Impact of Nonmedical Factors on Neurobehavior and Language Outcomes of Preterm Infants

Elisabeth C. McGowan, MD,* Betty R. Vohr, MD*

*Warren Alpert Medical School of Brown University, and Department of Pediatrics, Women & Infants Hospital of Rhode Island, Providence, RI

Education Gap

It is important for health care professionals to understand and address not only the medical risk factors associated with extreme prematurity that affect preterm infant neurobehavior in the NICU and postdischarge outcomes, but also the powerful effects of maternal, NICU, and social environmental risk factors.

Abstract

Preterm infants are at increased risk for adverse neurodevelopmental outcomes. The impact of maternal, NICU, and social environmental factors on early neurobehavior and language outcomes of preterm infants is recognized. There is a need for health care professionals to have a clear understanding of the importance of facilitating positive mother-infant relationships, and to address not only the infant's sensory and language environment, but also focus on adverse maternal mental health and social adversities to optimize infant outcomes.

Objectives   After completing this article, readers should be able to:

1. Identify characteristics of the NICU environment that contribute to less optimal neonatal neurobehavior and short- and long-term language outcomes.

2. Explain why the development of early language skills is important.

3. Describe the relationship between environmental characteristics and brain development in preterm infants.

4. Identify maternal/parental interventions that should be encouraged in the NICU to improve short- and long-term language outcomes.

ABBREVIATIONS

AAP	American Academy of Pediatrics
BSID-III	Bayley Scales of Infant and Toddler Development, Third Edition
COPE	Creating Opportunities for Parent Empowerment
EEG	electroencephalography
FICare	Family Integrated Care
IDS	infant-directed speech
MRI	magnetic resonance imaging
NNNS	NICU Network Neurobehavioral Scale
SFR	single-family room

INTRODUCTION

Both biologic factors and a spectrum of environmental factors affect neonatal and postdischarge outcomes of preterm infants. (1) Infants flourish optimally in an

environment that includes maternal comforting touch, voice, and love beginning at birth and continuing in a stable secure home environment. (2)(3)(4) Maternal, NICU, environmental, and socioeconomic factors that are early predictors of neurobehavior and language outcomes of preterm infants have been described. (5)(6)(7)(8)(9) There is a need for health care professionals to have a clear understanding of the importance of facilitating positive mother-infant relationships beginning in the NICU, and the need to address adverse maternal mental health, social adversities, and the infant's sensory environment to optimize outcomes of preterm infants.

STRESS

Over the past decade, the adverse effects of stress have been well documented and described. Beginning with the landmark Adverse Childhood Experiences Study, (10) researchers started to appreciate not only the short-term but also the long-term negative implications of stress exposure. The repetitive, continuous, or extreme activation of the stress response system is linked to the term "toxic" stress. Risk factors for stress include early abuse, neglect, and parental mental health problems. The American Academy of Pediatrics (AAP) 2012 report on early adversity and toxic stress introduces an eco-bio-developmental framework that affects brain development and subsequent long-term health. (11) The current paradigm proposes that the convergence of genetics, environmental stresses, and developmental outcomes define health.

THE NICU ENVIRONMENT AND STRESS

By default of being born too early, the preterm infant's new extrauterine environment is an equipment-driven NICU, consisting of multiple, potentially toxic stressors, including reliance on complex technology coupled with separation from the mother. Of great concern is the influence of stress on the development of biologic systems, including the brain, (12)(13) endocrine, (14)(15)(16) and immune systems. (17)(18) The load of stress in the NICU, while lifesaving and necessary, is often chronic or repeated. Direct, early, painful stimuli can include intubations, mechanical ventilation, intravenous catheter placement, and heel sticks. (19)(20)(21) In a 2016 systematic review consisting of 18 observational studies, Cruz et al described an average of 8 to 18 invasive procedures per neonate per day in the NICU. (22) In addition, a rapid change to bright lighting that often accompanies critical procedures may contribute to physiologic dysregulation. (23)

The early infant-caregiver bond that is essential for healthy development is altered in the NICU as a consequence of the medical acuity and environmental constraints. During a period when nurturing is critical, preterm infants are separated from their mothers. Infants in the NICU are therefore deprived of maternal touch and skin-to-skin care.

Innovative animal research from Liu et al demonstrated that rat pups exposed to increased levels of maternal care, characterized by licking and grooming, had improved stress reactions measured by hypothalamic-pituitary-adrenal responses. (15) In humans, benefits of skin-to-skin contact are well documented and have been noted to promote various health benefits, including increased breastfeeding, (24) improved cardiorespiratory stability and growth, (25) and amelioration of procedural pain. (26)(27) For preterm infants in particular, early, consistent, and prolonged skin-to-skin contact has been shown to reduce rates of morbidities, such as bronchopulmonary dysplasia and nosocomial infection. (28) Yet ill infants are not often held because of concerns about adverse medical consequences. (29)(30) Importantly, benefits of skin-to-skin care may also extend to parents, with reports of decreased symptoms of depression and anxiety (31)(32) and more positive parent-child interactions. (33) In a systematic review of barriers to kangaroo care, Chan et al identified several deterrents, including lack of time, support, and family acceptance. (34)

It is important to recognize that while the mother and hospitalized infant are separated from each other physically, there is also a risk of emotional separation. (35) There are myriad reasons that mothers may feel isolated or "removed" from their role as mother. Loss of control, (36)(37) infant appearance and behavior, (38) and frightening NICU sights and sounds (38) may lead to parent withdrawal. Indeed, higher rates of symptoms of depression, anxiety, worry, and posttraumatic stress disorders are reported in mothers of preterm infants compared with mothers of term infants, (39)(40)(41) and some symptoms may start as early as the time of delivery. (42) Poor maternal mental well-being has been associated with decreased visitation, (43) decreased participation in bedside care, (44) and decreased parenting readiness. (45)

INTEGRATION OF THE FAMILY INTO NICU CARE

Acknowledging parents as key caregivers in the NICU, the National Perinatal Association recommends broadening the mindset of neonatal care to multidisciplinary family care in efforts to buffer acute and chronic NICU stressors. (46)(47)

(48) Sanders and Hall, as well as others, suggest that as trauma is experienced by both infant and parents in the NICU; staff provision of care to families shifts toward trauma-informed care to promote the mother-infant connection and improve the outcome for both the mother and her infant. (49)(50)

Several investigators have not only recognized the need for integrated, family-centered care to potentially buffer the effect of NICU stressors, but have designed interventions or models of care to help facilitate and encourage parental participation. In 2001, Melnyk and colleagues described a NICU-based intervention, Creating Opportunities for Parent Empowerment (COPE), an educational-behavioral curriculum for parents of preterm infants aimed at strengthening parent knowledge, role, and participation in needs and care. (51) Randomized controlled trials incorporating COPE have demonstrated less NICU maternal stress, depression, and anxiety, (52)(53)(54) and increased parent participation in infant care, (53) compared with control mothers. The Mother-Infant Transaction Program, (55) an intervention that teaches parents how to observe their infant's behavioral state and cues and how to facilitate engaging interaction, has also shown promise. Investigators reported improved mother-infant interactions, (55) including better responses to the infant's stress cues, (56) increased breastfeeding, (57) and reduced postpartum depression symptoms, (57) with some benefits persisting into early childhood. (58)(59)(60) A recent meta-analysis identified programs that were multifaceted, centering on integrating psychosocial support, parent education, and infant development support, which showed significant reduction in parental trauma and stress. (61)

Family Integrated Care (FICare), an innovative model that empowers parents to be integral primary caregivers in the NICU, has expanded family-centered care even further. (62) This model, which starts as early as the day of admission, is showing promising results; it teaches parents how to participate in bedside care, enhances staff/parent education, fosters active communication, and implements peer support in a supportive physical environment. (63)(64)(65) In 2018, O'Brien and colleagues reported results of a randomized controlled trial from 26 tertiary NICUs in Canada, Australia, and New Zealand. (66) Mothers in the FICare group, who committed to being present in the NICU for at least 6 hours/day, were compared with those receiving standard NICU care. At day 21, infants in the FICare group had greater weight gain and were more likely to exclusively receive breast milk, and FICare mothers had lower mean scores on anxiety and stress. Data from these different models clearly demonstrate the benefits of broadening the scope of family integration.

