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Impact of Hospital-Based Environmental Exposures on Neurodevelopmental Outcomes of Preterm Infants

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Abstract

Purpose of review—Over 300,000 infants are hospitalized in a neonatal intensive care unit (NICU) in the United States annually during a developmental period critical to later neurobehavioral function. Environmental exposures during the fetal period and infancy have been shown to impact long-term neurobehavioral outcomes. This review summarizes evidence linking NICU-based environmental exposures to neurodevelopmental outcomes of children born preterm,

Recent findings—Preterm infants experience multiple exposures important to neurodevelopment during the NICU hospitalization. The physical layout of the NICU, management of light and sound, social interactions with parents and NICU staff, and chemical exposures via medical equipment are important to long-term neurobehavioral outcomes in this highly vulnerable population.

Summary—Existing research documents NICU-based exposure to 1) neurotoxic chemicals, 2) aberrant light, 3) excess sound, and 4) restricted social interaction. In total, this creates an environment of co-existing excesses (chemicals, light, sound) and deprivation (touch, speech). The full impact of these co-exposures on the long-term neurodevelopment of preterm infants has not been adequately elucidated. Research into the importance of the NICU from an environmental health perspective is in its infancy, but could provide understanding about critical modifiable factors impacting the neurobehavioral health of hundreds of thousands of children each year.

Keywords

preterm birth; environmental health; neonatal intensive care unit; neurodevelopmental outcomes; neonate; chemical exposure; noise; light; sound; kangaroo care; NICU

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INTRODUCTION

The impact of the early life environment, broadly defined, on later child health and development is well recognized in both the scientific literature and lay press. Each year in the United States, hundreds of thousands of children spend a significant period of time in the hospital during infancy and early childhood. Although the hospital environment likely impacts developmental outcomes of all hospitalized children, the bulk of existing research in this field has focused on the neonatal intensive care unit (NICU). Preterm infants may spend months in the NICU during a critically important developmental period. The importance of hospital-based environmental exposures on long-term physical, psychological, and neurodevelopmental outcomes is now recognized (Figure 1). This review summarizes evidence linking NICU environmental exposures to neurodevelopmental outcomes of children born preterm, with a focus on human rather than animal or *in vitro* studies.

CHEMICAL EXPOSURE

Babies born preterm spend all or part of the third trimester developmental window in the NICU where *ex utero* hospital-based exposure to potentially harmful chemicals can be high. (1-5) Exposure to ubiquitous organic chemicals such as phthalates and phenols during this developmental period is associated with adverse neurodevelopmental outcomes.(6-12) Preterm infants have immature hepatic glucuronidation and renal clearance mechanisms that limit their ability to clear chemicals from the body. Small body size and a high surface area to body mass ratio put newborns at risk for higher mass per kilogram body weight exposure than older children or adults. Infants admitted to the NICU therefore represent a population particularly vulnerable to the effect of chemical exposures.

Phthalates and phenols are common constituents of medical materials used in NICU care. (13-15) Contaminating metals are also present in plastic materials. For example, silver is added to IV catheter components as an antimicrobial,(16) and parenteral nutrition (PN), frequently administered for long duration in the NICU, contains elemental metals that are generally not dosed with consideration for gestational maturity or size.(17, 18)

Five studies have linked the use of medical devices to elevated biomarkers of phthalate and phenol exposure in NICU inpatients.(1-5) In 2004, Calafat *et al.*(1) demonstrated that the use of plastic medical equipment is strongly associated with elevated urinary biomarkers of phthalates. The study found that infants undergoing high-intensity medical treatment had urinary phthalate metabolite concentrations significantly greater than infants undergoing low-intensity treatment or than the general population. These findings were confirmed in larger studies, and expanded to show similar associations between exposure to plastic intensive care equipment and biomarkers of phenol exposure.(2-5)

Only two studies have evaluated the association between hospital-based phthalate exposure during infancy and outcomes (timing of puberty, childhood growth, and cholestasis)(19, 20). Neither study used prospective or validated exposure assessment methods to characterize initial exposure, however, nor evaluated neurobehavioral outcomes specifically.

