various terms have been used to describe the social phenomenon: Physiological synchrony (Xu et al., 2024), biobehavioral synchrony, Concordance, Parent-infant synchrony (Feldman et al., 2011), Biological synchrony, Linkage, Physiological relatedness (van Puyvelde et al., 2015), Attunement, Covariation, Emotional engagement, Entrainment, Inter-individual synchronization, Physio-behavioral coupling, among others.

We refer to this phenomenon as 'autonomic co-regulation', by which we mean that the two autonomic nervous systems are inter-dependent, as opposed to independent. This interdependency starts *in utero* and continues after birth and is tied to survival and motivation and mental and physical health throughout development.

We theorize autonomic co-regulation with the mother to be the primary biological need of the baby. It is a function that carries with it individual and species survival value. When the mother is not available following birth, other family members can substitute, including the father. Family members can always play a critical role in the mother's emotional and physical support, and in some cases the infant's survival and development. Adoptive parents can also play a critical role in the development of the infant/child (Welch et al., 2006). However, if there is one key point we want all readers to take away from the FNI-NICU trials, it is that *the autonomic co-regulatory relationship between the mother and infant needs to be assessed, supported and treated in the NICU prior to discharge*.

Such autonomic co-regulation has been well-documented by the animal studies of FNI collaborator Myron A. Hofer. Hofer concluded that "in human development, early regulatory interactions may provide a bridge between biological and psychological processes in the development of our earliest mental representations" (Hofer, 1994). Indeed, our FNI findings lend support to Hofer's hypothesis.

While we have proposed such a theory of change for FNI (Welch et al., 2020a), which includes experiencing mother infant autonomic co-regulation during calming sessions, establishment of mother/infant AEC, and counter conditioning adverse NICU experiences, we did not test this theory in the first RCT of FNI. Thus, explicating this underlying mechanism for early interventions remains a gap in the field. We are analyzing data from the FNI replication trial, which included repeated acquisition of mother and infant Heart Rate and RSA to better quantify mother/infant co-regulation over time as an index of autonomic conditioning. In another study we assessed emotional connection using the uWECS to test the hypothesis that emotional connection underlies effectiveness of the intervention.

Behavioral constructs and assessment

Autonomic emotional connection

The autonomic emotional connection (AEC) is a novel behavioral construct that describes the mutual behaviors of mother and baby that are triggered by the autonomic nervous system of each. There was no such construct prior to the FNI trials. Behaviors triggered by autonomic state require special assessment to differentiate them from psychologically triggered behaviors. In the first FNI trial, we had to use conventionally validated assessment tools that are based on conventional 'attachment' and 'bonding' theory and constructs (Pathak et al., 2023). Such tools measure separate *psychological* behaviors of infant and mother but not the dyad's mutual contingent behaviors.

A recent review of the literature confirms that despite the emerging body of literature on mother-to-infant 'bonding' and the associated variables, there is a lack of consensus on the definition of the bonding construct, as well as a lack of a comprehensive conceptual framework of antecedents and consequences of bonding that would guide empirical work (Nakic Rados et al., 2023).

As our research progressed, we observed the same phenomenon Welch had seen in her prior clinical work: significant positive changes in the emotional relationship between the mother and the baby, which were not reflected in the conventional assessment tools. This led to an effort to validate a new instrument that would track the state of and then the change in the mother–child autonomic emotional relationship.

Emotional connection and autonomic 'state'

The behaviors measured by the uWECS are theorized to correlate with the dyad's mutual autonomic '*states*' at the time of observation, as opposed to their more or less fixed individual personality '*traits*'. This assumption produced new testable hypotheses regarding mother/infant approach-avoidance behaviors and the correlation between dyadic emotional behaviors (as measured on the uWECS) and autonomic physiology, such as heart rate and heart rate variability. For example, we could test the hypothesis that avoidant AEC behaviors (low uWECS score) correlate with higher HR and lower HRV. Conversely, AEC behavior (high WECS score) should hypothetically correlate with lower HR and higher HRV.

Being able to correlate behavioral data (e.g., uWECS scores) with autonomic state data has several benefits. First, it makes the rapid 'in the moment' uWECS assessment a true relational health biomarker. The uWECS assessment in the NICU provides a simple measure to identify those dyads at risk for behavioral and developmental problems and a means of tracking progress or lack thereof throughout the NICU stay and at follow-up visits.

Second, being able to make a rapid uWECS assessment in the NICU means the clinician can act on that information. Steps can be taken by in the NICU to help change a dysregulated to a co-regulated state. Again, the uWECS assessment offers a simple way to determine whether an intervention has successfully changed the dyad's autonomic state.

The universal Welch emotional connection screen (uWECS)

We needed to create a new assessment tool to measure AEC. Based on her clinical observations, Dr. Welch was convinced that a few key mother–child behaviors could form the basis for assessing the autonomic emotional relationship between mother and infant and could be used to identify dyads at risk for behavioral and developmental problems. Using data from the first FNI trial, we validated the original WECS (oWECS) against a standard social engagement coding software (Hane et al., 2024) (See Figure 5, Panel A).

The oWECS was validated in the FNI sample at the 4-month follow-up. In addition to demonstrating the validity and feasibility of the WECS quick screening tool with labor-intensive observational software, the WECS also demonstrated construct validity. Dyads measured high on AEC by the oWECS were characterized by higher mutual approach behaviors and more optimal autonomic regulation following the stress of the maternal still-face disruption (Hane et al., 2019).

The process validated a subset of four measurable mutual mother/infant behaviors: *attraction, vocal communication, verbal communication and sensitivity/reciprocity*. As predicted, the four behavioral subsets correlated with the preterm infant's autonomic state physiology (cardiac response to stress) (Hane et al., 2019). These findings support the idea that during close face to face contact the mother/infant behaviors, as measured by the oWECS, are a mirror of the dyad's autonomic physiology. This makes the oWECS a new way of assessing the dyad's emotional relationship at the time of observation.

The oWECS was a key clinical and research advance validated with the FNI trials. The oWECS offers a fast, simple and actionable behavioral assessment tool that correlates with autonomic physiology, so the tool can be used to determine risk for impaired socioemotional and relational health throughout development. A validation study of full term infants showed that ratings on the oWECS at infant age six months are associated with child behavioral problems at age three years (Frosch et al., 2019). An oWECS study in a pediatric resident training course found the instrument improved residents' attitudes, self-efficacy, and perceived professional norms pertaining to early relational health. The oWECS improved accuracy in recognizing the dyadic AEC (O'Banion et al., 2021).

While employing the oWECS in FNI studies globally, confusion arose over the English language words used to describe the behavioral subscales. Therefore, providing a universally accessible language to describe the positive and negative opposite behaviors associated with the subscales became an imperative. This was especially true because mother/infant AEC is theorized to be a foundational building block of all human relationships, regardless of language or culture. A chance encounter with a linguist, author Ulla Vanhatalo, working with author Cliff Goddard, an expert in the field of Natural Semantic Metalanguage (i.e., how meanings are packaged and expressed differently in different languages) led to a two-year collaboration, during which the English oWECS was translated into the ~65 words of universally clear, explicit translatable language (Goddard et al., 2018). The resulting version is referred to as the Universal WECS (uWECS). The uWECS has replaced the oWECS as the recommended assessment tool (See Figure 5, Panel B).

The uWECS has fulfilled the goal of an easily translatable screen. Thus far, it has been translated from the original English into Akan, Arabic, Chinese, Finnish, German, Turkish, Polish, Russian and Spanish with few difficulties. The advantage of the uWECS is that it requires no.

training beyond the form itself. In fact, a recent study showed that scores by coders reading only the uWECS descriptions were highly correlated with scores by coders trained on the oWECS. Further, the oWECS has high criterion-related validity in assessing the efficacy of nurture-based intervention (Hane et al., 2024). Results indicate the uWECS can produce relatively fast reliability among diverse coders. Easy translatability allows non-English speakers to assess mother-infant or mother/child autonomic emotional connection to improve pediatric relational health. It serves as both an assessment tool and a guide for parent-facing clinicians and parents.

Theory of change

Calming cycle theory

Calming cycle theory provides a novel explanation of how a maladaptive mother/infant emotional relationship can be changed to adaptive following birth (Welch, 2016). Conventional wisdom has held that instinctive or innate mother-infant behaviors are inherited and to some degree '*genetically*' fixed at birth. A growing consensus holds that behavior can be influenced '*epigenetically*' by the environment, prenatal as well as postnatal (Ludwig and Welch, 2019). Both positions assume, as Darwin believed, that emotional behavior is self-regulated or self-controlled via conscious higher brain function within the central nervous system. Accordingly, many NICU care strategies have aimed at getting the infant to self-regulate their physiology and emotional behavior, in line with attachment and bonding theory, which still drives many current therapies. There are notable exceptions that promote mother/infant '*co-regulation*', such as kangaroo mother care (Arya et al., 2021; Adejuyigbe et al., 2023), or developmental care (White et al., 2023; Lehtonen et al., 2017). However, there is no consensus regarding the mechanisms involved.

A central tenet of calming cycle theory is that autonomic co-conditioning between mother and fetus during gestation and the postnatal period promotes co-regulation of autonomic states and emotional connection, which underlie improved socioemotional function over time. According to calming cycle theory, the autonomic states and behavior of mother and infant/child are co-regulated via a subcortical autonomic conditioning mechanism. After repeated calming, paired with sensory contact between mother and infant (i.e., a calming cycle), a conditioned autonomic calming reflex is triggered upon each further contact. This co-regulation phenomenon manifests itself behaviorally as mother–infant AEC and correlates with a high uWECS score. If practiced regularly, the calming cycle leads to less dysregulation and stronger emotional connection. In turn, the deeper the emotional connection provides a faster way to resolve autonomic dysregulation when it occurs.

The term "co-regulation" has been used with various definitions and connotations in animal and human research to describe co-dependency of physiological and behavioral activities between humans and even with other mammals. However, when the term has been used in reference to behavior, the process has invariably been discussed within a psychological framework (Butler and Randall, 2013). That is, cognitive mechanisms have conventionally been assumed to account for the effects of social interaction. Mother and infant systems have long been considered to be separate and independent (Guo et al., 2015). More recently, interest has grown in cognitive EEG 'hyperscanning' techniques, which are used to measure brain activity from more than one participant simultaneously, to understand the neural underpinnings of social interactions (Czeszumski et al., 2020).

Our interest centers around the assessment of autonomic co-regulation of the mother and infant's autonomic nervous systems, which we posit are dynamically and continuously linked separately from the central nervous system. Accordingly, calming cycle theory holds that the dramatic impact of FNI on brain development reported above was mediated by co-conditioned changes in the dyadic autonomic nervous systems during and following the intervention.

Is FNI-NICU scalable?

Scaling the exact FNI-NICU protocol is not practicable or scalable, nor was it our intention to do so. However, we believe the new tools and ideas from such as the trials are scalable. Implementing the mother-infant calming cycle, with its emphasis on autonomic emotional expression (AEE) requires little training and can be implemented within standard care or as part of other systems with little expense. The calming cycle can be implemented, for example, within the widely promoted KMC intervention or within Family Centered Care. The uWECS provides a simple monitoring tool for assessing the mother-infant autonomic emotional connection in as little as 3-min of observation. It is free and easily translatable into any language by a dual-language speaker.

The real barrier to scaling is resistance to new ideas. We note that the FNI study protocol was published in 2012, near the end of the first trial. This was not because there was uncertainty about method, goals and objectives at the beginning of the trial. The delay was mainly due to intense debates within our group over definitions, terminology and theory (Hofer, 2006). It took, for example, nearly a year of debate to settle on the word "nurture" to describe the intervention, which was at the time the object of derision among serious scientists. Another debate revolved around the hypothesis that autonomic conditioning was somehow involved in the intervention and that it could be tested. Despite ongoing debates over terminology and theory, by 2015 a consensus emerged in our group that FNI results require a rethinking of very long held assumptions about mother and infant behavior and the mother-infant relationship.

Part of validating the WECS instrument involved validating the theoretical association between specific behaviors between mother and infant and autonomic physiology. This involved obtaining simultaneous autonomic measures. Because of their association with early emotional health (Chiera et al., 2020), we chose heart rate (HR) and heart rate variability (HRV). We were able to show positive changes in infant HR (Ludwig et al., 2021) and HRV (Porges et al., 2019) following the intervention. Studies looking at the hypothesized pairing of changes in AEC as measured by the uWECS and maternal–infant/child physiological co-regulation are on-going.