SINGLE-FAMILY ROOM VERSUS OPEN-BAY NICU

With the intent of supporting enhanced family-centered care models, the single-family room (SFR) environment has been adopted in many NICUs. Benefits for preterm infants have included increased rates of breastfeeding (67)(68); reductions in mortality, infections, apnea, and time to full enteric feeds; and decreased length of initial hospitalization and hospital readmissions. (63)(67)(69)(70)(71) A recently published meta-analysis by van Veenendaal and colleagues (72) that included 13 distinct study populations (consisting of 1 randomized trial, 5 nonrandomized trials, and 7 before-and-after studies on relocation to new NICU environments), found that infants in SFR units had a lower incidence of sepsis (relative risk [RR] 0.63; confidence interval [CI] 0.5–0.78) and higher rates of exclusive breastfeeding (RR 1.31; CI 1.07–1.61). (72) There were no differences in mortality, length of hospital stay, growth, or major morbidities.

Greater parent satisfaction has been reported among families in SFR NICUs, including increased privacy, more comfortable surroundings, decreased noise, and opportunities for longer nurse-parent interactions. (67)(73)(74)(75)(76) Lester et al noted that mothers in SFR NICUs reported not only increased satisfaction, but more involvement in their infant's care, including skin-to-skin care, and less stress, compared with mothers in open-bay NICUs. (71) In addition, improved infant growth and decreased number of medical procedures were mediated by increased developmental support and maternal involvement. Intuitively, it seems reasonable that a comfortable, quiet, family-centered private room environment would lead to increased parental presence. In a Norwegian prospective survey study of preterm infants, Tandberg et al found that mothers in SFRs spent significantly more time in the NICU compared with mothers in an open-bay unit (median of 20 hours/day vs 7 hours/day; $P<.001$). (77) However, it is important to note that in the Lester et al cohort, (71) maternal involvement was related to higher socioeconomic status, and in the Tandberg cohort, (77) mothers were in general highly educated, with nearly 80% of the mothers in SFRs being college-educated compared with 70% of those in open-bay units. Although maternal visitation and involvement is critical to the mother-infant dyad, not all parents are able to spend equal amount of time at the bedside. Sociodemographic factors that may limit presence in the NICU include young maternal age, single parent, greater number of children at home, maternal psychologic distress, and economic challenges. (38)(43)(78)(79) Thus, when

implementing interventions or support for both parents and their infants, success will be maximized if stressors and barriers are recognized and addressed.

Very few studies have looked at sustained benefits and outcomes of infants cared for in SFR NICUs. Lester et al identified increased family-centered care, developmental support, and maternal involvement associated with improved 18-month Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III) cognitive and language scores. (80) In a larger cohort from the same NICU, Vohr et al reported that at 18 to 24 months of age, SFR NICU was associated with a 2.5-point increase in BSID-III cognitive scores and a 3.7-point increase in language scores compared with open-bay units. (81) However, in separate models based on insurance type, the beneficial effects of SFR remained significant only for infant language scores in families with private insurance. The findings of associations between increased BSID-III scores and high maternal involvement and socioeconomic status may partially explain the contrasting results reported by Pineda and colleagues. (82) In a cohort of infants born at less than 30 weeks' gestation, infants in private rooms had lower language and motor scores, but the authors noted that this cohort had high rates of public insurance and low parental visitation. Although more studies examining long-term neurodevelopmental outcomes are needed to explore how to optimize the NICU environment, most experts agree about the importance of including sensory-appropriate stimuli in the setting of maximizing parental visitation and involvement.

INFANT NEUROBEHAVIOR AND ENVIRONMENT

Engaging parents in infant bedside care and developmental support brings to light an aspect of development that is not often recognized, or even assessed in the ICU setting. Infant neurobehavior, which in part is a reflection of the relationship between central nervous system functioning and behavioral adaptations to the environment, can offer early insight into a neonate's functional reactions to biologic, sensory, and social stress. Different assessment tools have been used in various NICU settings, one of which is the NICU Network Neurobehavioral Scale (NNNS). The NNNS is a 20- to 30-minute validated, standardized, comprehensive evaluation that incorporates neurologic, behavioral, and stress measures with strong interrater reliability. (83)(84) (85) Certified examiners assess tone, reflexes, items that reflect physical maturity, social/behavioral functions, including auditory and visual orientation, and comprehensive stress signs, which are organized by organ system. Thirteen summary scores are used to summarize the

clinical examination. Much of the early NNNS work centered on term infants, and by providing normative reference values, investigators were able to evaluate term infants in various high-risk medical and psychosocial settings. (86)(87)(88)(89)(90)

More recently, the NNNS has been used in cohorts of preterm infants. Compared with term infants, preterm infants display more nonoptimal reflexes, poorer quality of movements, less attention, and more difficulties regulating stress. (91) However, supportive environments may help optimize neurobehavior. Lester et al reported that preterm infants in SFR NICUs had less lethargy, hypertonicity, and physiologic stress signs, and showed better attention at term-age compared with infants in open-bay units. (71) Findings were mediated by increased maternal involvement and developmental support. Similarly, Pineda et al observed that increased parent holding and skin-to-skin contact was associated with better reflexes and less asymmetry at term postmenstrual age. (78)

As expected, medical complications also have negative effects on neurodevelopment; chronic lung disease, intraventricular hemorrhage, necrotizing enterocolitis, and gray and white matter abnormalities seen on magnetic resonance imaging (MRI) have all been associated with abnormal NNNS summary scores. (92)(93) Smith et al reported that increased Neonatal Infant Stressor Scale scores were associated with altered NNNS motor scores. (7) Patterns of summary scores may also be categorized in mutually exclusive "profiles," which represent an overall repertoire of the infant's neurobehavior functioning and interactions. (94) Profiles may be helpful for parents and clinicians to have an overall "picture" of an infant's neurobehavior. NNNS profiles, which can be categorized from most typical (low risk) to most atypical (high risk) have also been useful, because atypical profiles have been shown to be predictive of early childhood motor, cognitive, and behavior problems in a cohort of infants of less than 37 weeks' gestation with prenatal substance exposure. (95)

NICU LANGUAGE ENVIRONMENT

More recently, social and sensory isolation in the NICU have been recognized as possible contributors to adverse outcomes. (4)(96)(97)(98)(99) Preterm infants in the NICU have multiple caretakers, repeated painful procedures, dependency on complex technology, and absence of continued caretaking by their mothers. (21)(100) The noise environment of the NICU is accentuated by monitors, respiratory equipment, and number of staff. (101) Although the AAP recommends maintaining noise levels at 45 dB,

levels are reported to be consistently higher. (102) Pineda et al reported that the average NICU sound level was 58.9 dB, with an average peak level of 86.9 dB. (8) Noise level was significantly related to medical interventions. The NICU environment can be contrasted with that of the healthy full-term infant who is exposed to typical touch, talk, and social interactions of a family unit and goes home from the birthing hospital in 1 to 3 days. In the Pineda et al study, parent presence and parent holding of the infant in the NICU were both associated with increased adult word exposure. (8)

The question then arises: "Is the infant in the NICU physiologically ready for language exposure?" In fact, auditory reception occurs as early as 24 to 26 weeks of gestation when the cochlea of the inner ear completes development. The fetus responds to vibroacoustic stimuli by 24 to 25 weeks and has consistent responses by 27 to 28 weeks' gestation. (103) Changes in fetal heart rate in response to maternal voice as early as 32 to 37 weeks' gestation have been interpreted as a preattention reaction. (104) Three-day-old term infants prefer their mothers' voice to other female voices. (105)