In 1997, Bishop *et al.*(17) published a randomized trial of standard vs aluminum-depleted PN in the NICU. They found that infants exposed to standard PN performed significantly worse on the Bayley Scales of Infant and Toddler Development than those who received less aluminum. Guidelines for aluminum content of PN were subsequently changed to restrict aluminum exposure. Studies of exposure to other metals in the NICU have not been published.

SOUND

Sound is a vibration that propagates by a mechanical wave of pressure and displacement. (21) Both sound frequency and intensity can be measured. In the hospital setting, sound can be categorized as speech, equipment noise, therapeutic sound, and ambient noise of staff activity. In 1997, The American Academy of Pediatrics recommended that noise intensity in the NICU should remain below 45 dB;(22) however, noise exceeding these levels in the NICU is well documented.(23-25) Mean sound intensity of 53.9-61dB for up to 94% of the day has been documented in multiple NICU-based studies.(24-26) This noise is largely attributable to the sound of staff activity, rather than equipment noise or directed speech.(25)

Loud noises have negative short-term physiological effects on preterm infants including increased heart rate, decreased oxygen saturation, increased blood pressure, changes in respiratory rate, apnea, and alterations in sleep-wake state.(23, 27) NICU-based noise reduction interventions have been explored using earmuffs(28) and earplugs.(29, 30) The use of earmuffs is associated with improvements in mean oxygen saturation and oxygen saturation fluctuation.(28) The use of earplugs is associated with improved weight gain,(29) and improved sleep with decreased fussy behavior.(30) Noise reduction has not been directly associated with improved long-term neurocognitive performance in any study, although both cardiorespiratory stability and weight gain during the NICU hospitalization are associated with improved long-term neurobehavioral outcomes.(31, 32)

Therapeutic Sound

The use of entrained breathing and heart sounds has been shown to increase oxygen saturation, nonnutritive sucking, and weight gain.(33) Music therapy in the NICU has been shown to prolong time spent with a normal heart rate, increase oxygen saturation, increase the amount of time spent sleeping,(34, 35) and calm previously agitated infants.(36, 37) A meta-analysis of music therapy in the NICU showed significant benefits on measures of heart rate, behavioral state, oxygen saturation, sucking/feeding ability, and length of stay.(38)

Speech

The maternal voice *in-utero* is an important stimulus for development.(39) It is widely acknowledged that the fetus perceives and reacts to sound starting from 26-28 weeks gestation(40) and that the capacity for prenatal learning and language acquisition can begin as early as 35 weeks.(41) Exposure to the maternal voice in the NICU has been associated with fewer episodes of feeding intolerance(39) as well as more stable oxygen saturation levels and heart rate, and more time spent in the quiet-alert state.(42)

Doheny *et al.*(43) examined the frequency of negative cardiorespiratory events in infants exposed to a recording of maternal voice and heartbeat sounds. Improved cardiorespiratory stability was observed during the intervention in infants 33 weeks post-menstrual age (PMA), suggesting a therapeutic window for such an intervention.

Picciolini *et al.*(44) exposed preterm infants to maternal voice through bone conduction, mimicking the way a fetus hear its mother's voice *in utero*.(45) Infants in the treatment group had lower heart rate variability and less skin mottling than the control group. Moreover, the treatment group performed better in visual orientation and general movement assessments at term. At three months corrected age, the intervention group also received better scores on a neurofunctional assessment. However, no difference was seen amongst scores at 6 months of age. This study suggests that maternal voice through bone conduction may promote physiologic maturation of the infant's auditory system, which could in turn positively impact cortex functional organization.

Caskey *et al.*(46) examined the effects of exposure to speech and language in general, not just maternal speech, on preterm development. Recordings of the NICU sound environment were made and analyzed for adult word counts, infant vocalizations, and conversational turns. Infant vocalizations were present as early as 32 weeks PMA. Exposure to parent speech was found to be a significantly stronger predictor of infant vocalization at 32 weeks PMA and conversational turns at 32 and 36 weeks PMA than speech from other adults.(47) In a follow-up study, adult word counts in the NICU were positively correlated with performance on the Bayley Scales at 7 and 18 months.