Summary

In retrospect, despite the optimism expressed when we started the FNI trials, it is understandable that many scientific experts were skeptical that anything useful would come out of them. The proposed rationale and theory supporting the FNI protocol was completely unfamiliar to reviewers. The trials challenged orthodox and conventional thinking at almost every step. In the end, it took very large and generous gifts over 25 years from a handful of private donors who believed in our research vision and cause to complete the research.

We have introduced many new constructs, theories, tools and biomarkers in this review, each of which will benefit from ongoing testing and validation. Hopefully, the evidence we assembled will lead to substantive changes in NICU care, including an emphasis on autonomic emotional connection and affording mothers and infants the time and support needed to establish and maintain their positive autonomic socioemotional reflex with each other. We are certain that the field will benefit from further exploring these promising evidence-based pathways, which could ultimately impact-real-world clinical practice (Hidalgo-Mazzei et al., 2018).

Finally, in closing we hope that the FNI trials inspire clinicians and researchers worldwide to consider acting on the lessons presented here. Imbedded in the material reviewed above is a scalable *blueprint for improving preterm birth outcomes*: (1) Encourage mother-baby autonomic emotional expression as a means of reconnecting the mother and baby. (2) Promote a daily calming cycle routine to strengthen and maintain an autonomic emotional connection. (3) Use the uWECS tool to monitor the autonomic emotional connection throughout development. (4) Use the uWECS as a clinical guide for families to improve autonomic emotional connection.

Author contributions

RL: Conceptualization, Funding acquisition, Investigation, Methodology, Resources, Visualization, Writing – original draft, Writing – review & editing. MM: Data curation, Formal analysis, Investigation, Methodology, Software, Validation, Writing – review & editing. MW: Conceptualization, Formal analysis, Funding acquisition, Investigation, Methodology, Resources, Supervision, Validation, Visualization, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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EDITED BY
Sara Uccella,
University of Genoa, Italy

REVIEWED BY
Daniela Flores Mosri,
Universidad Intercontinental, Mexico
Deborah Preiti,
Giannina Gaslini Institute (IRCCS), Italy

*CORRESPONDENCE
Livio Provenzi
✉ livio.provenzi@unipv.it

†These authors share first authorship

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2-Brain Regulation for Improved Neuroprotection during Early Development (2-BRAINED): a translational hyperscanning research project

Lucia Billeci[1†], Valentina Riva[2†], Elena Capelli[3], Serena Grumi[4], Miriam Paola Pili[3], Maddalena Cassa[2], Eleonora Siri[2], Elisa Roberti[4], Renato Borgatti[3,5] and Livio Provenzi[3,4]*

[1]Clinical Physiology Institute, National Research Council of Italy (IFC-CNR), Pisa, Italy, [2]Child Psychopathology Unit, Scientific Institute IRCCS E. Medea, Bosisio Parini, Italy, [3]Department of Brain and Behavioral Sciences, University of Pavia, Pavia, Italy, [4]Developmental Psychobiology Lab, IRCCS Mondino Foundation, Pavia, Italy, [5]Child Neurology and Psychiatry Unit, IRCCS Mondino Foundation, Pavia, Italy

Introduction: Very preterm (VPT) birth is a major risk condition for child development and parental wellbeing, mainly due to multiple sources of stress (e.g., separation and pain exposure) during the neonatal intensive care unit (NICU) stay. Early video-feedback (VF) interventions proved effective in promoting VOT infants' development and parental wellbeing. Electroencephalography (EEG) hyperscanning allows the assessment of brain-to-brain co-regulation during live interaction between infants and parents, offering promising insights into the mechanisms behind the interactive benefits of early VF interventions.

Goals: This study aimed to compare indices of brain-to-brain co-regulation between dyads of full-term (FT) and VPT infants interacting with their mothers and investigate the effect of an early post-discharge VF intervention on the brain-to-brain co-regulation indices of VPT dyads.

Methods and analysis: VPT and FT dyads will be enrolled at birth, and the former will be randomly allocated to one of two arms: VF intervention or care as usual. Short-term effectiveness will be assessed through ratings of mother–infant interaction videotaped before and after the VF intervention or care as usual. Mothers of VPT and FT infants will report on their mental state, parenting stress and bonding, and infant temperament and sensory profile at 3 and 6 months (corrected age, CA). At 9 months CA, all dyads will participate in a lab-based EEG-hyperscanning paradigm to assess brain-to-brain co-regulation through phase-locking value (PLV) and other explorative indices.

Ethics and dissemination: This study was funded by the Italian Ministry of Health and received approval by the Ethics Committee of Pavia (Italy) and participating hospitals. Research findings will be reported in scientific publications, presented at international conferences, and disseminated to the general public.

Study registration number: GR-2021-12375213 (Italian Ministry of Health registry).

KEYWORDS

EEG, hyperscanning, infant, parent, preterm, synchrony, video-feedback

Introduction

Very preterm (VPT) birth is a major challenge for healthcare systems worldwide (Beam et al., 2020), representing the leading cause of long-lasting chronic diseases in childhood and child mortality (Ohuma et al., 2023). While VPT infants are exposed to heightened medical risk and several stress sources from the neonatal intensive care unit (NICU) environment (Cong et al., 2017; Provenzi et al., 2018), their parents also may face critical levels of psychological distress leading to increased risk for depression, anxiety, and parenting stress in the postpartum period (Caporali et al., 2020).

Notably, biobehavioral dysregulation patterns have been observed in dyads of VPT infants and their caregivers in the first months of life (Jean and Stack, 2012; Montirosso et al., 2010; Neugebauer et al., 2022; Provenzi et al., 2019), suggesting that VPT birth and NICU-related stress may affect child development and parental adjustment by altering critical processes of dyadic co-regulation during the first 1,000 days (Feldman, 2006; Linnér and Almgren, 2020). Early interventions that promote parent–infant closeness may help foster the establishment of similar psychobiological co-regulatory processes (Ionio et al., 2021; Lordier et al., 2019; Mörelius et al., 2015; Welch and Ludwig, 2017), providing buffering and protective benefits for both child development and parental wellbeing (Burke, 2018; He et al., 2021; Thomson et al., 2020).

Video-feedback (VF) interventions are well-validated parenting support programs that focus on parent–infant closeness, promote parental sensitivity, facilitate co-regulatory processes, and provide neuroprotective effects for child development (Balldin et al., 2018; Poslawsky et al., 2015; Provenzi et al., 2020; Tryphonopoulos and Letourneau, 2020). VF interventions include a diverse range of procedures and methodologies aimed at promoting positive parenting. They capitalize on allowing parents to observe themselves and their interactions with their infant "from the outside," thereby facilitating mentalization and reflective functions (Leyton et al., 2019; Riva Crugnola et al., 2021). Although different theoretical and methodological VF approaches have been described (Provenzi et al., 2020), previous research highlighted benefits for child development and the quality of parent–child interaction in different clinical contexts and populations, including preterm infants and their caregivers (Barlow et al., 2016; Hoffenkamp et al., 2015). More recently, a clinical trial by Pisoni et al. (2021) highlighted long-term improvement in the developmental quotient scores of 24-month-old VPT infants of age following a VF intervention, adding to the evidence that remote video consultation may be an effective home care approach (Hägi-Pedersen et al., 2021; Suir et al., 2022).

Hyperscanning is a relatively recent approach to the study of brain-to-brain co-regulation in live interactive partners using different electrophysiological and neuroimaging techniques (Bi et al., 2023; Nguyen et al., 2020). By simultaneously recording multiple brains' activity, hyperscanning allows the acquisition of neurophysiological measures of human dyadic or group-based neurophysiological coordination (Czeszumski et al., 2020). Among the different available techniques, EEG offers special advantages when the hyperscanning paradigm is applied to pediatric and even newborn populations. Wireless EEG devices are relatively non-invasive and allow for freedom of movement, making them ideal for studying mother–infant interactions in both laboratory and ecological settings during the first months of life. By using EEG-hyperscanning paradigms, Leong et al. (2017) highlighted how gaze direction during face-to-face interactions between adults and 8-month-old infants affects patterns of dyadic neural connectivity. Similarly, different patterns of theta power fluctuations were observed when 12-month-old infants play solo in the presence of the caregiver or when they actively interact together (Wass et al., 2018). More recently, the phase-locking values (PLVs) indicating the strength of brain-to-brain co-regulation in theta and alpha frequency bands were computed during 7-month-old infants' interaction with the caregiver compared to an adult stranger (Endevelt-Shapira et al., 2021). The study reported greater inter-brain attunement when infants were interacting with the mother, despite the addition of maternal chemo-signals in the setting of infant–stranger interaction attenuated the significant difference.

As the field of parent–infant hyperscanning research is rapidly growing, the accumulating knowledge is contributing to a pivotal epistemic and theoretical shift in developmental neurosciences from a mono-personal account to a strongly relational perspective (Dumas, 2011). The application of hyperscanning paradigms to the study of parent–infant brain-to-brain co-regulation in at-risk and clinical pediatric populations holds promises to acquire innovative data on the mechanisms by which the early caregiving environment fosters and promotes child neurodevelopment (Provenzi et al., 2023). Moreover, as specific indices of brain-to-brain co-regulation become validated in typical development, they may also be embedded into a novel set of neurobehavioral markers to assess the benefit of early interventions. Such *translational hyperscanning* vision has been recently framed in the affective neuroscience literature (Provenzi et al., 2023), yet there is a lack of research on the brain-to-brain co-regulation of VPT infants and their parents and on the potentially beneficial neuroprotective effects of early parenting interventions in this population.

Study AIMS

General and specific aims

The *2-Brain Regulation to Achieve Improved Neuroprotection during Early Development* (2-BRAINED) research project is funded by the Italian Ministry of Health under the Ricerca Finalizzata 2021 program (research line: Giovani Ricercatori, project code: GR-2021-12375213). It is aimed to assess brain-to-brain co-regulation patterns in dyads of VPT infants and their caregivers and further explore how an early VF intervention may facilitate specific inter-brain regulatory indices.

The first specific aim (Aim 1) is to assess the presence of statistically significant differences in a set of brain-to-brain co-regulation indices—primarily, PLV measure—between dyads of caregivers and VPT compared to FT infants. Previous research gave evidence of specific markers of lower co-regulation in behavioral synchrony (Montirosso et al., 2010), physiological coupling (Feldman and Eidelman, 2007; Porges et al., 2019), and neuroendocrine attunement (Provenzi et al., 2019) in dyads of VPT infants during the first year of life. Consistently, we hypothesized that VPT infants and their caregivers would show less strong brain-to-brain co-regulation indices compared to dyads of FT counterparts at 9 months (corrected age for prematurity, CA).

The second specific aim (Aim 2) is to investigate the effect of an early VF intervention for parents of VPT infants on the selected indices of brain-to-brain co-regulation at 9 months CA. By comparing EEG-hyperscanning-derived indices of inter-brain coupling between dyads of VPT infants exposed to the VF intervention and dyads exposed to care as usual during the 3 months following NICU discharge, we hypothesize to describe greater brain-to-brain co-regulation in the former group.

Additional exploratory aims

The longitudinal nature of this study and the possibility to collect a multi-layer set of data for what pertains to the neurobehavioral development of FT and VPT infants as well as the parenting environment during the first year of life allow us to set the stage for a number of exploratory analyses that will further guide future spin-off studies stemming from the 2-BRAINED research project. In this study, we highlight five main exploratory aims that appear relevant for future translational research in the field of affective neuroscience and developmental psychobiology.

First, the availability of behavioral and EEG physiological data from the 9-month interactive procedure (see below, *Study design and procedures*) will allow for the exploration of patterns of bio-neurophysiological coupling within dyads. Previous research produced limited evidence for the presence of correlations between specific interactive behaviors and EEG signaling during interactive tasks (Liu et al., 2018). Similarly, in VPT infants and their caregivers, the presence of a matched coupling or overlapping regulatory profiles between interactive behaviors and neuroendocrine or physiological oscillations is debated (Provenzi et al., 2019). This study will provide a suitable data setup to further explore the presence of significant coupling between interactive behaviors and neurophysiological brain activity in typically developing and at-risk pediatric populations.