A study of preterm infants of 25 to 30 weeks' gestation who were exposed to alternate feedings with exposure to either standard NICU sounds or 30-minute recordings of their mothers' heart rate and voice identified that the infant's heart rate decreased significantly in response to maternal sounds. (106) This was interpreted as greater comfort/relaxation of infants when exposed to their mother's sounds. Other beneficial effects of recorded mother's voices that have been reported include decreased apnea and bradycardia, (107) increased weight gain velocity, (108) increased attending behavior, (109) earlier enteral feedings, (110) and increased visual attention and quality of movements. (111) Caskey et al reported that very preterm infants in the NICU have vocalizations other than cry, that these vocalizations increase between 32 and 36 weeks' gestation in the NICU, and that preterm infants vocalize and respond preferentially to their mother's voice over the nurse's voice as early as 32 weeks' gestation. (6)

LANGUAGE OUTCOMES INCREASED RISK

Language skills are key to successful communication, social-emotional development, and academic success. An extensive body of evidence has demonstrated that preterm infants are at increased risk of short-term and long-term mild to moderate delays in speech and language, (112)(113)(114) including vocabulary development, (115) phonological processing, (116)(117) language

comprehension, (118) verbal short-term memory, (119) and grammatical development. (120) Numerous studies and reviews (121) have reported preterm infant delays and impairments in both simple language function and complex language functions. (112)

Language delays among preterm infants are often found in association with additional cognitive (122) and behavioral challenges. (123)(124) Language delays and impairments in preterm infants have been associated with neonatal illness severity, such as brain injury including grade 3 to 4 intraventricular hemorrhage, chronic lung disease, prolonged assisted ventilation, prolonged hospitalization, and hearing loss. (121) More recently, increased attention has focused on the impact of maternal IQ, adverse mental health, single parent, and nonoptimal parent involvement. (125)(126)(127)(128)

BRAIN AND LANGUAGE

Evidence shows that exposure of the preterm brain to the extrauterine environment alters neuronal differentiation, which may alter subsequent development. (129)(130)(131) The question is then posed: "Does language exposure in the NICU make a difference in brain development and in language outcomes for the preterm infant?" Brain areas of importance for speech and language include the Broca area (both expressive speech and comprehension) in the prefrontal cortex, the auditory cortex and Wernicke area (comprehension), and adjacent parietal areas. Radiographic studies have identified decreased gray matter in the temporal lobes and decreased white matter in the frontal, temporal, and parietal lobes. (132)(133)(134) Very preterm birth is associated with decreased regional brain volumes particularly of the midtemporal cortex, the premotor cortex, and the sensorimotor cortex. (132) Monson et al examined the rates of primary and nonprimary auditory cortex maturation in very preterm infants cared for in either an open-bay or SFR NICU. (135) MRI diffusion parameters of the auditory cortex at term equivalent differed between preterm and term controls. (135) The authors suggest that this reflects either delayed maturation or injury among preterm infants. The preterm infants with disturbed maturation of the nonprimary auditory cortex had poorer 2-year BSID-III receptive and expressive language scores. Room type had no effect.

Variability in outcomes of language studies may be related, in part, to the characteristics of the speech to which the infant is exposed. (136) Infant-directed speech (IDS) also referred to as "parentese," is more appealing to infants. (137) It is characterized by slower tempo and speech rate, regular

rhythm, higher emotional content, higher pitch and greater pitch range, simplified structure, and acoustic exaggeration of speech sounds, and by the facial expression of the speaker (smiles, raises eyebrows, makes eye contact with the infant). Studies show increased cortical activity in frontal and temporal regions in response to IDS to 12 months of age using both near-infrared spectroscopy and electroencephalography (EEG). In addition, significantly greater activations were elicited in the frontal areas by IDS of the infant's own mother compared with the IDS of unfamiliar women. (137)(138)(139) A study comparing EEG cortical tracking to IDS and adult-directed speech at 7 months of age identified stronger low-frequency cortical tracking in response to IDS. The authors suggest that maternal utterances are important in activating infant brain function and that this process may facilitate early speech processing and language development. (138)

In a report of 40 preterm infants of 25 to 32 weeks' gestation randomized to either maternal sounds (voice and heart rate) or standard NICU sounds during feedings, cranial ultrasonography was performed at 30 days of age. The preterm infants randomized to maternal sound exposure had a significantly larger bilateral temporal auditory cortex, suggesting early brain plasticity, specifically in response to maternal sounds. (140)

MRI scans for neuroanatomic measurements identified regional vulnerability of brain volumes in a cohort of 8-year-old very preterm infants with birthweights of less than or equal to 1,250 g, with the largest decreases observed in the sensorimotor cortex, premotor cortex, and midtemporal cortex. (132) A second study of 8-year-old preterm children reported that those with the lowest verbal comprehension task scores did not fully engage normal semantic processing pathways. Aberrant processing of semantic content may account in part for their lower Peabody Picture Vocabulary Test scores. (141)

RECOVERY

Evidence shows recovery of language skills with increasing age. In the indomethacin cohort of infants weighing less than 1,250 g, preterm children had continued catch-up on the Peabody Picture Vocabulary Test between 3 and 12 years and gained 1.2 points per year across the study period. Severe brain injury was the strongest predictor of poor language outcomes. (142) Continued assessment at 16 years identified that very preterm adolescents had deficits in higher-order language skills (phonological awareness and phonemic decoding) compared with term controls. (143) Hierarchical growth-curve modeling was used to delineate 4

clusters of cognitive and receptive vocabulary growth among the preterm children. Two clusters of preterm children caught up to term children with increasing age (55% caught up in vocabulary). The children who caught up had lower rates of neurosensory impairment, had more educated mothers, and were less likely to be from an ethnic non-minority. (114)

Nguyen et al described language trajectories of very preterm children compared with full-term controls examined at 2, 5, 7, and 13 years. (144) They identified 5 distinct language trajectory groups using latent growth mixture modeling, allowing for linear and quadratic time trends. The 5 groups included stable normal (32% of cohort), resilient development showing catch-up (36%), precocious language skills (7%), stable low (17%), and high-risk (5%) development. Trajectories that represented poorer language development were present in 40% of very preterm and 6% of term children. Greater social risk was associated with poorer language development with increasing age. The association of lower socioeconomic status with a less optimal language development trajectory with increasing age has been recognized in both term and preterm children. (145)(146)

An example of alterations in functional connectivity was observed in 12-year-old preterm versus term controls in a functional MRI task to examine lexical semantic processing. The preterm and term children performed equally on a semantic association task (identify similar versus dissimilar words). Both preterm and term groups activated regions known to be associated with semantic processing (inferior frontal gyrus and the midtemporal gyrus). However, there were differences in connectivity between regions for both preterm and term children. (147) For the lexical semantic processing task, the left inferior frontal gyrus correlated with accuracy for term children, the left sensory motor areas correlated with accuracy for preterm children, and the left middle temporal gyri correlated with task accuracy for both groups. The preterm and term children overall performed equally well on the task at 12 years, suggesting that plasticity in network connections may provide the opportunity for improving language skills observed with increasing age in preterm infants.

A recent study of term 4- to 6-year-old children reported that both higher socioeconomic status and increased conversations recorded between parents and their child were associated with better language skills. (148) In addition, a higher number of conversation turns between parent and child were associated with increased MRI activation of the left inferior frontal gyrus, a key area for language processing. A mediation model showed that the effect of

conversation turns on language was mediated by the left inferior frontal gyrus activation. The identification of this mechanism of parent-child conversation turns affecting brain activation raises the possibility that early enhanced language enrichment in the NICU can affect the language outcomes of preterm infants.