LIGHT

Light is radiant energy that can be measured in both illuminance (the quantity of light, measured in lux) and irradiance (the kind of light).(21) The recommended illuminance for a NICU is 10-600 lux, however, standard levels of hospital lighting are 400 to 1000 lux.(48, 49) It has been postulated that the presence of continuous light in the NICU may impede the development of circadian rhythms in infants, which may lead to abnormal cortisol production, sleep-wake patterns, and stress.

Reduced lighting has been found to stabilize infant heart rate, respiratory rate, blood pressure, and motor activity.(21, 50, 51) Multiple studies have shown that reduced lighting is associated with improved stability and growth in preterm infants.(48, 50-53) Lighting can be a significant source of stress to the infant, which may alter physiologic processes and CNS organization at a time when the infant is still rapidly developing.(54)

Many studies have examined the effects of cycled versus non-cycled lighting in the NICU. Infants assigned to cycled lighting conditions experience improved feeding and weight gain, improved respiratory function, less hyperbilirubinemia, and enhanced motor coordination compared to infants in continuous lighting.(51) Brandon *et al.*(52) found significant improvement in weight gain and short-term medical outcomes in infants exposed to cycled light in the NICU compared with a control group kept in near darkness. Mann *et al.*(50) found that infants exposed to cycled light slept, ate, and gained weight better than controls. Interestingly, the increased time asleep for infants exposed to cycled light in this study was

evenly distributed throughout the 24 hour day, and was not associated with the development of a circadian rhythm.

One concern with these studies is that low lighting conditions may affect staff behavior to reduce ambient noise levels or frequency of handling by caregivers, and that study effects may be due to differences in staff behavior rather than illuminance.(55) In order to separate these effects, Kennedy *et al.*(55) placed light reducing goggles on preterm infants continuously for the first four weeks of the NICU hospitalization to provide darkness only to the infant rather than to the NICU as a whole. No significant difference in medical outcomes was found between the experimental and control groups.

In a similar study focused on the effect of cyclical lighting rather than continuous low lighting, Vasquez-Ruiz *et al.*(53) used acrylic helmets to reduce infant exposure to light on a cycled schedule. The intervention group had improved weight gain and decreased length of hospital stay. Furthermore, light-dark cycling was associated with improved oxygen saturation and heart rate stability, and establishment of a daily melatonin rhythm. Watanabe *et al.*(56) conducted a similar study using a light filter placed over the incubator. The intervention group had significantly improved weight gain. These studies indicate that exposure to cycled light may be important to infant development regardless of caregiver behavior.

THE SOCIAL ENVIRONMENT

Parents and medical staff provide the social environment for the preterm infant in the NICU. Early socializations between the infant and caregiver may influence the infant's behavioral development and organization.(21) The incubator-based NICU environment could deprive the developing infant of tactile stimulation.(54)

Multiple studies have examined the impact of physical contact between hospitalized preterm infants and caregivers on neurobehavioral outcomes. Reynolds *et al.*(57) evaluated the relationship between parental visitation and skin-to-skin contact during the NICU hospitalization and neurobehavioral performance at term. The study found that visitation and holding were associated with improved quality of movement and tone, and less negative arousal and stress. Smith *et al.*(58) tested the effectiveness of a method of gentle touch suitable for very fragile infants on preterm neurodevelopment. No differences were found in a neurobehavioral assessment at term. Other outcomes including growth velocity, cardiorespiratory stability, and behavioral state were improved after the intervention.

The positive effect of massage on weight gain in preterm infants has been well-reported.(59, 60) Other reported beneficial effects of preterm massage therapy include improved digestion and gastric motility,(61) reduced hospital stay and incidence of late-onset sepsis,(62) decreased pain and stress,(63-65) improved immune function,(66) and improved motor development.(67) Arora *et al.*(68) found no difference on a neurobehavioral assessment performed in infancy between infants receiving massage therapy and controls. In contrast, Procianoy *et al.*(69) found that preterm infants who received maternal massage therapy performed better on the Bayley Scales at 2 years of age. In another study, Guzetta *et al.*(70)

found that massage accelerated the maturation of encephalographic activity as well as visual function, particularly visual acuity, in preterm infants.