Second, it will be possible to explore how brain-to-brain co-regulation in typically developing FT infants and their caregivers is affected by different dimensions that characterize infants' development (e.g., sensory profile and temperament) and the caregiving environment (e.g., affective symptoms, parenting stress, and parent–infant bonding). It is well known that different behavioral indices of caregiver–infant co-regulation (e.g., matching, synchrony, and dyadic reparation (Provenzi et al., 2018)) are shaped by individual characteristics and contributions by parent and infant behavior. For instance, Fuertes et al. (2006) have suggested that infant temperament may play a critical role in the emergence of early attachment patterns and co-regulation of socio-emotional stress in full-term infants. Similarly, maternal affective symptoms may result in different dyadic organizations of critical behaviors signaling reciprocal attention and socio-emotional availability, such as gaze direction (Lotzin et al., 2015) and emotional cues (Bigelow et al., 2018).

Third, the role of sensory profile and environmental sensitivity to sensory inputs is recognized as an important contributor to child socio-emotional stress regulation (Greven et al., 2019; Lionetti et al., 2018). Previous research has highlighted how infants with diverse sensory profiles (e.g., sensation seekers or passive encoders) may exhibit differences in their resting state EEG activity (Pierce et al., 2021). Additionally, sensory reactivity in FT and VPT infants at 12 months has been found to be associated with later behavioral problems in toddlerhood (Maitre et al., 2020). The role of infants' sensory profile in setting the stage for different gradients of brain-to-brain co-regulation is yet to be explored, and such investigation may shed light on genetic-informed individual differences in the early establishment of parent–infant relationship.

Fourth, consistent with the previous exploratory goal, it can be speculated that VPT infants—due to early adverse sensory stimulations during the NICU stay (Aita et al., 2013; Pineda et al., 2019)—may exhibit specifically altered profiles of sensory regulation compared to FT counterparts. Niutanen et al. (2020) recently conducted a review of the literature highlighting how VPT infants may exhibit abnormal regulation of sensory inputs with consequences for sensory-motor integration and stress regulation. As the sensory regulation profile of VPT infants may be partially learned from attempts to adapt to the NICU, the present study may also help identify how early alterations in the sensory environment influence the emergence of precocious forms of brain-to-brain co-regulation with the caregiver.

Finally, by collecting quantitative data on the parents' experience of the NICU hospitalization—including both psychological stress and perceived support from the staff—it will be possible to estimate how caring for parents' wellbeing during the NICU stay may promote later electrophysiological caregiver–infant attunement. Previous research has highlighted that mothers of VPT infants may exhibit lower sensitivity to their infants' facial and bodily cues (Butti et al., 2018). However, their brain reactivity to emotional pictures of their own VPT infants appears heightened compared to that of FT infants' mothers (Montirosso et al., 2017). These preliminary findings suggest that the brains of VPT infants' caregivers may process interactive-salient stimuli differently, potentially influenced by the stressful experience of NICU hospitalization and early parent–infant separation. The present study will allow us to study how the brain activity of VPT infants' mothers processes relevant social cues during real-life face-to-face interactions, further contributing to understanding how caregivers' brain adapts to preterm birth and hospitalization. In this context, NICU-related stress and perceived support from staff could be considered potential moderators of the caregivers' EEG activity when interacting with their VPT infant—with relevant consequences for the observed brain-to-brain co-regulation.

Methods and procedures

Study design and procedures

The 2-BRAINED project is a randomized-controlled trial (RCT) with three arms. The first arm includes VPT infants and their caregivers randomly allocated to the intervention arm (VPT-VF). The second arm includes VPT infants and their caregivers randomly allocated to the care as usual arm (VPT-CU). This arm will act as a control group matched to preterm conditions of VPT-VF. The third arm includes FT infants and their caregivers and will act as an additional control group unmatched by preterm conditions. Both VPT-CU and FT arms will receive no VF intervention.

Population, enrollment, and arm allocation

VPT and FT infants will be enrolled at birth by contacting their caregivers within the first 48 h after delivery. Informed consent will be obtained. VPT infants will be considered eligible in the presence of the following conditions, as reported in medical charts: gestational age below 35 weeks, absence of major brain lesions as documented by

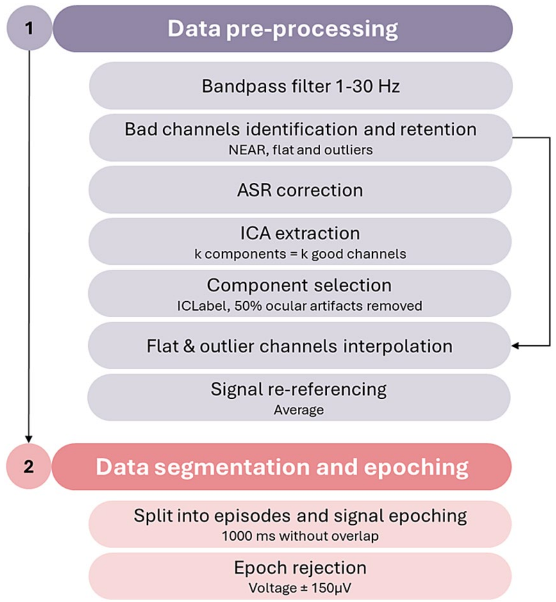

FIGURE 1
EEG data pre-processing pipeline. NEAR, Neonatal EEG Artifact Removal; ASR, artifact subspace reconstruction; ICA, independent component analysis.

cerebral ultra-sound, no neuro-sensory deficits including retinopathy of prematurity (ROP) equal or above stage 2, absence of genetic syndrome, or malformations involving the central nervous system. FT infants will be considered eligible if they meet the following conditions: a gestational age of 37 weeks or more, are healthy, and show no evident signs of neurodevelopmental risk or morbidities. For both groups, exclusion criteria will include single-parent families, parental age under 18 years, lack of Italian language mastery, and the presence of documented psychiatric disorders.

Study timeline

The 2-BRAINED study features five data collection waves (see Figure 1). The VF intervention is delivered after wave T1 (NICU discharge) and before wave T2 (3 months CA) to subjects allocated to the VPT-VF arm. The EEG-hyperscanning task will occur for all subjects at wave T4 (9 months CA) and will feature the videotaping of mother–infant interaction according to a modified Face-to-Face Still-Face (FFSF) procedure (Tronick et al., 1978) and the simultaneous EEG data collection from both the interactive partner. At each wave, parents will receive questionnaires by email using REDCap.[1]

VF intervention

Remote videotaping

Before (T1) and after (T2) the VF intervention sessions for participants allocated to VPT-VF—and at the same timepoints for participants allocated to VPT-CU—a 15-min mother–infant interaction will be videotaped remotely. Before videotaping, mothers will be asked to position the webcam or smartphone to have the widest possible view of the play area and see the entire body of both the mother and the infant. The interaction paradigm includes 10-min unrestrained face-to-face play followed by a 6-min FFSF procedure (Tronick et al., 1978) as described here: During the 2-min Play episode, mothers will be asked to play with the infant as they usually do (e.g., the infant can stay in an infant seat or on a carpet); during the 2-min Still-Face episode, mothers will be asked to interrupt any communication and maintain a still, poker face while keeping eye-contact with their infant; unconstrained interaction will be resumed during the 2-min Reunion episode.

Intervention details

The remote VF intervention has been adapted according to previous research from our group (Grumi et al., 2021). It comprises six weekly 1-h sessions organized in two subsequent phases: four *sharing the focus* sessions and two *integration* sessions. *Sharing the focus* sessions are dedicated to the discussion between the psychologist and the mother of specific themes related to parenting and parent–infant interaction: physical stimulation, responsiveness, teaching, and parenting experience (see Table 1). During these sessions, a purposively trained psychologist invites the mother to jointly review and discuss brief clips obtained from the pre-intervention videotaped interaction, usually starting from potential curiosity, comments, or requests from the mother herself. The goal of the *sharing of the focus* sessions is to develop insights about the infants' behavioral signals, how to respond contingently and appropriately, how to promote emotion regulation, and how to sustain cognitive and behavioral achievements. In the subsequent two *integration* sessions, the mother plays with the infant while the psychologist provides guidance based on insights co-developed during the previous four sessions. The goal is to promote a pragmatic translation of the insights into interactive skills.

FFSF procedure

At 9 months (CA for VPT participants), mothers and infants will take part in a FFSF procedure in the laboratory. The FFSF will include three episodes: During the Play episode (2 min), mothers and infants will interact face-to-face avoiding the use of toys and pacifier; during the Still-Face episode (1 min), mothers will be asked to interrupt any communication toward the infant, to maintain a still, poker face, while maintaining eye-contact; and during the Reunion episode (2 min), unconstrained interaction will be resumed. The procedure has been previously adopted to assess biobehavioral dimensions (Provenzi et al., 2019; Provenzi et al., 2017) and physiological underpinnings (Montirosso et al., 2010; Mantis et al., 2014) of socio-emotional stress regulation in VPT infants. The entire procedure will be videotaped for the offline coding of specific maternal and infant interactive behaviors (see *Measures* for details).

Neurophysiological procedures

EEG data acquisition will occur at 500 Hz sampling frequency during the 9-month FFSF procedure employing the Smarting Pro (mBrainTrain, Belgrade, Serbia) system equipped with two 32-channel EEG caps featuring wireless Bluetooth connection between the amplifiers and the mBrainTrain Streamer software installed on two separate laptops. The laptops receiving data will be linked to each other via a network cable to ensure synced data collection. The use of wireless EEG caps will allow greater flexibility and comfort for participating dyads.

1 https://www.project-redcap.org/

TABLE 1 Description of the thematic focus of the four *sharing the focus* sessions of the video-feedback (VF) intervention.

Thematic cluster	Key topic	Goal
Sensory stimulation and regulation	Sensory channels	Highlighting infant preference or avoidance of specific sensory channels and stimuli.
	Intensity of stimulation	Regulating intensity of physical stimulation and understanding infant sensory thresholds.
	Affective social touch	Facilitating parental affective touch to promote infant state regulation, postural stability, and attention orientation.
Nurturing and sensitive caregiving	Parental sensitivity	Promoting parental perception, interpretation, and appropriate responsiveness to infant communicative signals.
	Sense of agency	Detecting and supporting the infant's interactive initiatives (e.g., vocalizations and attention orienting).
	Exploration and safety	Supporting the infant exploration of the environment and building safety and trust in parental secure base.
	Rhythm and reparation	Facilitating the emergence of a proto-conversational rhythm in the dyad and supporting reparative actions of interactive perturbations.
Cognitive sensitivity and scaffolding	Attention skills	Supporting and scaffolding infant sustained and focused attention to the physical and social environment.
	Modeling and guidance	Providing a model to foster observational learning and the functional use of tools and toys.
	Proximal development zone	Improving caregiver awareness of the cognitive abilities of the infant to make appropriate play proposals and support infant emerging abilities.
Parenting experience and mental state	Mind-mindedness	Improving awareness about parental representations of the infant mind and keeping high levels of curiosity about infant behaviors.
	Self-care and self-regulation	Highlighting the importance of parental psychological wellbeing and reflective functions; promoting parental psychological self-care and compassion.
	Self-efficacy	Strengthening the caregiver's sense of efficacy as a parent and nourishing trust in the parent's own experience and mental representations of the infant.

Upon arrival, the infant will be familiarized with the setting: A play mat and toys will be available to aid in acclimatization to the environment. The researchers will debrief parents with a comprehensive explanation of the study's aims and procedures. Cap sizes will be selected to fit participants' head circumference. The caps fitting process will commence with the caregiver to ensure greater infant comfort and familiarity with the equipment. The conductive gel will be applied to optimize signal conductivity and minimize artifacts.

Measures

Demographic (e.g., parental age, parental job, and parental educational level), neonatal (e.g., gestational age, birth weight, and Apgar score), and clinical variables (e.g., NICU length of stay and minor morbidities) will be obtained from medical charts. Parent-report questionnaires are summarized and described in Table 2. As for behavioral coding purposes, the videotapes obtained from two cameras during the lab FFSF procedure will be edited offline using Movavi Video Suite 2020 software and a single synced video showing both frontal views of the caregiver and the infant's face, hands, and torso will be produced. Videos will be micro-analytically coded for infants' and caregivers' target interactive behaviors according to an adaptation of the Parent–Infant Coding Scheme (PICS, Version 4.0; Brambilla et al., 2023) as reported in Table 2. PICS codes will be computed as a percentage of time for each FFSF episode (Table 3).

Plan of EEG data elaboration

Pre-processing pipeline

Dyadic EEG data will be pre-processed with a fully automated pipeline built using the MATLAB-based (The MathWorks Inc., 2024) interacting toolbox EEGLAB (Delorme and Makeig, 2004). A brief description of the main pre-processing steps is available in Figure 2.