In the Caskey et al cohort, follow-up of the effects of the NICU language environment identified that increased parent talk with preterm infants in the NICU was associated with higher 7- and 18-month corrected age BSID-III language and cognitive scores. (149)(150) Every increase in 100 adult words per hour at 32 weeks' gestation in the NICU was associated with a 2-point increase in BSID language composite score and 0.5-point increase in expressive communication score at age 18 months. (149) These findings support the importance of parent talk in the NICU as a strong predictor of early infant vocalizations and of language outcomes 18 to 24 months after discharge. It is reassuring that more NICUs are initiating parent reading programs in an effort to enrich the infant's language environment in the NICU. (151)(152) Child-directed conversations beginning in the NICU may be the key to improved preterm outcomes. Addressing family social adversities while infants are in the NICU and encouraging involvement of both parents and NICU staff in providing language nutrition and socialization offers the possibility of improving the language outcomes of preterm infants.

SUMMARY

Although extreme prematurity and associated medical morbidities remain risk factors for altered neurobehavior, language delays, and impairments, subgroups of preterm infants can improve their language skills with increasing age. Factors in the NICU environment including parent presence, parent caretaking, joint attention, and IDS have positive effects on early language development. Higher level of maternal education, 2-parent households, and other factors associated with higher socioeconomic status are also linked with improving language outcomes. An optimal language environment provided by both parents and staff in the NICU and subsequently in the home can potentially contribute to improved language and school age outcomes. Provision of multidisciplinary support to families and their infants in the NICU, referral of either parent to appropriate support services as needed, and referral of high-risk preterm infants for early intervention services at NICU discharge are recommended to improve outcomes.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the evolution of neurodevelopmental impairments during development and the difference between transient and permanent impairments in NICU graduates (eg, developmental delay vs. intellectual disability; tone abnormalities vs. cerebral palsy)
- Know the effects of socioeconomic factors on the results and generalizability of outcome studies of NICU graduates
- Know the effects of family risk factors (low socioeconomic status, mental health problems) on cognitive outcomes

References

1. Howard K, Roberts G, Lim J, et al. Biological and environmental factors as predictors of language skills in very preterm children at 5 years of age. *J Dev Behav Pediatr*. 2011;32(3):239–249

2. Caskey M, Vohr B. Assessing language and language environment of high-risk infants and children: a new approach. *Acta Paediatr*. 2013;102(5):451–461

3. Leffel K, Suskind D. Parent-directed approaches to enrich the early language environments of children living in poverty. *Semin Speech Lang*. 2013;34(4):267–278

4. Rand K, Lahav A. Impact of the NICU environment on language deprivation in preterm infants. *Acta Paediatr*. 2014;103(3):243–248

5. 5Lester BM, Andreozzi-Fontaine L, Tronick E, Bigsby R. Assessment and evaluation of the high risk neonate: the NICU Network Neurobehavioral Scale. *J Vis Exp*. 2014;(90). doi: 10.3791/3368

6. Caskey M, Stephens B, Tucker R, Vohr B. Importance of parent talk on the development of preterm infant vocalizations. *Pediatrics*. 2011;128(5):910–916

7. Smith GC, Gutovich J, Smyser C, et al. Neonatal intensive care unit stress is associated with brain development in preterm infants. *Ann Neurol*. 2011;70(4):541–549

8. Pineda R, Durant P, Mathur A, Inder T, Wallendorf M, Schlaggar BL. Auditory exposure in the neonatal intensive care unit: room type and other predictors. *J Pediatr*. 2017;183:56–66.e53

9. Montirosso R, Del Prete A, Bellù R, Tronick E, Borgatti R; Neonatal Adequate Care for Quality of Life (NEO-ACQUA) Study Group. Level of NICU quality of developmental care and neurobehavioral performance in very preterm infants. *Pediatrics*. 2012;129(5):e1129–e1137

10. Felitti VJ, Anda RF, Nordenberg D, et al. Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults. The Adverse Childhood Experiences (ACE) Study. *Am J Preventive Med*. 1998;14(4):245–258

11. Shonkoff JP, Garner AS, Committee on Psychosocial Aspects of Child and Family Health; Committee on Early Childhood, Adoption, and Dependent Care; Section on Developmental and Behavioral Pediatrics. The lifelong effects of early childhood adversity and toxic stress. *Pediatrics*. 2012;129(1):e232–e246

12. Schroeder A, Notaras M, Du X, Hill RA. On the developmental timing of stress: delineating sex-specific effects of stress across development on adult behavior. *Brain Sci.* 2018;8(7):E121

13. van den Bergh BRH, Dahnke R, Mennes M. Prenatal stress and the developing brain: Risks for neurodevelopmental disorders. *Dev Psychopathol.* 2018;30(3):743–762

14. Kapoor A, Dunn E, Kostaki A, Andrews MH, Matthews SG. Fetal programming of hypothalamo-pituitary-adrenal function: prenatal stress and glucocorticoids. *J Physiol.* 2006;572(pt 1):31–44

15. Liu D, Diorio J, Tannenbaum B, et al. Maternal care, hippocampal glucocorticoid receptors, and hypothalamic-pituitary-adrenal responses to stress. *Science.* 1997;277(5332):1659–1662

16. Meaney MJ, Szyf M. Environmental programming of stress responses through DNA methylation: life at the interface between a dynamic environment and a fixed genome. *Dialogues Clin Neurosci.* 2005;7(2):103–123

17. Merlot E, Couret D, Otten W. Prenatal stress, fetal imprinting and immunity. *Brain Behav Immun.* 2008;22(1):42–51

18. Beydoun H, Saftlas AF. Physical and mental health outcomes of prenatal maternal stress in human and animal studies: a review of recent evidence. *Paediatr Perinat Epidemiol.* 2008;22(5):438–466

19. Newnham CA, Inder TE, Milgrom J. Measuring preterm cumulative stressors within the NICU: the Neonatal Infant Stressor Scale. *Early Hum Dev.* 2009;85(9):549–555

20. Carbajal R, Rousset A, Danan C, et al. Epidemiology and treatment of painful procedures in neonates in intensive care units. *JAMA.* 2008;300(1):60–70

21. Grunau RE. Neonatal pain in very preterm infants: long-term effects on brain, neurodevelopment and pain reactivity. *Rambam Maimonides Med J.* 2013;4(4):e0025

22. Cruz MD, Fernandes AM, Oliveira CR. Epidemiology of painful procedures performed in neonates: A systematic review of observational studies. *Eur J Pain.* 2016;20(4):489–498

23. Ozawa M, Sasaki M, Kanda K. Effect of procedure light on the physiological responses of preterm infants. *Jpn J Nurs Sci.* 2010;7(1):76–83

24. Moore ER, Bergman N, Anderson GC, Medley N. Early skin-to-skin contact for mothers and their healthy newborn infants. *Cochrane Database Syst Rev.* 2016;11:CD003519

25. Sharma D, Murki S, Pratap OT. The effect of kangaroo ward care in comparison with "intermediate intensive care" on the growth velocity in preterm infant with birth weight <1100 g: randomized control trial. *Eur J Pediatr.* 2016;175(10):1317–1324

26. Johnston C, Campbell-Yeo M, Disher T, et al. Skin-to-skin care for procedural pain in neonates. *Cochrane Database Syst Rev.* 2017;2:CD008435

27. Moore T, Hennessy EM, Myles J, et al. Neurological and developmental outcome in extremely preterm children born in England in 1995 and 2006: the EPICure studies. *BMJ.* 2012;345:e7961

28. Casper C, Sarapuk I, Pavlyshyn H. Regular and prolonged skin-to-skin contact improves short-term outcomes for very preterm infants: a dose-dependent intervention. *Arch Pediatr.* 2018;25(8):469–475

29. Niela-Vilén H, Axelin A, Salanterä S, et al. Early physical contact between a mother and her NICU-infant in two university hospitals in Finland. *Midwifery.* 2013;29(12):1321–1330