Other methods of touch have been examined in association with preterm health, including gentle-human touch,(71) proscribed manual stimulation,(72) and kangaroo care.(73, 74) The most common of these is kangaroo care, where the infant is swaddling skin-to-skin directly on the caregiver's chest. Preterm infants exposed to kangaroo care exhibit greater cardiorespiratory stability in the NICU(75) and better autonomic regulation and sleep organization at term equivalent.(76) Follow-up at 10 years for these infants showed better stress response and improved executive functioning.(76) Various reviews summarize the findings of the multitude of touch techniques on preterm infants.(59, 74)

THE BUILT ENVIRONMENT

As elsewhere in the hospital, private rooms have gained favor over the more traditional open-bay design in the NICU.(77) It has been proposed that private rooms may decrease the amount of environmental stressors that the preterm infant experiences. Indeed, studies report lower sound levels in private rooms compared to open bay wards(78-80) and lighting in private rooms can be tailored to an individual infant's needs.

Studies examining the impact of NICU design on visitation report significantly more visitation hours among infants in private rooms.(81, 82) This supports the notion that more accommodating environments can lead to increased parental interaction. Increased parental visitation could lead to increased exposure to adult speech as well as skin-to-skin holding, both of which can improve developmental outcomes.(44, 57)

Private room NICUs may also decrease the incidence of nosocomial infections.(78, 80) Private rooms may decrease the incidence of infection by preventing overcrowding, as well as by promoting hand washing, as each private room typically has its own hand washing station. Indeed, nurses report increased hand washing after relocating from an open bay to a private-room NICU.(80) As sepsis during the NICU stay is a significant predictor of neurodevelopmental outcome,(83) reduction of NICU-based infection is a significant environmental consideration.

Despite these benefits, concerns about infant isolation in private-room NICUs exist. Private rooms present challenges with staff communication, education, and quality of care.(80) Two studies have evaluated the link between NICU room type and neurodevelopment. Pineda *et al.*(84) found that preterm infants cared for in private rooms had reduced cerebral maturation at term by magnetic resonance imaging and electroencephalography compared to those cared for in an identically-managed open bay unit. These same infants had worse language scores and more externalizing behaviors at 2 years of age. The study hypothesizes that the findings may be explained by sensory and social deprivation of infants in private rooms.

In contrast, Lester *et al.*(85) found that admission to a private room compared to an open bay NICU was associated with reduced infection rate and physiological stress, and improved weight gain, feeding tolerance, attention, and tone.

CONCLUSION

Survival of preterm infants has improved dramatically since the advent of neonatal intensive care. As mortality rates have fallen, morbidities from developmental disorders now represent a significant public health challenge for the 12% of the United States population currently born preterm. As prevention of preterm birth remains elusive, the possibility of improving neurobehavioral outcomes for preterm infants by optimizing the NICU experience is a tantalizing opportunity. Further research in this area is needed to better define targets for intervention. Studies should focus on practical, inexpensive interventions that can be implemented broadly in the existing array of NICU settings.

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Abbreviations

NICU	neonatal intensive care unit
PMA	post-menstrual age
PN	parenteral nutrition

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KEY POINTS

- Preterm infants represent a highly vulnerable population for environmental exposures with negative neurodevelopmental impact.
- Chemical exposures, toxic light and sound, and social deprivation are environmental health concerns for the hospitalized neonate.
- Optimizing the NICU environment could improve neurobehavioral outcomes for the hundreds of thousands of children born preterm in the United States each year.

FIGURE.

Multiple environmental factors contribute to a preterm infant's physiological and psychological development during the NICU hospitalization. As they occur during a critical period for neurodevelopment, NICU-based environmental exposures can have a life-long impact on neurobehavioral outcomes.