The parent and infant signals will be pre-processed separately with the same steps and parameters for both. First, data filtering will be performed with the application of a bandpass 1–30 Hz filter as the planned analyses (see below) will be conducted on the lower (theta and alpha) frequency bands. Subsequently, flat and outlier channels will be detected using the Neonatal EEG Artifact Removal (NEAR) plugin (Kumaravel et al., 2022) and retained (i.e., put in a separate temporary matrix) for later interpolation. Dyads in which at least one of the members displays a signal with more than 15% ($N > 5$) of flagged channels will be excluded from further analyses. The EEG signal from all non-flagged channels will undergo noise correction through the artifact subspace reconstruction (ASR; Chang et al., 2020), with burst criterion (k) set at 10; subsequently, analysis of the components of the signal will be performed through the independent component analysis (ICA; runica function with default settings), producing as many components as the number of good channels. The resulting components will be then classified through the ICLabel (Pion-Tonachini et al., 2019) plugin. Every component flagged as having a 50% or more probability of being an ocular artifact will be rejected. At this stage, the matrix containing the flat and outlier channels will be re-merged with the EEG matrix, and the bad channels

TABLE 2 Details of questionnaires included in the study.

Construct	Questionnaire	Reference	Item N	Likert scale	Description	Study wave(s)
Parental NICU-related stress	Parental Stressor Scale—NICU (PSS-NICU)	Miles et al. (1993)	46	5-point	Three main factor scores representing stress related to infants' appearance, environmental sights and sounds, and parental role alteration	T1 (only VPT)
Sensory profile	Sensory Profile-2 (SP-2)	Dunn (2014)	54	5-point	The infant version (0–6 months) identifies 5 sensory patterns. The toddler version (7–35 months) identifies four sensory patterns.	T2, T3, T4
Anxiety symptoms	State–Trait Anxiety Inventory (STAI-Y)	Spielberger et al. (1983)	40	4-point	One trait score representing a tendency to feel anxiety and one state score representing the present levels of anxiety	T2, T4
Depression symptoms	Beck Depression Inventory (BDI-II)	Beck et al. (1996)	21	4-point	Global score representing a quantitative appreciation of the severity of symptoms of depression	T2, T4
Parenting stress	Parenting Stress Index—Short Form (PSI-SF)	Abidin et al. (2006)	36	5-point	Three subscale scores addressing parental distress, parent–child dysfunctional interaction, and stress related to difficult child behavior. A global score is also obtained.	T2, T3, T4
Temperament	Infant Behavior Questionnaire-Revised (IBQ-R) very short form	Gartstein and Rothbart (2003)	37	7-point	Three subscale factor scores addressing negative affectivity, surgency, and regulatory capacity.	T2, T3, T4

VPT, very preterm; NICU, neonatal intensive care unit.

will be interpolated through spherical interpolation using the pre-processed signal. The signal will be then re-referenced to the average signal of the channels and split into three different sets containing each phase of the experimental procedure (Play, Still-Face, and Reunion): Each of these sets will be subsequently segmented into 1,000 ms epochs avoiding overlaps. Bad data segments containing residual artifacts in each of the three phases will be identified. All segments in which at least one of the target channels used for estimates of dyadic co-regulation (see below) displays a voltage exceeding ±150 μV (Debnath et al., 2020) will be marked as rejected. The rejected epochs in the infant's and parent's signals will be merged to obtain the final pool of rejected epochs for the dyad. This ensures that all the rejected epochs for one interactive member of the dyad will be similarly mirrored for the other partner. Dyadic data will undergo further analyses if their signal contains at least 30 good epochs in both the Play and Reunion phases; if this criterion is not met, their signal will undergo manual epoch rejection performed by an expert EEG coder. In case after the manual epoch rejection, the dyad will result having less than 30 good merged epochs in at least one of the FFSF episodes, the signal will be excluded from further analyses.

Estimating indices of inter-brain co-regulation

Several inter-brain synchronization indices have been proposed so far to estimate the coupling between two brains (Czeszumski et al., 2020). Since there is still debate on the appropriateness of each inter-brain synchronization measure, we plan to compute and compare several indices (see Table 4). To further check for spurious findings and gather stronger evidence that the obtained co-regulation

TABLE 3 Selection of codes from the Parent-Infant Coding Scheme (PICS, Version 4.0).

Variable	Levels	Description
A. Both interactive partners		
Emotional state	Negative	Clear display of negative emotionality (e.g., eyes, mouth, general movements of the face or the body, and other vocal or non-vocal signals) including fussing and crying.
	Neutral	No clear display of negative or positive emotionality.
	Positive	Clear display of positive emotionality (e.g., eyes, mouth, general movements of the face or the body, and other vocal or non-vocal signals) including smiles and laughs.
Gaze direction	Face-directed	Attention focus is on the interactive partner's face
	Object-directed	Attention focus is on the interactive partner body (e.g., hands and torso) or other objects.
	Avoiding	The subject is actively avoiding eye contact as displayed by head and body movements/posture.
Approach/withdrawal	Withdrawal	Evident leaning backward and/or turning the head away to avoid interaction
	Neutral	No evident backward or forward movements.
	Approach	Evident leaning forward and/or reaching forward to engage in interactive behaviors.
B. Parental-specific codes		
Vocal inputs	No voice	No vocal productions.
	Negative	Vocal comments that convey explicit critique or rejection of infants' behaviors or state.
	Pragmatic	Vocal comments that are finalized to modify or instruct the interactive partner's cognitive state, such as requests, attention-getting, and explanations.
	Social	Vocal comments that convey playful and social engagement such as singing, laughing, and playing nursery rhymes.
	Nurturing	Vocal comments that express appreciation or acceptance of infants' behaviors or state or are finalized to soothe infants' stress. These also include mind-related comments (e.g., "you think" and "you want") and mirroring of infants' communicative bids.
Tactile inputs	No touch	No tactile stimulations.
	Negative	Tactile stimulations that clearly appear intrusive and/or provoke or increase a negative emotionality state in the interactive partner.
	Pragmatic	Tactile stimulations that are finalized to modify or instruct the interactive partner postures or movements in the environment, such as holding, shadowing, and attention-getting.
	Social	Tactile stimulations that convey playful and social engagement such as tickling, squeezing, and any other appropriate entertaining tactile stimulations that are fast-paced, dynamic, repetitive, and/or characterized by quick cinematic features.
	Nurturing	Tactile stimulations that are finalized to soothe or regulate the behavioral state of the interactive partners. These include stroking, kissing, massaging, and any other appropriate tactile stimulations with clear regulatory functions and conveying a sense of affective closeness.

The complete coding manual is available upon request to the corresponding author.

estimations are not artifact production, we will compare the synchronization indices obtained from the real dyads to surrogate data generated by randomly pairing mothers and infants from different dyads.

The computation of synchronization measures will preferentially occur considering homologous channels for the sake of interpretability and computational costs. However, as an exploratory analysis, we will also compute synchronization between non-homologous channels because we can hypothesize that synchronization tasks between mother and infant can involve different brain areas in the two actors (Endevelt-Shapira et al., 2021).

Regarding the frequency bands on which the synchronization measures will be computed, we will mainly consider alpha and theta. Indeed, these frequencies have been found to be involved in parent–infant social tasks, with theta fluctuations linked to changes in shared attention during joint play of parent and infant (Wass et al., 2018), enhancement of alpha and theta power linked to changes in directed gaze (Leong et al., 2017), and fluctuations in alpha band linked to changes in emotional states of mother and child (Santamaria et al., 2020).

Moreover, since we are interested in the dynamic evolution of brain-to-brain synchronization, we plan to evaluate the trend of each synchronization index over time (i.e., over the epochs). In particular, we are interested in the change between an asynchronous to a synchronous state, which is defined as reparation. Reparation is a dyadic process in which unmatched dyadic states are transformed into matched dyadic states. We will compute the rate and the latency of reparation considering the EEG synchronization indices as previously performed in synchronized behaviors assessment (Provenzi et al., 2015).

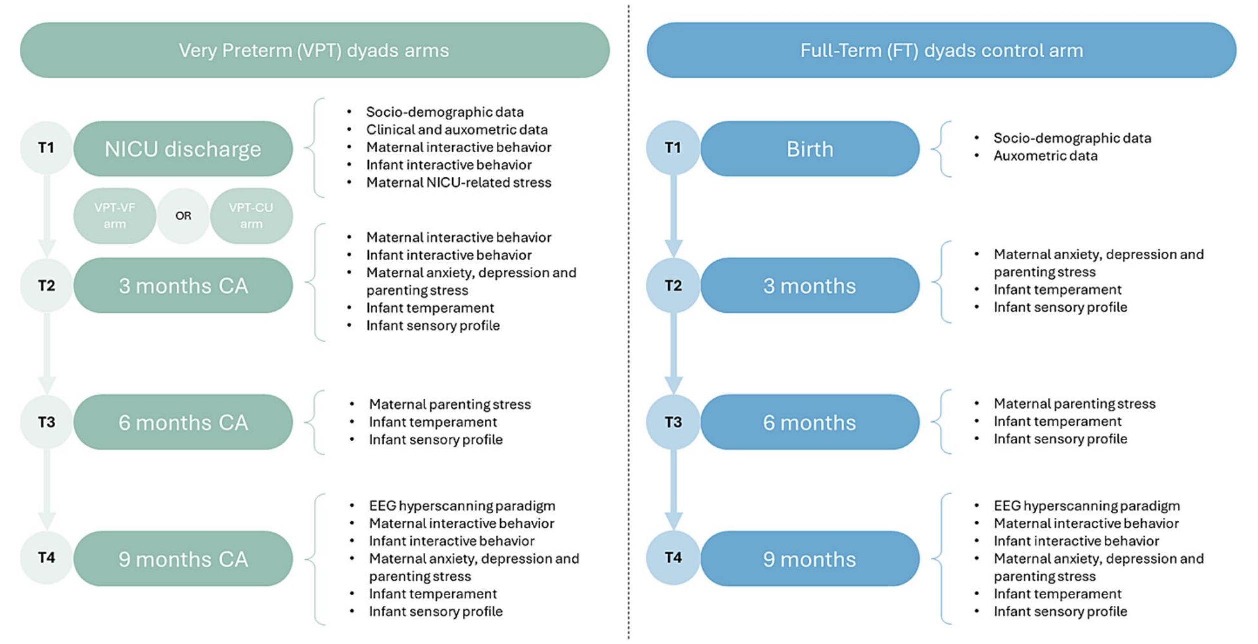

FIGURE 2
Study design. NICU, neonatal intensive care unit; VF, video-feedback intervention; CU, care as usual; CA, corrected age.

TABLE 4 Indices of inter-brain co-regulation adopted in the 2-BRAINED study.

Index	Description	Notes	Reference
Phase-Locking Value (PLV)	Frequency-specific transients of phase locking independent of amplitude. The value ranges from 0 to 1: values closer to 0 indicate random signals with unsynchronized phases; values closer to 1 indicate stronger coupling between the two signals.	While previous studies focused mainly on infant frequency bands, cross-frequency PLV indices will be obtained for the purposes of the 2-BRAINED study.	Lachaux et al. (1999); Canolty and Knight (2010)
Imaginary Coherence (ICoh)	Computed through spectral density (power) of each participant and cross-spectral density between them to estimate the average phase difference and consistency of phase difference synchronization.	ICoh is expressed as a complex number: the real part represents how much the coherence is driven by instantaneous interactions; the imaginary part shows how much the coherence is based on lagged interactions.	Dikker et al. (2021); Turk et al. (2022)
Amplitude-Amplitude Coupling (AAC)	Expressed as Pearson's correlation coefficient between normalized power time courses of the two signals.	Amplitude coupling was suggested as a valid alternative to phase coupling for three main reasons: amplitude changes are more easily estimated; amplitude modulations are more extensively characterized across EEG studies; amplitude modulations are more sensitive to neural coupling phenomena non-detectable with other phase-related measures.	Haresign et al. (2022); Koul et al. (2023)

Statistical power and sample size estimates

The sample size has been estimated according to over-arching Aim 2, setting parameters as follows: medium effect size, $f = 0.25$, *alpha* = 0.05, *beta* = 0.20, number of groups = 3 (VPT-VF, VPT-CU, and FT). The procedure yielded a total sample size of 159 subjects (53 subjects per RCT arm). Nonetheless, considering the longitudinal nature of the study and the attrition rate related to EEG tasks with infants, an oversampling of $n = 80$ (~ +50%) subjects per RCT arm was planned to secure the minimum sample size for appropriately powered statistical analyses.