30. Strand H, Blomqvist YT, Gradin M, Nyqvist KH. Kangaroo mother care in the neonatal intensive care unit: staff attitudes and beliefs and opportunities for parents. *Acta Paediatr.* 2014;103(4):373–378

31. Mendelson T, Cluxton-Keller F, Vullo GC, Tandon SD, Noazin S. NICU-based interventions to reduce maternal depressive and anxiety symptoms: a meta-analysis. *Pediatrics.* 2017;139(3):e20161870

32. Shorey S, He HG, Morelius E. Skin-to-skin contact by fathers and the impact on infant and paternal outcomes: an integrative review. *Midwifery.* 2016;40:207–217

33. Athanasopoulou E, Fox JR. Effects of kangaroo mother care on maternal mood and interaction patterns between parents and their preterm, low birth weight infants: a systematic review. *Infant Ment Health J.* 2014;35(3):245–262

34. Chan G, Bergelson I, Smith ER, Skotnes T, Wall S. Barriers and enablers of kangaroo mother care implementation from a health systems perspective: a systematic review. *Health Policy Plan.* 2017;32(10):1466–1475

35. Flacking R, Lehtonen L, Thomson G, et al; Separation and Closeness Experiences in the Neonatal Environment (SCENE) group. Closeness and separation in neonatal intensive care. *Acta Paediatr.* 2012;101(10):1032–1037

36. Jackson K, Ternestedt BM, Schollin J. From alienation to familiarity: experiences of mothers and fathers of preterm infants. *J Adv Nurs.* 2003;43(2):120–129

37. Flacking R, Ewald U, Nyqvist KH, Starrin B. Trustful bonds: a key to "becoming a mother" and to reciprocal breastfeeding. Stories of mothers of very preterm infants at a neonatal unit. *Soc Sci Med.* 2006;62(1):70–80

38. Franck LS, Cox S, Allen A, Winter I. Measuring neonatal intensive care unit-related parental stress. *J Adv Nurs.* 2005;49(6):608–615

39. Brandon DH, Tully KP, Silva SG, et al. Emotional responses of mothers of late-preterm and term infants. *J Obstet Gynecol Neonatal Nurs.* 2011;40(6):719–731

40. Harris R, Gibbs D, Mangin-Heimos K, Pineda R. Maternal mental health during the neonatal period: Relationships to the occupation of parenting. *Early Hum Dev.* 2018;120:31–39

41. Tahirkheli NN, Cherry AS, Tackett AP, McCaffree MA, Gillaspy SR. Postpartum depression on the neonatal intensive care unit: current perspectives. *Int J Womens Health.* 2014;6:975–987

42. Trumello C, Candelori C, Cofini M, et al. Mothers' depression, anxiety, and mental representations after preterm birth: a study during the infant's hospitalization in a neonatal intensive care unit. *Front Public Health.* 2018;6:359

43. Greene MM, Rossman B, Patra K, Kratovil A, Khan S, Meier PP. Maternal psychological distress and visitation to the neonatal intensive care unit. *Acta Paediatr.* 2015;104(7):e306–e313

44. Gonya J, Nelin LD. Factors associated with maternal visitation and participation in skin-to-skin care in an all referral level IIIc NICU. *Acta Paediatr.* 2013;102(2):e53–e56

45. McGowan EC, Du N, Hawes K, Tucker R, O'Donnell M, Vohr B. Maternal mental health and neonatal intensive care unit discharge readiness in mothers of preterm infants. *J Pediatr.* 2017;184:68–74

46. Hynan MT, Hall SL. Psychosocial program standards for NICU parents. *J Perinatol.* 2015;35(suppl 1):S1–S4

47. Hynan MT, Steinberg Z, Baker L, et al. Recommendations for mental health professionals in the NICU. *J Perinatol.* 2015;35(suppl 1):S14–S18

48. Hall SL, Ryan DJ, Beatty J, Grubbs L. Recommendations for peer-to-peer support for NICU parents. *J Perinatol.* 2015;35(suppl 1):S9–S13

49. Sanders MR, Hall SL. Trauma-informed care in the newborn intensive care unit: promoting safety, security and connectedness. *J Perinatol.* 2018;38(1):3–10

50. D'Agata AL, Young EE, Cong X, Grasso DJ, McGrath JM. Infant Medical Trauma in the Neonatal Intensive Care Unit (IMTN): a proposed concept for science and practice. *Adv Neonatal Care.* 2016;16(4):289–297

51. Melnyk BM, Alpert-Gillis L, Feinstein NF, et al. Improving cognitive development of low-birth-weight premature infants with the COPE program: a pilot study of the benefit of early NICU intervention with mothers. *Res Nurs Health.* 2001;24(5):373–389

52. Borimnejad L, Mehrnoosh N, Fatemi NS, Haghani H. Impacts of creating opportunities for parent empowerment on maternal stress: a quasi-experimental study. *Iran J Nurs Midwifery Res.* 2013;18(3):218–221

53. Mianaei SJ, Karahroudy FA, Rassouli M, Tafreshi MZ. The effect of Creating Opportunities for Parent Empowerment program on maternal stress, anxiety, and participation in NICU wards in Iran. *Iran J Nurs Midwifery Res.* 2014;19(1):94–100

54. Melnyk BM, Feinstein NF, Alpert-Gillis L, et al. Reducing premature infants' length of stay and improving parents' mental health outcomes with the Creating Opportunities for Parent Empowerment (COPE) neonatal intensive care unit program: a randomized, controlled trial. *Pediatrics.* 2006;118(5):e1414–e1427

55. Newnham CA, Milgrom J, Skouteris H. Effectiveness of a modified Mother-Infant Transaction Program on outcomes for preterm infants from 3 to 24 months of age. *Infant Behav Dev.* 2009;32(1):17–26

56. Milgrom J, Newnham C, Martin PR, et al. Early communication in preterm infants following intervention in the NICU. *Early Hum Dev.* 2013;89(9):755–762

57. Ravn IH, Smith L, Smeby NA, et al. Effects of early mother-infant intervention on outcomes in mothers and moderately and late preterm infants at age 1 year: a randomized controlled trial. *Infant Behav Dev.* 2012;35(1):36–47

58. Landsem IP, Handegård BH, Tunby J, Ulvund SE, Rønning JA. Early intervention program reduces stress in parents of preterms during childhood, a randomized controlled trial. *Trials.* 2014;15:387

59. Landsem IP, Handegård BH, Ulvund SE, Tunby J, Kaaresen PI, Rønning JA. Does an early intervention influence behavioral development until age 9 in children born prematurely? *Child Dev.* 2015;86(4):1063–1079

60. Nordhov SM, Rønning JA, Ulvund SE, Dahl LB, Kaaresen PI. Early intervention improves behavioral outcomes for preterm infants: randomized controlled trial. *Pediatrics.* 2012;129(1):e9–e16

61. Sabnis A, Fojo S, Nayak SS, Lopez E, Tarn DM, Zeltzer L. Reducing parental trauma and stress in neonatal intensive care: systematic review and meta-analysis of hospital interventions. *J Perinatol.* 2019;39(3):375–386

62. Patel N, Ballantyne A, Bowker G, Weightman J, Weightman S; Helping Us Grow Group (HUGG). Family Integrated Care: changing the culture in the neonatal unit. *Arch Dis Child.* 2018;103(5):415–419

63. Ortenstrand A, Westrup B, Broström EB, et al. The Stockholm Neonatal Family Centered Care Study: effects on length of stay and infant morbidity. *Pediatrics.* 2010;125(2):e278–e285

64. Bhutta ZA, Khan I, Salat S, Raza F, Ara H. Reducing length of stay in hospital for very low birthweight infants by involving mothers in a stepdown unit: an experience from Karachi (Pakistan). *BMJ.* 2004;329(7475):1151–1155