Plan of statistical analyses

Preliminary analyses

Specific aim 1

General linear models (GLMs) will be carried out to compare VPT and FT dyadic brain-to-brain co-regulation indices during the experimental procedure phases. Theoretically relevant (e.g., gestational age) and statistically identified (e.g., any variable significantly linked with the outcome variables) confounding variables will be controlled for in the analytical model.

Specific aim 2

Separate analyses of variance (ANOVA) will be used with dyadic brain-to-brain co-regulation indices as the dependent variable and groups (FT, VPT-VF, and VPT-CU) as the independent variable. Theoretically relevant (e.g., gestational age) and statistically identified (e.g., any variable significantly linked with the outcome variables) confounding variables will be controlled for in the analytical model.

Additional aims

Models to track early developmental trajectories will be estimated in Mplus by latent class growth analysis with inter-individual variations in time of assessment and mixed-effect linear models with repeated measures to assess group differences in rates of temperament, emotional, and sensory profiles.

Discussion

The present protocol describes an RCT study that aims to assess the benefits of an early post-discharge video-feedback intervention to enhance and promote both parental and VPT infants' outcomes. By collecting dual-source EEG data in a hyper-scanning paradigm and from face-to-face real-time interactions between parents and infants, the study also aims at providing estimations of the effects of such intervention not only for the individual adjustment of caregivers and infants but also for the emergence of dyadic co-regulatory biobehavioral processes. Such co-regulation profiles are meant to be critical indicators of a nurturing caregiving environment during the first months of life fostering affective wellbeing and stress resilience (Feldman, 2020; Levy and Feldman, 2019).

Sources of bias and mitigation strategies

The heterogeneity of VPT infants' conditions should not be underestimated. Even in the absence of severe comorbidities and brain injuries, the experience of NICU hospitalization might be very different for each infant and their parents. To avoid extreme variations, the gestational age range will be constrained between 28 and 35 weeks. Moreover, stress related to the NICU environment will be evaluated and quantified with a well-validated questionnaire (Miles et al., 1993). Selection issues might affect random allocation plans in RCT arms. The allocation to VPT-VF and VPT-CU arms will occur by using an automatically generated list of binary codes that will be consecutively matched with the enrolled families across consecutive sampling. This will reduce the risk of self-selection. To further avoid confounding by infant sex and assure sex distribution balancing, the random allocation will be stratified by infant sex by *post-hoc* controls every 20 enrollments. Parental gender will also be unconstrained, inviting the primary caregiver—and not explicitly the mother—to participate in the study, VF intervention, and observational procedures. EEG procedural steps and artifacts might easily result in the loss of subjects in a longitudinal study; a 50% oversampling was planned to achieve the minimum sample size for adequately powered statistical analyses.

Expected results and impact

The project represents a translational application of the emerging field of hyper-scanning in developmental neuroscience (Provenzi et al., 2023). As neuroscience is moving toward a radical shift in considering interpersonal exchanges as the primary unit of analysis and observation (Leong et al., 2019; Hoehl and Markova, 2018), clinical applications are meant to be implemented to innovate healthcare. Previous proposals have been advanced to apply such a bi-personal neuroscientific approach to the field of adult psychiatry (Saul et al., 2022) and child development (Nguyen et al., 2020).

In this study, we aim to innovate the field of family-centered care in pediatric settings by embedding a cutting-edge approach to the study of parent–infant interaction and co-regulation processes into well-validated approaches to parental support and child development promotion. As the video-feedback intervention is well-acknowledged for its beneficial implications for parental wellbeing, child development, and quality of the early parent–child relationship (Fukkink et al., 2011; Montirosso et al., 2020), it represents an élite clinical setting to test the advantages of new neuroscientific-inspired metrics that specifically focus on the assessment of brain-to-brain co-regulatory processes. In this context, the present study has multifaceted implications.

From a scientific perspective, this study will provide first-of-a-kind quantitative estimations of inter-brain coupling and co-regulation in a sample of VPT infants and their caregivers. While previous research has highlighted functional and structural alterations in VPT infants' brains (Dereymaeker et al., 2017; Hüppi et al., 1998; Pittet et al., 2019), very little is known about VPT neurophysiological functioning in real-life settings. Moreover, the study will provide insights into "how much" inter-brain synchrony should be expected in typical and atypical developmental trajectories. As medium levels of attunement and matching have been suggested to be optimal in terms of behavioral co-regulation during the first months (Provenzi et al., 2016), similar expectations appear to be plausible for what pertains to inter-brain coupling.

From a clinical point of view, the 2-BRAINED project is expected to produce evidence of the efficacy of an early intervention for VPT infants and their parents that is delivered after NICU discharge. This is a critical window for continuity of care as parents transition from potentially high-quality family-centered care during NICU stay to a lack of appropriate and tailored support at home (Lundqvist et al., 2019; Provenzi et al., 2016). From this perspective, this study will explore the efficacy of an intervention aimed at granting continuity of care from the hospital to the house, extending and empowering family-centered care for VPT infants' parents.

From a translational neuroscience perspective, the study will also offer an unprecedented opportunity to obtain first-hand dyadic neurophysiological target outcomes of well-validated early family-centered VF intervention. While the road to developing qualitative and quantitative measures of the effectiveness and efficacy of such family-centered interventions is yet to be fully implemented, the integration of behavioral, self-report, and neurobiological markers is promising for future advances.

Patient and public involvement

Active engagement of families will be pursued through public-dedicated web/social communications, digital content, and newsletters describing the achieved goals and implications of the study. Parental associations and professional orders will be engaged through online webinars to capitalize on the data obtained from the present study to further fuel a culture of family-centered care for preterm infants and their parents.

Ethics and dissemination

Ethics, privacy, and data management

The Ethics Committee Pavia and collaborating partners granted approval for the study on 16 February 2023 (protocol number: 0008588/23) and officially launched on 24 April 2023 (GR-2021-12375213). All procedures align with the ethical principles outlined in the Declaration of Helsinki for research involving human subjects, ensuring no harm to participants. The study intervention offers additional opportunities for families without altering standard mother–infant care programs. Infants will undergo planned diagnostic and therapeutic interventions at the child neurology and psychiatric unit IRCCS Mondino Foundation, Pavia, Italy, and the Scientific Institute IRCCS *E. Medea*, Bosisio Parini, Italy.

Data management will occur in accordance with the General Data Protection Regulation (Regulation 2016/279, commonly known as GDPR), to guarantee the privacy and the security of the gathered data. In this sense, all the infants' parents will sign an informed consent module after that the study's aims and modalities will be clearly explained and eventual doubts will be solved. Each subject will be assigned a code, and data will be stored in a pseudonymized form. After the period of conservation (25 years), data will be made completely anonymous. In line with the open science principle, the anonymized data collected for the study will be published on a publicly accessible "repository" (i.e., Zenodo) to promote the dissemination of research results with a view to furthering the research itself and the scientific community.

Dissemination

The dissemination strategy involves presenting findings at national and international scientific meetings, publishing in developmental psychology journals, and engaging in outreach activities with families and healthcare specialists. This aims to promote early family-centered intervention and share insights with the wider public.

Ethics statement

The studies involving humans were approved by Comitato Etico, Policlinico San Matteo, Pavia (Italy). The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

LB: Methodology, Supervision, Writing – original draft, Writing – review & editing. VR: Conceptualization, Methodology, Supervision, Writing – original draft, Writing – review & editing. EC: Writing – original draft, Writing – review & editing. SG: Writing – original draft, Writing – review & editing. MP: Writing – original draft, Writing – review & editing. MC: Writing – original draft, Writing – review & editing. ES: Writing – original draft, Writing – review & editing. ER: Writing – original draft, Writing – review & editing. RB: Writing – original draft, Writing – review & editing. LP: Conceptualization, Funding acquisition, Methodology, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author LP declared that he was an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

Generative AI statement

The author(s) declare that no Gen AI was used in the creation of this manuscript.

Publisher's note

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EDITED BY
Livio Provenzi,
University of Pavia, Italy

REVIEWED BY
Flora Koliouli,
Aristotle University of Thessaloniki, Greece
Grazyna Kmita,
University of Warsaw, Poland

*CORRESPONDENCE
Manuela Filippa
✉ manuela.filippa@unige.ch

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Maternal singing and speech have beneficial effects on preterm infant's general movements at term equivalent age and at 3 months: an RCT

Manuela Filippa[1]*, Gianluca Filippa[2], Elisa Della Casa[3], Alberto Berardi[4], Odoardo Picciolini[5], Sara Chiara Meloni[5], Clara Lunardi[6], Alessandra Cecchi[7], Alessandra Sansavini[8], Luigi Corvaglia[9,10], Didier Grandjean[1], EVC Group and Fabrizio Ferrari[4]

[1]Department of Psychology and Educational Sciences, University of Geneva, Geneva, Switzerland, [2]Independent Researcher, Aosta, Italy, [3]Neonatal Intensive Care Unit, Women's and Children's Health Department, University Hospital of Modena, Modena, Italy, [4]Department of Medical and Surgical Sciences of Mother, Children and Adults, University Hospital of Modena, Modena, Italy, [5]Pediatric Physical Medicine & Rehabilitation Unit, IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy, [6]Department of Neurosciences, Psychology, Drug Research and Child Health, Careggi University Hospital of Florence, Florence, Italy, [7]Division of Neonatology, Careggi University Hospital, School of Medicine, University of Florence, Florence, Italy, [8]Department of Psychology "Renzo Canestrari", University of Bologna, Bologna, Italy, [9]Neonatal Intensive Care Unit, IRCCS AOU Bologna, Bologna, Italy, [10]Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy

Background: General Movements (GMs) are part of the spontaneous movement repertoire and assessing them helps to determine the integrity of the central nervous system in newborns. The aim of this study was to investigate the effects of maternal singing and speaking in the Neonatal Intensive Care Unit (NICU) on preterm infants' GMs at term equivalent age and at 3 months.

Methods: In this multi-center randomized clinical trial, 56 stable preterm infants (25–32 weeks) were randomized to either an intervention group – in which mothers were asked to speak and sing to their infants for 20 min, 3 times per week, for 2 weeks – or to a control group. GMs were recorded both before and after the intervention – which took place at term equivalent age – and again at 3 months corrected age. The GMs were blindly coded based on the muted video tracks to produce both a general score and a detailed score.

Results: Before the intervention, there were no significant differences between the two groups. The intervention wielded a significant effect on the GMs general score ($p < 0.05$). The effect was also marginally significant for the GMs detailed score ($p = 0.06$). To avoid influencing outcomes, future research should control for differences in maternal engagement outside of the intervention.

Conclusion: Live maternal singing and speaking are fundamental human practices that, in this study, enhanced preterm infants' general movements and potentially supported their neurobehavioral development. Integrating and supporting early vocal interaction into routine NICU care is crucial for at-risk populations.

KEYWORDS

prematurity, maternal voice, general movements, early intervention, sensorimotor system

1 Introduction

Worldwide, rates of preterm birth have barely changed in recent decades, with an increase only in defined areas (Ohuma et al., 2023; Organization, W. H, 2023). In 21 European countries, the preterm birth rates in 2020 were, on average, 4% lower than the rates predicted based on trends from the previous 5 years, with comparable estimations across all socioeconomic groups (Zeitlin et al., 2024).

Despite advancements in neonatal care leading to improved survival rates, prematurity remains associated with various health challenges. These include both short-and long-term complications for the newborns and their families, as well as a broader societal burden (Ashorn et al., 2023; Blencowe et al., 2012).

Among a subset of extremely preterm babies (22–26 weeks' gestation), reported survival without neurodevelopmental impairment at 2 years ranges from 20 to 42% (Moore et al., 2012; Serenius et al., 2013; Younge et al., 2017). In very and moderately preterm babies, the rates of survival without severe or moderate neuromotor and sensory disabilities at 2 years corrected age, exceed 90% (Lugli et al., 2021; Pierrat et al., 2017). While the incidence of cerebral palsy in preterm babies is decreasing (under 10%), rates of severe functional disability and cerebral palsy are higher in neonates with a lower gestational age (Lugli et al., 2021; Pascal et al., 2018; Pierrat et al., 2017). These preterm children are also at higher risk of developing minor neurological dysfunction: a typical neurological profile includes difficulties with posture, muscle tone, regulation, and balance, as well as mildly abnormal reflexes, coordination, and cranial nerve function; these issues may affect everyday functioning and can also be associated with learning and cognitive problems (Broström et al., 2018). Early parental interventions in the neonatal period, such as skin-to-skin contact (Moore et al., 2012) during the first weeks of life in the NICU, represent a promising approach to improving the later developmental outcomes of preterm infants (Spittle and Treyvaud, 2016), with positive, clinically meaningful effects extending to the age of 36 months (Vanderveen et al., 2009).

Preterm birth, especially with gestational age at or below 32 weeks, increases the risk of language delay (Barre et al., 2011), affecting one in four and one in three very preterm children at 30 months and 42 months corrected age, respectively (Sansavini et al., 2010). Language difficulties have also been identified in less immature 24-month-old preterm children (Charkaluk et al., 2019; Sansavini et al., 2021) and can persist in preterm children up to school age, with cascading effects on literacy and educational attainment (Guarini et al., 2016; Putnick et al., 2017; van Noort-van der Spek et al., 2012).

The causes of atypical developmental trajectories in preterm infants extend beyond medical factors. Environmental influences, such as atypical sensory inputs incompatible with the developing brain's needs and sensorimotor development, play a significant role. Additionally, repeated painful procedures and early separation from caretakers during NICU admission contribute to an accumulation of stress factors (Cheong et al., 2020; Filippa et al., 2019b).

To reduce neonatal stress, individualized care practices are increasingly being implemented in the NICU. These measures include regulating harmful sensory stimuli, introducing non-pharmacological pain management strategies, and actively involving parents in the care of hospitalized neonates (Beltrán et al., 2022; Hassankhani et al., 2020; Waddington et al., 2021).

The publication of specific guidelines developed by an interdisciplinary group of experts (van den Hoogen, 2019), including pediatricians, parents, neonatologists, psychologists, and therapists has greatly furthered the process of active family inclusion, although the presence of parents on hospital wards still varies greatly from facility to facility (Kokorelias et al., 2019).

1.1 Maternal singing and speech in the NICU: the vocal contact

Recent systematic reviews have shown that when hospitalized preterm infants hear their mother's live voice directed towards them, this improves their physiological stability, has positive effects on their nutritional status, and helps reduce maternal anxiety, thus also benefiting the parents (Bieleninik et al., 2016; Filippa et al., 2017; Provenzi et al., 2018). Early and constant exposure to the voice of a parent in a multimodal context such as skin-to-skin contact can have both short-and long-term effects on infants' linguistic abilities (Caskey et al., 2014). In the long term, increased exposure to live directed speech during a preterm infant's stay in the NICU enhances parental word count and positively impacts preterm infant's linguistic scores at 2 years (McGowan et al., 2024). These gains may be underpinned by early neural mechanisms, such the enhanced neural discrimination of sound changes (Kostilainen et al., 2021) and more marked responses to deviant sounds (Partanen et al., 2022).

Maternal speech and singing during a painful procedure also act as analgesics, reducing the expression of pain and increasing oxytocin levels, significantly so in the case of singing (Filippa et al., 2021b); at the same time, they boost the mothers' own levels of oxytocin thereby mitigating maternal anxiety (Filippa et al., 2023b).

In terms of longitudinal research, the Cochrane review by Haslbeck et al. (2023) acknowledges the potential of musical and vocal interventions to benefit preterm infants, though it highlights that current evidence regarding their direct impact on developmental outcomes, such as those assessed by the Bayley Scales of Infant and Toddler Development, is of low certainty and inconclusive (Haslbeck et al., 2023). However, a small number of interesting studies have shown that hearing the maternal voice – recorded or live – can have significant effects on the preterm infant over the longer term. In one set of studies for example, the transmission of recorded maternal voices via bone conduction was associated with significantly improved neurofunction in preterm infants (Picciolini et al., 2022) at 3 months corrected age (Picciolini et al., 2014), though it yielded no significant difference at 6 months corrected age. Another study on the long-term effects of early voice exposure showed that the quantity of live adult speech in the NICU was positively correlated with infants' early social development (face preference) at 7 months corrected age, suggesting potential long-term effects of voice/speech exposure at neonatal intensive care facilities. Moreover, early exposure to voices plays a pivotal role in facilitating brain changes (Romeo et al., 2018) that in turn support cognitive, language, and motor development in early childhood (McGowan et al., 2024). Finally, early exposure or deprivation to voices remains crucial for key processes like auditory processing which is foundational for broader neurodevelopment (Adam-Darque et al., 2020; Filippa et al., 2023a). Notably, when newborns hear voices, as opposed to silence or instrumental music, sensorimotor areas and salience networks—brain regions associated with memory, cognition, and motor function—are activated (Loukas et al., 2024). Taken together, the aforementioned studies suggest that vocal exposure may influence infants' neurodevelopmental trajectories and may serve as a compensatory mechanism to mitigate neurodevelopmental delays in preterm infants, although its effects on specific developmental domains warrant precise investigation.

1.2 General movements assessment

General Movements (GMs) are a type of spontaneous motor activity that is frequently studied in fetuses, preterm and term-born neonates, and young infants (Prechtl et al., 1979). It is now widely accepted that the brain and central nervous system can generate a vast repertoire of endogenous activities even in the absence of specific stimuli. GMs are generalized movements that involve the entire body in a varied sequence of movements. They begin and end gradually. They have been characterized as limb rotations and motor trajectories effected with elegance, continuity, and fluidity (Prechtl, 1990). GM patterns are part of the repertoire of spontaneous motor behaviors, and their origins, characteristics, and clinical function as early markers for neurological deficits have all been extensively described in the scientific literature (Ferrari et al., 1990; Prechtl et al., 1997). Abnormal general movements, in particular, have been identified as reliable markers for the early detection of later neurodevelopmental disorders (Bosanquet et al., 2013). The GMs assessment has been widely used in the preterm infant population as a non-invasive method for evaluating young infants' neurological development, and indeed preterm infants carrying high neurobiological risk may already exhibit abnormal GMs during the first few days of life (De Vries and Bos, 2010).

In some cases, the quality of preterms' GMs normalizes over the first weeks of life or before term age equivalent (Cioni et al., 1997; De Vries and Bos, 2010). In other cases, particularly when birth weight is low, preterm infants' movements continue to differ from those of full-term infants (De Vries and Bos, 2011). Preterm infants exhibit less varied movements than their term-matched counterparts, resulting in a lower complexity index.

"Fidgety movements" are specific, small-amplitude movements of the neck, trunk, and limbs that typically emerge between 6 and 9 weeks after term birth and can be assessed starting at 3 months of age (Einspieler and Prechtl, 2005). These movement patterns manifest as micro-movements of the neck, trunk, and limbs with different rates, directions, and accelerations (Prechtl et al., 1997).

The absence or rarity of fidgety movements between 3 and 5 months is a significant marker of risk for severe neurological deficits (Einspieler et al., 2015).

This randomized controlled trial is part of a larger investigation examining the effects of early vocal contact between parents and preterm newborns in the NICU (Filippa et al., 2021a). Multiple assessment measures were used to evaluate the short-and long-term effects of this early parental intervention on the maturation of the newborns' autonomic nervous system (Filippa et al., 2024b) and their long-term linguistic development (Filippa et al., 2021a).

The present study evaluates the effects of the vocal contact—through singing and speaking—on the general movements (GMs) of preterm infants during NICU hospitalization, assessed at term equivalent age and 3 months of corrected age. The primary aim was to enhance early vocal contact between parents and preterm infants in the NICU, with the secondary aim of improving neurodevelopmental outcomes as measured by GM assessments. The study tested the hypothesis that a structured maternal vocal intervention would be positively associated with better GM scores at both time points.

2 Methods

2.1 Study sample

In this randomized controlled study, 56 preterm infants born between 25 and 33 weeks gestational age (GA), were recruited at four sites in Italy between February 2019 and November 2020. The inclusion criteria for the study stipulated that the newborns were required to have been born at the participating center, with a gestational age at birth of between 25 and 33 weeks, a birth weight that was appropriate for their gestational age (>3rd percentile, <97th percentile), a birth cranial circumference greater than the 10th percentile, and an Apgar score of >7 at 10 min. At the time of enrollment, newborns were expected to be in a stable condition. They were either spontaneously breathing or receiving respiratory support via a low-flow nasal cannula. Infants requiring respiratory support with a high-flow nasal cannula, non-invasive ventilation, or invasive ventilation, as well as those experiencing hyperbilirubinemia requiring exchange transfusions during hospitalization, were ineligible for participation.

Infants with congenital malformations and/or genetic abnormalities, as well as those diagnosed with severe conditions such as periventricular leukomalacia grade III and IV, intraventricular hemorrhage grade III and IV, or severe sepsis, were excluded from the study. Additionally infants whose parents did not sign an informed consent form were also excluded. Furthermore, mothers were excluded from the study if they exhibited evident depressive symptoms, had a history of drug abuse during pregnancy, or were under 18 years of age. The psychologists stationed in the participating NICUs conducted assessments for maternal post-partum depression. In the presence of one or more risk factors for depression, standardized protocols were implemented and, where appropriate, the mother was referred to the perinatal psychiatric specialist to explore the need for pharmacological intervention. Mothers who were assessed for mental health issues were not included in the study. Finally, mothers were also excluded if their level of Italian language proficiency precluded them from completing the study questionnaires and from fully understanding the informed consent form. The level of maternal education was assessed and no significant differences were found between the two groups.

2.2 Study setting

The participating healthcare facilities were Bologna University Sant'Orsola-Malpighi Hospital (Bologna), NICU Fondazione IRCCS

Ca′ Granda Ospedale Maggiore Policlinico, Careggi University Hospital (Florence), and Modena University Hospital (Modena).

All these centers are third-level units providing the same level of care to seriously-ill newborns. The four NICU levels range from Level 1 (the mildest) to Level 4 (the most severe). At the third level, fragile preterm newborns require the support of hi-tech incubators and mechanical ventilators and usually spend long periods in the NICU to ensure stabilization and recovery before hospital discharge. All the centers in the study apply the principles of Family-Centered Care as defined by the European Standards for Newborn Care (Kostenzer et al., 2022). These standards underscore the importance of nurturing the well-being of both the newborn infants and their families. At the core of these standards is a commitment to providing 24-h access to the unit for both mothers and fathers, thereby fostering an environment of inclusivity and support. The standards also prioritize effective pain management strategies for newborns, recognizing the importance of minimizing discomfort and optimizing comfort levels. Finally, they emphasize the importance of catering for the needs of parents by creating a supportive environment for families.

At 6, 12, and 24 months corrected age, the children selected for participation in the study underwent routine general neurological examinations (EON) conducted by trained researchers. The final EON assessment yielded a positive or negative rating. When an infant obtained a final negative score, they were excluded from the current analyses.

The clinical characteristics of the sample are reported in Table 1.

2.3 Study design

Centralized patient randomization was conducted using a secure, web-based randomization system, via which the research investigators at each center registered new patients and obtained intervention arm assignment. Stata statistical software was used to build a block allocation sequence with various block sizes stratified by GA at birth and gender (StataCorp, College Station, TX, USA). In the case of twins, randomization was applied at the family level such that sets of twins (8%) were assigned to the same group.

The study was independently approved by each center's Ethical Committee: Modena Health Authority's Independent Ethics Committee of Area Vasta Emilia Nord (P.0006292/18); Bologna Health Authority's Independent Ethics Committee (P.348/2018/Sper/AOUBo); Milan Mangiagalli CE (P.205); and Florence Careggi Hospital CE (P.77/2017). The infants' postnatal data was recorded for further analysis. The study was conducted in accordance with the ethical standards of the Declaration of Helsinki (Association, W. M, 2013) and written parental consent was obtained for all participating infants.

2.4 Power analysis

This study is part of a larger research project designed to investigate the effects of early maternal vocal interventions on various neurodevelopmental and physiological outcomes in preterm infants. The sample size for the present study was calculated based on the primary outcome measure: heart rate variability (Filippa et al., 2024b). To account for an estimated 20% attrition rate, the target sample size was set at 80 participants (40 per group). This sample size is in concordance with the specific literature, which supports similar population sizes for assessing the effects of early interventions on preterm infants' general movements (Spittle et al., 2015).