65. Roué JM, Kuhn P, Lopez Maestro M, et al. Eight principles for patient-centred and family-centred care for newborns in the neonatal intensive care unit. *Arch Dis Child Fetal Neonatal Ed.* 2017;102(4):F364–F368

66. O'Brien K, Robson K, Bracht M, et al; FICare Study Group and FICare Parent Advisory Board. Effectiveness of Family Integrated Care in neonatal intensive care units on infant and parent outcomes: a multicentre, multinational, cluster-randomised controlled trial. *Lancet Child Adolesc Health.* 2018;2(4):245–254

67. Domanico R, Davis DK, Coleman F, Davis BO. Documenting the NICU design dilemma: comparative patient progress in open-ward and single family room units. *J Perinatol.* 2011;31(4):281–288

68. Jones R, Jones L, Feary AM. The effects of single-family rooms on parenting behavior and maternal psychological factors. *J Obstet Gynecol Neonatal Nurs.* 2016;45(3):359–370

69. Erdeve O, Arsan S, Yigit S, Armangil D, Atasay B, Korkmaz A. The impact of individual room on rehospitalization and health service utilization in preterms after discharge. *Acta Paediatr.* 2008;97(10):1351–1357

70. Stevens DC, Helseth CC, Thompson PA, Pottala JV, Khan MA, Munson DP. A comprehensive comparison of open-bay and single-family-room neonatal intensive care units at Sanford Children's Hospital. *HERD.* 2012;5(4):23–39

71. Lester BM, Hawes K, Abar B, et al. Single-family room care and neurobehavioral and medical outcomes in preterm infants. *Pediatrics.* 2014;134(4):754–760

72. van Veenendaal NR, Heideman WH, Limpens J, et al. Hospitalising preterm infants in single family rooms versus open bay units: a systematic review and meta-analysis. *Lancet Child Adolesc Health.* 2019;3(3):147–157

73. 73Carter BS, Carter A, Bennett S. Families' views upon experiencing change in the neonatal intensive care unit environment: from the 'baby barn' to the private room. *J Perinatol.* 2008;28(12):827–829

74. Stevens DC, Helseth CC, Khan MA, Munson DP, Reid EJ. A comparison of parent satisfaction in an open-bay and single-family room neonatal intensive care unit. *HERD.* 2011;4(3):110–123

75. Toivonen M, Lehtonen L, Löyttyniemi E, Axelin A. Effects of single-family rooms on nurse-parent and nurse-infant interaction in neonatal intensive care unit. *Early Hum Dev.* 2017;106-107:59–62

76. Bodack E, Schenk O, Karutz H. Single patient room design in the neonatal intensive care unit - parent perceptions of open ward vs. single patient room units [in German]. *Z Geburtshilfe Neonatol.* 2016;220(3):124–129

77. Tandberg BS, Frøslie KF, Flacking R, Grundt H, Lehtonen L, Moen A. Parent-infant closeness, parents' participation, and nursing support in single-family room and open bay NICUs. *J Perinat Neonatal Nurs.* 2018;32(4):E22–E32

78. Pineda R, Bender J, Hall B, Shabosky L, Annecca A, Smith J. Parent participation in the neonatal intensive care unit: Predictors and relationships to neurobehavior and developmental outcomes. *Early Hum Dev.* 2018;117:32–38

79. Northrup TF, Evans PW, Lillie ML, Tyson JE. A free parking trial to increase visitation and improve extremely low birth weight infant outcomes. *J Perinatol.* 2016;36(12):1112–1115

80. Lester BM, Salisbury AL, Hawes K, et al. 18-Month follow-up of infants cared for in a single-family room neonatal intensive care unit. *J Pediatr.* 2016;177:84–89

81. Vohr B, McGowan E, McKinley L, Tucker R, Keszler L, Alksninis B. Differential effects of the single-family room neonatal intensive care unit on 18- to 24-Month Bayley Scores of preterm infants. *J Pediatr.* 2017;185:42–48.e1

82. Pineda RG, Neil J, Dierker D, et al. Alterations in brain structure and neurodevelopmental outcome in preterm infants hospitalized

in different neonatal intensive care unit environments. *J Pediatr.* 2014;164(1):52–60.e52

83. Lester BM, Tronick EZ, Brazelton TB. The Neonatal Intensive Care Unit Network Neurobehavioral Scale procedures. *Pediatrics.* 2004;113(3 pt 2):641–667

84. Eeles AL, Walsh JM, Olsen JE, et al. Continuum of neurobehaviour and its associations with brain MRI in infants born preterm. *BMJ Paediatr Open.* 2017;1(1):e000136

85. Eeles AL, Olsen JE, Walsh JM, et al. Reliability of neurobehavioral assessments from birth to term equivalent age in preterm and term born infants. *Phys Occup Ther Pediatr.* 2017;37(1):108–119

86. Lester BM, Tronick EZ, LaGasse L, et al. The maternal lifestyle study: effects of substance exposure during pregnancy on neurodevelopmental outcome in 1-month-old infants. *Pediatrics.* 2002;110(6):1182–1192

87. LaGasse LL, Wouldes T, Newman E, et al. Prenatal methamphetamine exposure and neonatal neurobehavioral outcome in the USA and New Zealand. *Neurotoxicol Teratol.* 2011;33(1):166–175

88. Jones HE, O'Grady KE, Johnson RE, Velez M, Jansson LM. Infant neurobehavior following prenatal exposure to methadone or buprenorphine: results from the neonatal intensive care unit network neurobehavioral scale. *Subst Use Misuse.* 2010;45(13):2244–2257

89. Barros MC, Mitsuhiro SS, Chalem E, Laranjeira RR, Guinsburg R. Depression during gestation in adolescent mothers interferes with neonatal neurobehavior. *Br J Psychiatry.* 2013;35(4):353–359

90. Massaro AN, Evangelou I, Brown J, et al. Neonatal neurobehavior after therapeutic hypothermia for hypoxic ischemic encephalopathy. *Early Hum Dev.* 2015;91(10):593–599

91. Montirosso R, Del Prete A, Cavallini A, Cozzi P; Gruppo di Studio NEO-ACQUA. Neurobehavioral profile in a group of healthy preterm infants: utilization of the NICU Network Neurobehavioral Scale (NNNS). *Child Dev Disabil Saggi.* 2009;3:96–116. doi: 10.3280/CDD2009-003005

92. Brown NC, Doyle LW, Bear MJ, Inder TE. Alterations in neurobehavior at term reflect differing perinatal exposures in very preterm infants. *Pediatrics.* 2006;118(6):2461–2471

93. Brown NC, Inder TE, Bear MJ, Hunt RW, Anderson PJ, Doyle LW. Neurobehavior at term and white and gray matter abnormalities in very preterm infants. *J Pediatr.* 2009;155(1):32–38.e31

94. Lester BM, Marsit CJ, Giarraputo J, Hawes K, LaGasse LL, Padbury JF. Neurobehavior related to epigenetic differences in preterm infants. *Epigenomics.* 2015;7(7):1123–1136

95. Liu J, Bann C, Lester B, et al. Neonatal neurobehavior predicts medical and behavioral outcome. *Pediatrics.* 2010;125(1):e90–e98

96. Gonya J, Feldman K, Brown K, et al. Human interaction in the NICU and its association with outcomes on the Brief Infant-Toddler Social and Emotional Assessment (BITSEA). *Early Hum Dev.* 2018;127:6–14

97. Lean RE, Rogers CE, Paul RA, Gerstein ED. NICU hospitalization: long-term implications on parenting and child behaviors. *Curr Treat Options Pediatr.* 2018;4(1):49–69

98. Lagercrantz H. Are extremely preterm born children with autism the victims of too much isolation in the incubator? *Acta Paediatr.* 2017;106(8):1246–1247