2.5 The live vocal intervention

The intervention group mothers were asked to talk (10 min) and sing (10 min) to their infants three times a week for 2 weeks, over the hour following afternoon feeding. The mothers were asked to speak in their own language and then to sing familiar songs while observing their baby's reactions. They were asked not to touch their infant during the intervention itself. The order of the two vocalizations, speaking and singing, was strictly alternated across the six sessions.

The intervention began once the inclusion criteria had been met. For further details, see Postnatal Days at Intervention Start and Postmenstrual Age at Intervention Start in Table 1. Additional information such as the median values and percentiles 25–75 are included in Supplementary Table S1.

The intervention took place on the hospital ward, while the infants were in active sleep, quiet wakefulness, or active wakefulness phases, but not in deep sleep or crying. This meant that deep sleep and sleep cycles were not disrupted by the intervention. Also, in stable preterm newborns, quiet wakefulness is known to be the most favorable condition for family members to initiate early sensory interventions and engagement (Westrup, 2007).

TABLE 1 Clinical characteristics of the intervention and control groups.

Variables	Intervention (*M, SD*) (*n* = 29)	Control (*M, SD*) (*n* = 27)	*p*
Gestational age at birth (weeks), *M (SD)*	29.84 (1.97)	29.98 (1.59)	0.39
Birthweight (grams), *M (SD)*	1201.38 (264.66)	1305.30 (269.05)	0.15
Apgar score at 5 Min, *M (SD)*	7.45 (1.68)	7.25 (1.77)	0.75
Mother's age (years), *M (SD)*	36.79 (4.22)	34.88 (6.96)	0.23
Postmenstrual age at intervention start (weeks), *M (SD)*	34.05 (1.56)	34.35 (1.27)	0.48
Weight at intervention start (weeks), *M (SD)*	1683.66 (342.43)	1770.19 (298.38)	0.33
Postnatal age at intervention start (days), *M (SD)*	29.28 (18.04)	31.89 (14.90)	0.59

We encouraged the mothers to position their faces in front of the incubator opening, as close to their infant's head as possible. Concurrent medical procedures were not permitted during the intervention to optimize adherence to the protocol.

The mothers in the intervention group were guided by a formal protocol devised by the first author of the manuscript and by the research supervisor, who is the last author. The instructions were clear and straightforward. The mothers were directed to engage in both talking and singing, but in two distinct phases of the intervention, preferably using their mother tongue (although they were free to choose their own preferred language). They were allowed to freely select the content of their conversation and songs.

While the mothers were encouraged to discuss topics of their own choice, where suggestions were sought, the researcher recommended conversations about their home routines or future family plans post-hospitalization. Regarding the singing, the researchers were allowed to make suggestions, upon request, such as choosing familiar and emotionally resonant songs sung during pregnancy or songs embedded in the mothers' musical memories. Researchers also conveyed that mothers could opt for wordless humming, and that repeating the same song multiple times was acceptable, all while attentively observing the babies' behaviors and reactions.

The researchers at each of the centers ensured that the protocol was followed correctly by being present during the recording of the sessions. If the mothers preferred privacy, the researchers viewed the recordings afterwards in order to discard any sessions where mothers failed to communicate vocally. No sessions were excluded from the final sample.

For the first time in research on early vocal contact, we also collected data from an active control group. The mothers assigned to this group were encouraged to spend the same amount of time by the incubator as the intervention group mothers, while observing their infant's behaviors based on a standard set of cues. This control condition was designed both to include the silent live presence of mothers next to the incubator as a benchmark for comparison as well as to actively include these mothers in the study.

The active control group mothers engaged in an observational program, focusing on observing their babies' behaviors. They were instructed to refrain from speaking or singing only during the observation sessions (20 min per day, three times per week, for 2 weeks). Outside of the observation sessions, standard parental and medical care continued as usual.

The intervention and control sessions were all video recorded, and adherence to the protocol was verified for both groups by a trained researcher.

2.6 Video recording of spontaneous movements

Digital video recordings of the infants' movements were made before the intervention, between 32-and 34-weeks GA, at the end of the intervention, at term equivalent age, and again at 3 months corrected age. Of the planned 168 recordings (56 × 3), 14 are missing due to technical or logistical difficulties. Each video recording lasted 3–5 min. The following protocol was put in place to ensure consistency of measurement. The infant was placed in a supine position in a semi-open nest, wearing a nappy and a baby bodysuit. It was recommended to lay the infant on a blue cloth for the purposes of filming. All infants were in a waking state; given that behavioral states are not always well defined at low gestational ages, the researcher waited until the infant initiated movement to begin recording. The use of a pacifier was not allowed during the recording of the infants' general movements (GMs) because this could have altered the quality of the GMs.

The camera was placed on a tripod about 1.5 m high, about 50 cm above the infant's incubator. All centers used a camera of the same make and model.

2.7 GMs assessment

General movements are gross movements involving the entire body and are identifiable from the early fetal stage up to 3–5 months post-term. According to Prechtl's method of assessment (Einspieler and Prechtl, 2005), two distinct patterns of normal general movements may be observed: writhing and fidgety movements. Writhing GMs occur preterm, at term, and up to 6–8 weeks post-term, and are of small to moderate amplitude and slow to moderate speed. Fidgety movements, which may be observed from 6 to 20 weeks post-term, are small-amplitude, moderate-speed, and multi-directional movements of the neck, trunk, and limbs, and are continual in the awake infant. Abnormal patterns of general movements include so-called poor repertoire general movements (PR), which occur between term age and 6–9 weeks and are a monotonous sequence of movements that lack the complexity that distinguishes normal GMs. A second type of abnormal GMs are labelled cramped-synchronized GMs (CS): these movements appear rigid as opposed to smooth and fluent, and the infant's limbs and trunk contract and relax almost simultaneously (Ferrari et al., 2002; Ferrari et al., 1990).

For the purposes of the present analysis, three or four episodes of GMs (excluding periods of crying) were selected and first digitalized and then edited using Adobe Premium Pro software (v.2.0 for Windows). At each of the participating centers, a blinded researcher made a compilation of the GMs video recordings at each of the three ages and stored each compilation in a separate file.

The quality of the GMs was independently analyzed for each infant by two observers, an experienced GMs trainer (FF, see authors) and an experienced GMs researcher (DE, see authors). The coders were blind to the infants' pre-, peri-and postnatal medical history, clinical status, and group assignment. DE was totally blind to the imaging, outcomes, and perinatal history of the infants from the centers in Pisa, Milano and Bologna. Interobserver agreement was 92%. To resolve any disagreement in coding, the GMs of the individual case were jointly reviewed, and consensus was reached after discussion.

The assessment of GMs relies on visual Gestalt perception.

Gestalt perception is a sophisticated visual technique used to assess complex phenomena (Lorenz, 1971). In the general movement assessment, it allows to capture their overall qualities, including complexity, fluency, and elegance. This approach relies on the observer's ability to perceive patterns holistically rather than focusing on individual details, making it an irreplaceable tool for evaluating the quality of movements in preterm infants (Prechtl, 1990). Among trained and experienced coders, inter-rater reliability is strong, ranging from 89 to

93% (Einspieler and Prechtl, 2005). In this study, the blinded assessment of the individual video compilations yielded two types of outcome: a Global score and a Detailed score. The global score was based on the assessment of writhing and fidgety movements according to the standard methodological principles of Prechtl's approach to evaluating the quality of GMs (Einspieler and Prechtl, 2005). The global analysis thus involved the recognition and coding of normal (writhing or fidgety) versus non-normal GMs (i.e., poor repertoire, cramped-synchronized, or absent or exaggerated fidgety GMs). More specifically, three distinct categories were assessed both before the intervention (T0) and after the intervention (T1): cramped-synchronized GMs (CS), poor repertoire GMs (PR), and Normal GMs (N)(for details see Table 2). At 3 months corrected age the global score corresponds to the assessment of fidgety movements via three categories, namely Normal, Abnormal and Absent Fidgety Movements (for details see Table 3).

The detailed scoring for the writhing period (which spans both preterm and term age) is based on the assessment of the individual components of general movement (Einspieler and Prechtl, 2005). A refined procedure for scoring these components has been proposed by Einspieler et al. (2015). The detailed score reflects the quality of the various components of GMs, such as amplitude, speed, special range, proximal and distal rotations, onset and offset, and tremulous and cramped components of the upper and lower extremities. The optimality concept may be applied to the detailed evaluation of GMs to yield an optimality score (GMOS). The GMOS quantifies the detailed characteristics of GMs (Einspieler et al., 2016), with a score of 42 indicating maximum performance both at T0 before the intervention and at T1, after the intervention.

At 3 months corrected age, the detailed evaluation of GMs encompasses the assessment of five additional subcategories to yield the Motor Optimality Score (MOS), ranging from a maximum of 28 points (optimum performance) to a minimum of 5 points (worst possible performance).

The detailed assessment and corresponding optimality score help to identify early markers of cerebral palsy during the neonatal period (Einspieler et al., 2019).

2.8 Environmental measures

Background noise levels at each of the participating NICUs were monitored using a calibrated sound level meter (Voltcraft Phonometer SL-10; Conrad Electronic, Hirschau, Germany). Three sets of measurements were taken: two before the intervention began, one inside the intervention room and one inside the incubator, and one during each session, at 10 cm from the infants' heads. This last measurement was required to guarantee that the infant could hear the mother's voice (which needed to be at least 10 dBA louder than the background noise). These values were not subjected to any further analysis.

TABLE 2 GMs global scores at T0, before the intervention, and at T1 after the intervention.

Group	Time point	CS	PR	*N*	NA	Total
Intervention	T0	0	6	22	1	28
Intervention	T1	0	8	18	3	26
Control	T0	2	7	16	2	25
Control	T1	1	8	16	2	25

CS, cramped-synchronized GMs; PR, poor repertoire GMs; N, normal GMs; NA, not available.

2.9 Statistical analysis

Differences between groups (intervention vs. control) and over time (i.e., T0 vs. T1 and T2) were tested using nonlinear mixed effect models estimated with the lme4 R software package (Bates et al., 2014). Nonlinear mixed effect models are particularly suitable for small sample size and when normality assumptions are violated. Moreover, while we acknowledge that small sample size remains an issue of this study we partially overcame this problem by adopting a permutation approach (i.e., permutation t-test to assess differences among clinical characteristics between intervention and control groups at T0; see Table 1).

Intervention and time were viewed as fixed effects, while the subjects were treated as random effect. Differences over time (a three-level factor) were tested using the Tukey Honest Significant Difference *post hoc* test performed with the multcomp R software package (Hothorn et al., 2008). *p*-values were viewed as highly significant when $p < 0.01$ and as significant when $p < 0.05$. Permutation t-test (1,000 replications) was used to assess differences among clinical characteristics between intervention and control groups at T0.

3 Results

The independent variables were Group assignment (Preterm Intervention and Preterm Control), and Time, measured at three different time points (T0, before the intervention, T1 after the intervention, and T2 at 3 months corrected age). The dependent variables were Global GMs (see Tables 2, 3) and Detailed GMs (see Tables 4, 5).

Although a visual inspection suggests that the control group included relatively more infants with CS and PR, this difference was not statistically significant when assessed using appropriate statistical analyses.

Before the intervention, at baseline T0, there were no significant differences between the Control and Intervention Groups in terms of their main clinical characteristics, as assessed via a permutation *t*-test (1,000 replications). The *p*-values are reported in Table 1.

The following tables present the raw mean Global and Detailed scores at the different timepoints.

No significant differences between the two groups at T0, before the intervention, in terms of either the Global or Detailed GMs scores.

The non-linear mixed-effects model revealed that the intervention had a significant effect on GMs global scores, $p < 0.05$ (see Table 6), while accounting for time and the time × group interaction. Similarly, there was a marginally significant effect of the intervention on GMs detailed scores, $p = 0.06$ (see Table 6). In addition, time had a significant effect on the Global score between T0 (before the intervention) and T2 (at 3 months corrected age), $p < 0.05$ (see Table 6). However, no significant

TABLE 3 GMs global score (Fidgety Assessment) at 3 months corrected age.

Group	Time Point	Normal FMs	Abnormal FMs	Absent FMs	NA	Total
Intervention	3 months	24	0	0	5	29
Control	3 months	18	1	1	7	27

FMs, Fidgety movements; NA, not available.

TABLE 4 GMs detailed scores (optimality scores, GMOS) at T0, before the intervention, and at T1 after the intervention.

Group	Time point	Mean GMOS	NA	Total
Intervention	T0	38.28	1	28
Intervention	T1	37.77	3	26
Control	T0	34.76	2	25
Control	T1	35.81	2	25

GMOS, general movements optimality scores; NA, not available.

TABLE 5 GMs detailed scores (motor optimality scores, MOS) at 3 months corrected age.

Group	Time point	Mean MOS	NA	Total
Intervention	3 months	26.24	4	25
Control	3 months	25.66	6	21

MOS, motor optimality scores; NA, not available.

TABLE 6 Linear mixed effect models for global and detailed scores.

Dependent variable	Estimate	Standard error	*t* value	Pr(>|t|)
GMs global scores				
Intervention	−0.23801	0.11926	−1.996	0.0496 *
Time	0.21582	0.08794	2.454	0.0194 *
Group*Time	0.04133	0.13248	0.312	0.7569
GMs detailed scores				
Intervention	−0.08853	0.04709	−1.880	0.0637^
Time	0.02889	0.03770	0.766	0.4479
Group*Time	0.05389	0.05576	0.966	0.3392

* Significant differences ($p < 0.05$); ^marginally significant differences ($0.1 < p < 0.05$).

effect of time was found for GMs detailed scores, and the interaction term was not significant for either the Global or detailed scores (see Table 6).

Although we collected video recordings and the infants participated in the follow-up at T2, there were cases where the recordings were not suitable for evaluation. These missing evaluations were included with the data for preterm infants who did not have their last measurement at 3 months and are reported as NA in Tables 3, 5.

Supplementary Table S1 provides comprehensive information about the clinical characteristics of the Intervention and Control Groups, including the median, percentile, and range values. It also provides a more detailed account of the Cramped-Synchronized (CS), Poor Repertoire (PR), and Normal (N) GMs assessments.

4 Discussion

While promising evidence has been gathered demonstrating the short-term effects of early acoustic interventions, based on exposure to parents' voices or live or recorded music in the NICU (Haslbeck et al., 2020; Kostilainen et al., 2021; Lordier et al., 2019), the longer-term impacts on preterm infant's cognitive, linguistic, emotional, and general neurobehavioral development are still discordant (Filippa et al., 2024a; Haslbeck et al., 2021; Kostilainen et al., 2023; Lejeune et al., 2019; McGowan et al., 2024).

In the current study, we demonstrated a potential sustained effect of live maternal singing and speech on the neurobehavioral development of preterm infants, as measured via the General Movement Assessment, at term equivalent age and 3 months corrected age.

The current findings align with previous research. In a 2014 study (Picciolini et al., 2014) with 71 preterm infants, the recorded maternal voice was transmitted via bone conduction. At 3 months corrected age, the infants in the intervention group obtained significantly higher GMs scores (Ferrari et al., 1990) and higher scores on a neurofunctional assessment (Picciolini et al., 2022) than the control group. No significant differences were detected at 6 months corrected age.

However, although the outcomes appear to align with our own research, the undergoing mechanisms might be different.

In the present study, the intervention was a live, infant-directed vocal interaction, in which the mothers would have modulated their voices based on behavioral cues received from their preterm infants (Filippa et al., 2018), for example by amplifying the emotional content of their vocalizations in response to signs of positive communication on the part of their infants (Filippa et al., 2019a, 2019b, 2020). Moreover, mothers who actively engage in live infant-directed vocal interaction showed reduced levels of anxiety (Arnon et al., 2014), increased synchrony with their baby (Palazzi et al., 2020) and higher oxytocin levels (Filippa et al., 2023a; Filippa et al., 2023b; Hirschel et al., 2023), with potential knock-on effects on their sensitivity.

Given that previous research indicates positive associations between increased maternal sensitivity and the characteristics of infants' spontaneous movements (Lev-Enacab et al., 2022), it is possible that the long-term beneficial effects of the present intervention rely on enhanced maternal sensitivity to the infant's communicative cues. Interestingly, the quality of infants' spontaneous movements at 3–4 months has been positively correlated with maternal sensitivity in terms of how mothers physically engage with their infants, but not in relation to the mother's vocalizations (Lev-Enacab et al., 2015), which was the core focus of the present study. Future research is needed to disentangle the interactional mechanisms underlying the long-term effects of early contact between parents and their offspring.

Another potential mechanism linking the specific effects of the present intervention with general movements involves the brain responses of preterm infants to maternal speech and singing. Maternal singing activates key neural networks in newborns, including sensorimotor and salience regions, which play crucial roles in motor coordination, attention, and memory (Loukas et al., 2024). These regions are integral to the neural pathways underlying the production and refinement of general movements, suggesting that auditory stimulation from maternal singing directly supports the maturation of sensorimotor integration in preterm infants. Additionally, rhythmic components of singing are highly predictive and structured, providing an optimal stimulus for infant motor responses. During development, infants naturally respond to singing with rhythmic movements, indicating an innate link between auditory and motor systems (Zentner and Eerola, 2010). This synchronization highlights how musical stimuli, such as maternal singing, can engage motor pathways. Similar effects have been observed with maternal speech. Newborns show right-hemispheric brain responses to their mother's voice, with activation patterns involving premotor and supplementary motor areas. These areas are essential for planning and coordinating movements, further supporting the connection between maternal vocalizations and motor development (Beauchemin et al., 2011).

Taken together, these findings highlight the potential brain mechanisms underpinning the effects of maternal singing and speech on the observed improvements in GMs in preterm infants.

On the other hand, our results are not consistent with those of earlier research in which music therapy in addition to kangaroo care versus kangaroo care alone had no significant impact on GMs scores (Span et al., 2021). This was possibly due to the post-natal age at which the preterms received the therapy, given that preterm infants with a post-natal age of <7 days obtained lower GM optimality scores than those with a post-natal age of >7 days. In the present study, the preterms were required to have attained stability before starting the intervention (for details see the Method section), and post-natal age at testing was very variable, ranging from 15 to 39 days in the intervention group and from 21 to 43 in the control group. Based on the above-mentioned findings of Span et al. with a larger sample, which prompted the authors to recommend postponing early live acoustic interventions until 7 days after birth, it is plausible to hypothesize that live vocal or musical intervention may lead to more favorable outcomes in stable preterm newborns, starting 1 or 2 weeks after birth. Nevertheless, further trials are needed to identify the optimum post-natal age for initiating parent-driven vocal and musical interventions.

Finally, the positive effects of the present vocal intervention inherently rely on parents' intuitive ability to care for their offspring. In previous studies, we demonstrated that live maternal singing and speech contribute to stabilizing preterm infants. This stabilization, in turn, promotes better attending behaviors and improved organization of the newborn's states (Filippa et al., 2013). Furthermore, live maternal interactions help to structure the behavioral organization of preterm infants, leading to an increase in their self-touching behaviors, such as hand-to-head movements (Filippa et al., 2020). Hand movements directed towards the head, face, and mouth are recognized as distinct self-regulation behaviors deployed by preterm newborns to modulate their levels of arousal (Als et al., 2005) and are viewed as crucial attempts at self-control or self-comforting. These basic interactive mechanisms lead to an increase in calm alert states accompanied by homeostatic behaviors, which impact in turn on maternal emotional availability (Filippa et al., 2019a) and on parents' ability, for example, to modulate their voice in interactive contexts (Filippa et al., 2018; Saliba et al., 2020).

Furthermore, early intervention with the active involvement of parents, during a sensitive period for the development of the relationship between mothers and their preterm born infants, impacts on the preterm infants' quality of movement and, consequently, on maternal responses and mutual regulation during early interactions (Lev-Enacab et al., 2022). Parents likely interpret regular, continuous, smooth, and fluent movements by their infants as an endearing signal of willingness to interact, which in turn may prompt more attuned maternal behavior (Kringelbach et al., 2016; Lev-Enacab et al., 2015).

Taken together, these observations point up specific basic mechanisms that also involve the modulation of the neuroendocrine system (Filippa et al., 2021b), the autonomous nervous system (Filippa et al., 2022b; Porges et al., 2019), and the brain (Filippa et al., 2023a; Welch et al., 2020b), thereby laying the ground for long-term and sustained effects on the development of newborns and children (Welch et al., 2020a).

The long-term, sustained effects of the early intervention tested in this study may be viewed as relatively certain, given that the intervention was largely based on the activation of biologically rooted and evolutionarily conserved parental behaviors and sensitivities (Rilling and Young, 2014), and given that it was implemented during a critical period in the brain development of preterm babies, during which the infant is particularly attentive and sensitive to acoustic stimuli (Benasich et al., 2014; Musacchia et al., 2017). Within a protective cycle of reciprocity, whereby parents both modulate and are affected by their infants' behaviors, infant conspecifics can trigger protective parental responses, shielding offspring from the impacts of changes in transcriptional regulation within specific brain regions associated with parenting (Stolzenberg and Mayer, 2019).

4.1 Limitations

We are limited in our ability to generalize the results of this study due to the small sample size. A key risk of a limited population is that the impact of a few individual positive responses to the intervention can disproportionately influence the overall effects. Additionally, the potential value of including a simple measure of the time mothers spent with their babies in the NICU in future studies to better account for the overall maternal engagement. However, as noted in the statistical analysis section, the robustness of the RCT design and the types of analyses used help ensure the reliability of the results. Another limitation to the generalizability of these findings is the relatively stable health condition of the recruited preterm newborns. As specified, only infants without congenital anomalies and atypical brain malformations were included. Further research should include more fragile preterm infants, with a view to assessing how an environment enriched with maternal stimuli (Cioni et al., 2011) may modify atypical brain development trajectories.

An additional constraint of this study is the lack of assessment of the newborn infants' overall language exposure and general interactional contact during and after hospitalization. Future studies should accurately assess, at various time points both during and after hospitalization, the average amount of adult words to which babies are exposed during the first months of life and the amount of time that dyads spend interacting. In the long term, the family's musical habits should also be monitored (Politimou et al., 2018), given that the musical environment in the home in early infancy is known to have an impact on children's language development (Franco et al., 2022).

Finally, our longitudinal analysis could have usefully been supplemented by additional forms of assessment. Future research should include neuroimaging techniques, which could provide insights into the underlying physiological mechanisms that contribute to GMs-related development, as well as assessment of mother–infant attunement as an outcome measure of efficacy for these forms of early intervention. Integrating multiple assessment approaches will further enhance our understanding of the evolution of GMs and provide a more complete picture of developmental pathways.

5 Conclusion

In the current study, we observed potential sustained effects of live maternal singing and speech on the neurobehavioral development of preterm infants, as measured by the General Movement Assessment, at term equivalent age and 3 months corrected age.

Supporting and enhancing parental speech and singing directed toward preterm infants has the potential not only to foster their linguistic development (McGowan et al., 2024) but also to stimulate sensorimotor integration, positively impacting neurobehavioral development as assessed by general movements. There is strong rationale for promoting early contact and interaction through infant-directed singing and speech within the framework of infant-and family-centered care (Filippa and Kuhn, 2024). Ensuring that caregivers and healthcare professionals are equipped to understand and implement early vocal and interactive strategies can improve outcomes for both infants and their families.

Future research should carefully control for interactional periods in the dyads during and after hospitalization and evaluate the effects of early parental intervention on parents' brain structures and behaviors, at multiple levels (neuroendocrine, neural, and behavioral), over the first weeks and months of life, while parents are interacting with and caring for their preterm infants. Changes in parental behaviors, combined with specific modifications to infant brain functionality, thanks to the early intervention, may enhance the long-term developmental trajectories of this at-risk population.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by the Ethical Committees of all participating centers: Modena Health Authority's Independent Ethics Committee of Area Vasta Emilia Nord (P.0006292/18); Milan Mangiagalli CE (P. 205); Bologna Health Authority's Independent Ethics Committee (P. 348/2018/Sper/AOUBo); and Florence Careggi Hospital CE (P. 77/2017). Freely given, informed consent to participate was obtained from all participants. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

MF: Conceptualization, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing. GF: Data curation, Formal analysis, Writing – original draft, Writing – review & editing. ED: Conceptualization, Investigation, Writing – original draft, Writing – review & editing. AB: Writing – review & editing. OP: Conceptualization, Writing – original draft, Writing – review & editing. SM: Investigation, Writing – review & editing. CL: Conceptualization, Investigation, Writing – review & editing. AC: Investigation, Writing – review & editing. AS: Conceptualization, Investigation, Methodology, Supervision, Writing – original draft, Writing – review & editing. LC: Writing – review & editing. DG: Writing – review & editing. FF: Conceptualization, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

Generative AI statement

The authors declare that no Generative AI was used in the creation of this manuscript.

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Supplementary material

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