99. Huppertz-Kessler CJ, Verveur D, Pöschl J. To what degree does the NICU environment influence neurodevelopment of preterm infants [in German]? *Klin Padiatr.* 2010;222(4):236–242

100. Grunau RE, Whitfield MF, Petrie-Thomas J, et al. Neonatal pain, parenting stress and interaction, in relation to cognitive and motor development at 8 and 18 months in preterm infants. *Pain.* 2009;143(1-2):138–146

101. Casavant SG, Bernier K, Andrews S, Bourgoin A. Noise in the neonatal intensive care unit: what does the evidence tell us? *Adv Neonatal Care.* 2017;17(4):265–273

102. Chawla S, Barach P, Dwaihy M, et al. A targeted noise reduction observational study for reducing noise in a neonatal intensive unit. *J Perinatol.* 2017;37(9):1060–1064

103. Birnholz JC, Benacerraf BR. The development of human fetal hearing. *Science.* 1983;222(4623):516–518

104. Kisilevsky BS, Hains SM, Brown CA, et al. Fetal sensitivity to properties of maternal speech and language. *Infant Behav Dev.* 2009;32(1):59–71

105. DeCasper AJ, Fifer WP. Of human bonding: newborns prefer their mothers' voices. *Science.* 1980;208(4448):1174–1176

106. Rand K, Lahav A. Maternal sounds elicit lower heart rate in preterm newborns in the first month of life. *Early Hum Dev.* 2014;90(10):679–683

107. Doheny L, Morey JA, Ringer SA, Lahav A. Reduced frequency of apnea and bradycardia episodes caused by exposure to biological maternal sounds. *Pediatr Int.* 2012;54(2):e1–e3

108. Zimmerman E, Keunen K, Norton M, Lahav A. Weight gain velocity in very low-birth-weight infants: effects of exposure to biological maternal sounds. *Am J Perinatol.* 2013;30(10):863–870

109. Bozzette M. Healthy preterm infant responses to taped maternal voice. *J Perinat Neonatal Nurs.* 2008;22(4):307–318

110. Krueger C, Parker L, Chiu SH, Theriaque D. Maternal voice and short-term outcomes in preterm infants. *Dev Psychobiol.* 2010;52(2):205–212

111. Picciolini O, Porro M, Meazza A, et al. Early exposure to maternal voice: effects on preterm infants development. *Early Hum Dev.* 2014;90(6):287–292

112. van Noort-van der Spek IL, Franken MC, Weisglas-Kuperus N. Language functions in preterm-born children: a systematic review and meta-analysis. *Pediatrics.* 2012;129(4):745–754

113. Foster-Cohen SH, Friesen MD, Champion PR, Woodward LJ. High prevalence/low severity language delay in preschool children born very preterm. *J Dev Behav Pediatr.* 2010;31(8):658–667

114. Luu TM, Vohr BR, Allan W, Schneider KC, Ment LR. Evidence for catch-up in cognition and receptive vocabulary among adolescents born very preterm. *Pediatrics.* 2011;128(2):313–322

115. Foster-Cohen S, Edgin JO, Champion PR, Woodward LJ. Early delayed language development in very preterm infants: evidence from the MacArthur-Bates CDI. *J Child Lang.* 2007;34(3):655–675

116. Sansavini A, Guarini A, Alessandroni R, Faldella G, Giovanelli G, Salvioli G. Are early grammatical and phonological working memory abilities affected by preterm birth? *J Commun Disord.* 2007;40(3):239–256

117. Jansson-Verkasalo E, Korpilahti P, Jäntti V, et al. Neurophysiologic correlates of deficient phonological representations and object naming in prematurely born children. *Clin Neurophysiol.* 2004;115(1):179–187

118. Luu TM, Vohr BR, Schneider KC, et al. Trajectories of receptive language development from 3 to 12 years of age for very preterm children. *Pediatrics.* 2009;124(1):333–341

119. Omizzolo C, Scratch SE, Stargatt R, et al. Neonatal brain abnormalities and memory and learning outcomes at 7 years in children born very preterm. *Memory.* 2014;22(6):605–615

120. Pietz J, Peter J, Graf R, et al. Physical growth and neurodevelopmental outcome of nonhandicapped low-risk children born preterm. *Early Hum Dev.* 2004;79(2):131–143

121. Vohr BR. Language and hearing outcomes of preterm infants. *Semin Perinatol.* 2016;40(8):510–519

122. Wolke D, Samara M, Bracewell M, Marlow N; EPICure Study Group. Specific language difficulties and school achievement in children born at 25 weeks of gestation or less. *J Pediatr.* 2008;152(2):256–262

123. Lowe JR, Fuller JF, Do BT, et al; Eunice Kennedy Shriver National Institute of Child Health; Human Development Neonatal Research Network. Behavioral problems are associated with cognitive and language scores in toddlers born extremely preterm. *Early Hum Dev.* 2019;128:48–54

124. Sanchez K, Spittle AJ, Cheong JL, et al. Language in 2-year-old children born preterm and term: a cohort study [published online ahead of print November 23]. *Arch Dis Child.* 2018

125. Lowe JR, Nolen TL, Vohr B, Adams-Chapman I, Duncan AF, Watterberg K. Effect of primary language on developmental testing in children born extremely preterm. *Acta Paediatr.* 2013;102(9):896–900

126. Duncan AF, Watterberg KL, Nolen TL, et al. Effect of ethnicity and race on cognitive and language testing at age 18-22 months in extremely preterm infants. *J Pediatr.* 2012;160(6):966–971.e962

127. Lean RE, Paul RA, Smyser CD, Rogers CE. Maternal intelligence quotient (IQ) predicts IQ and language in very preterm children at age 5 years. *J Child Psychol Psychiatry.* 2018;59(2):150–159

128. Lean RE, Paul RA, Smyser TA, Smyser CD, Rogers CE. Social adversity and cognitive, language, and motor development of very preterm children from 2 to 5 years of age. *J Pediatr.* 2018;203:177–184.e171

129. Hüppi PS, Warfield S, Kikinis R, et al. Quantitative magnetic resonance imaging of brain development in premature and mature newborns. *Ann Neurol.* 1998;43(2):224–235

130. Inder TE, Warfield SK, Wang H, Hüppi PS, Volpe JJ. Abnormal cerebral structure is present at term in premature infants. *Pediatrics.* 2005;115(2):286–294

131. Lubsen J, Vohr B, Myers E, et al. Microstructural and functional connectivity in the developing preterm brain. *Semin Perinatol.* 2011;35(1):34–43

132. Peterson BS, Vohr B, Staib LH, et al. Regional brain volume abnormalities and long-term cognitive outcome in preterm infants. *JAMA.* 2000;284(15):1939–1947

133. Kesler SR, Ment LR, Vohr B, et al. Volumetric analysis of regional cerebral development in preterm children. *Pediatr Neurol.* 2004;31(5):318–325

134. Constable RT, Ment LR, Vohr BR, et al. Prematurely born children demonstrate white matter microstructural differences at 12 years of age, relative to term control subjects: an investigation of group and gender effects. *Pediatrics.* 2008;121(2):306–316

135. Monson BB, Eaton-Rosen Z, Kapur K, et al. Differential rates of perinatal maturation of human primary and nonprimary auditory cortex. *eNeuro.* 2018;5(1). doi: 10.1523/ENEURO.0380-17.2017

136. Ramírez-Esparza N, García-Sierra A, Kuhl PK. Look who's talking: speech style and social context in language input to infants are linked to concurrent and future speech development. *Dev Sci.* 2014;17(6):880–891

137. Naoi N, Minagawa-Kawai Y, Kobayashi A, et al. Cerebral responses to infant-directed speech and the effect of talker familiarity. *Neuroimage.* 2012;59(2):1735–1744

138. Saito Y, Aoyama S, Kondo T, et al. Frontal cerebral blood flow change associated with infant-directed speech. *Arch Dis Child Fetal Neonatal Ed.* 2007;92(2):F113–F116

139. Saito Y, Kondo T, Aoyama S, et al. The function of the frontal lobe in neonates for response to a prosodic voice. *Early Hum Dev.* 2007;83(4):225–230

140. Webb AR, Heller HT, Benson CB, Lahav A. Mother's voice and heartbeat sounds elicit auditory plasticity in the human brain before full gestation. *Proc Natl Acad Sci USA.* 2015;112(10):3152–3157

141. Peterson BS, Vohr B, Kane MJ, et al. A functional magnetic resonance imaging study of language processing and its cognitive correlates in prematurely born children. *Pediatrics.* 2002;110(6):1153–1162

142. Luu TM, Ment LR, Schneider KC, Katz KH, Allan WC, Vohr BR. Lasting effects of preterm birth and neonatal brain hemorrhage at 12 years of age. *Pediatrics.* 2009;123(3):1037–1044

143. Luu TM, Ment L, Allan W, Schneider K, Vohr BR. Executive and memory function in adolescents born very preterm. *Pediatrics.* 2011;127(3):e639–e646

144. Nguyen TN, Spencer-Smith M, Haebich KM, et al. Language trajectories of children born very preterm and full term from early to late childhood. *J Pediatr.* 2018;202:86–91.e81

145. Hart B, Risley TR. *Meaningful Differences in the Everyday Experience of Young American Children.* Baltimore, MD: PH Brookes; 1995

146. Fernald A, Marchman VA, Weisleder A. SES differences in language processing skill and vocabulary are evident at 18 months. *Dev Sci.* 2013;16(2):234–248

147. Schafer RJ, Lacadie C, Vohr B, et al. Alterations in functional connectivity for language in prematurely born adolescents. *Brain.* 2009;132(Pt 3):661–670

148. Romeo RR, Leonard JA, Robinson ST, et al. Beyond the 30-million-word gap: children's conversational exposure is associated with language-related brain function. *Psychol Sci.* 2018;29(5):700–710

149. Caskey M, Stephens B, Tucker R, Vohr B. Adult talk in the NICU with preterm infants and developmental outcomes. *Pediatrics.* 2014;133(3):e578–e584

150. Bayley N. *Bayley Scales of Infant and Toddler Development.* 3rd ed. San Antonio, TX: Harcourt Assessment, Inc; 2006

151. Rubinos LH, Brown M, Bahrami L, Christ L, Hurt H. 'The story behind NICU reading programs'. *J Perinatol.* 2016;36(11):930–931

152. Darcy Mahoney A, Zauche LH, Hallowell S, Weldon A, Stapel-Wax J. Leveraging the skills of nurses and the power of language nutrition to ensure a better future for children. *Adv Neonatal Care.* 2017;17(1):45–52

NeoReviews Quiz

1. The landmark Adverse Childhood Experiences Study was the first to demonstrate the adverse effects of chronic stress exposure on long-term health outcomes. Preterm infants admitted to the NICU are exposed to daily stressors; in addition, they experience separation from their mother at a critical period of their development. Which of the following statements regarding the NICU environment and exposure to stress is CORRECT?

   A. A recent systematic review reported an average of 20 to 25 daily invasive procedures per neonate per day in the NICU.
   B. Consistent and prolonged skin-to-skin care has been shown to reduce the rates of bronchopulmonary dysplasia and nosocomial infections in preterm infants.
   C. Concerns for adverse medical consequences are the main deterrent to skin-to-skin care.
   D. Poor maternal mental health has been shown to lead to decreased participation at the bedside, but not decreased visitation.
   E. Skin-to-skin care has been shown to ameliorate procedural pain in term infants but not in preterm infants.

2. Family-centered care recognizes the importance of parents as key caregivers for their infant and may be an important avenue to buffer acute and chronic stress in the NICU. Which of the following statements regarding interventions to encourage and facilitate parental participation is CORRECT?

   A. Family Integrated Care (FICare) is a model of care fostering parent participation as early as the day of admission.
   B. Improvement noted in the Mother-Infant Transaction Program (MITP) trial did not persist into early childhood.
   C. The Creating Opportunities for Parent Empowerment (COPE) randomized controlled trial demonstrated improved breastfeeding rates in the intervention group compared with the control group.
   D. The FICare model requires maternal participation for a minimum of 6 hours weekly.
   E. The MITP focuses on strengthening mothers' knowledge of breastfeeding techniques and benefits.

3. NICU design plays an important role in facilitating family-centered care. Single-family rooms (SFRs) are increasingly being adopted to support NICU families. Which of the following statements regarding SFR NICUs is CORRECT?

   A. In a cohort study, Vohr et al (81) reported a 4.5-point increase in Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III) at 18 to 24 months for infants cared for in an SFR NICU.
   B. In a Norwegian prospective study, mothers in the SFR NICU spent more time at the bedside, particularly those with lower education level.
   C. In a recent meta-analysis by van Veenendaal et al, (72) infants in SFR NICUs had increased rates of exclusive breastfeeding and decreased length of stay.
   D. Pineda et al (82) found lower language and motor scores in a cohort of preterm infants cared for in SFRs.
   E. The benefits of an SFR NICU are independent of insurance type.

4. Social and sensory deprivation are now recognized as possible factors in adverse neurodevelopmental outcomes in preterm infants. Which of the following statements regarding the noise and language environment of the NICU is INCORRECT?

   A. Preterm infants exposed to a recording of their mothers' voice have decreased apnea and bradycardia and increased weight gain velocity.
   B. Preterm infants respond preferentially to their mother's voice over other female voices as early as 32 weeks' gestation.
   C. Studies indicate that the average sound level in the NICU is typically 45 dB, which meets the 25 dB recommended by the American Academy of Pediatrics; however, there are peaks that can sometimes exceed 100 dB in some instances.
   D. The fetus demonstrates consistent response to vibroacoustic stimuli by 27 to 28 weeks' gestation.
   E. Very preterm infant vocalizations increase between 32 and 36 weeks' gestation.

5. Preterm infants are at risk for language delays. Which of the following statements regarding language development and language outcomes in preterm infants is INCORRECT?

   A. Every increase in 100 adult words per hour at 32 weeks' gestation is associated with a 2-point increase in BSID-III language composite score.
   B. In the indomethacin cohort of infants, no catch-up on the Peabody Picture Vocabulary test was observed between 3 and 12 years.
   C. Poorer language developmental trajectories are observed in 40% of very preterm infants versus 6% of term infants.
   D. Preterm infants exposed to more parent talk have higher 7- and 18-month corrected age BSID-III language and cognitive scores.
   E. Very preterm infants demonstrate deficits in phonological awareness and phonemic decoding at age 16 years.

Impact of Nonmedical Factors on Neurobehavior and Language Outcomes of Preterm Infants

Elisabeth C. McGowan and Betty R. Vohr

Updated Information & Services	including high resolution figures, can be found at: http://neoreviews.aappublications.org/content/20/7/e372
References	This article cites 147 articles, 29 of which you can access for free at: http://neoreviews.aappublications.org/content/20/7/e372.full#ref-list-1
Subspecialty Collections	This article, along with others on similar topics, appears in the following collection(s): **Pediatric Drug Labeling Update** http://classic.neoreviews.aappublications.org/cgi/collection/pediatric_drug_labeling_update
Permissions & Licensing	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: https://shop.aap.org/licensing-permissions/
Reprints	Information about ordering reprints can be found online: http://classic.neoreviews.aappublications.org/content/reprints

Impact of Nonmedical Factors on Neurobehavior and Language Outcomes of Preterm Infants

Elisabeth C. McGowan and Betty R. Vohr

The online version of this article, along with updated information and services, is
located on the World Wide Web at:
http://neoreviews.aappublications.org/content/20/7/e372

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN®