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Randomized Clinical Trial Investigating the Effect of Consistent, Developmentally-appropriate, and Evidence-based Multi-sensory Exposures in the NICU

Roberta Pineda, PhD, OTR/L, CNT[1,2,3,4], **Joan Smith, PhD, RN, NNP-BC, FAAN**[5], **Jessica Roussin, BA, CCRP**[6], **Michael Wallendorf, PhD**[7], **Polly Kellner, MSOT OTR/L**[1], **Graham Colditz, DrPH, MD, MPH**[8]

[1]Chan Division of Occupational Science and Occupational Therapy, University of Southern California, Los Angeles, CA, USA

[2]Keck School of Medicine, Department of Pediatrics, Los Angeles, CA, USA

[3]University of Southern California, Gehr Family Center for Health Systems Science and Innovation, Los Angeles, CA, USA

[4]Program in Occupational Therapy, Washington University, St. Louis, MO, USA

[5]Department of Quality, Safety, and Practice Excellence, St. Louis Children's Hospital, St. Louis, MO, USA

[6]Department of Radiation Oncology, Washington University, St. Louis, MO, USA

[7]Department of Biostatistics, Washington University, St. Louis, MO, USA

[8]Washington University, Department of Surgery, St. Louis, MO, USA

Abstract

Objective: Evaluate the effect of a manualized multisensory program, applied across NICU hospitalization, on infant and parent outcomes.

Study Design: Seventy parent-infant dyads (born ≤ 32 weeks gestation) in a Level IV NICU were randomized at birth to the multisensory program or standard-of-care. Parents in the multisensory group administered prespecified amounts of age-appropriate, evidence-based sensory interventions to their infants each day during NICU hospitalization according to the Supporting and Enhancing NICU Sensory Experiences (SENSE) program.

Results: Infants who received the SENSE program had more lethargy on the NICU Network Neurobehavioral Scale (NNNS) (p=0.05), even after controlling for medical and social risk (p=0.043), and had higher Communication scores on the Ages and Stages Questionnaire (p=0.04)

Author Correspondence: Roberta Pineda, PhD, OTR/L, University of Southern California, Chan Division of Occupational Science and Occupational Therapy, Los Angeles, CA, USA; bobbi.pineda@chan.usc.edu.

Conflict of Interest: Roberta Pineda and Joan Smith are authors of the SENSE program. The SENSE program is owned by the Washington University Office of Technology Management and is available to clinicians and researchers 'at cost' through exclusive distribution rights at University of Southern California. The authors receive no financial gain from purchases of the SENSE program.

at one-year corrected age, but this relationship failed to reach significance after controlling for medical and social risk (p=0.12).

Conclusion: The SENSE program shows promise for improving outcomes, but more research with larger sample sizes is needed.

Keywords

stimulation; preterm; outcomes; development; environment; auditory; tactile; parents; guideline; SENSE program; Supporting and Enhancing NICU Sensory Experiences program

Introduction.

The neonatal intensive care unit (NICU) environment includes experiences of procedural touch/handling, movement, smell, sound, light, frequent nociceptive pain, and disruption of sleep (1). For preterm infants, there is also an interruption in the predictable pattern of sensory exposures during a critical period of brain development (2). Intense or poorly-timed sensory exposures in the NICU environment may be harmful to the developing sensory system (1, 3). Further compounding preterm infants' altered sensory experiences is the change in NICU architectural design to private rooms, which may be instrumental in decreasing stressors during periods of acute medical compromise and extreme immaturity (4). However, our research team has observed poorer cerebral maturation scores, alterations in cerebral structure, and poorer language outcome at 2 years among infants in low stimulation private rooms compared to noisier open wards in an urban NICU with decreased parent involvement (5). Further study demonstrated variation in auditory exposure across room type, with an average of 3 hours more silence in a 16-hour period among infants in private rooms. Much of the sound exposure in the NICU was high volume and from non-natural sounds, with very little language exposure (4). Although auditory experiences are important, the NICU environment is made up of multisensory stimuli, and one sensory exposure impacts the others (2, 6, 7), making it important to address the full scope of sensory experiences impacting the high-risk infant in the NICU.

Just as poorly timed or noxious sensory exposures can negatively impact the development of the preterm infant, appropriately timed and positive sensory experiences enhance healthy brain development. Functional relatedness of different brain regions is immature in preterm infants, and prematurity can lead to a reduction in neuronal activity. Neuronal growth and connectivity increase in strength and organization as postmenstrual age (PMA) advances, and this can be optimized with appropriate multisensory experiences (8). Because the neonatal brain is highly susceptible to external stimuli (9), positive early experiences drive electrocortical activity that facilitates healthy brain development. Electrocortical activity from positive sensory experiences promotes structural plasticity, axonal sprouting, and formation of dendritic spines and synapses in the primary sensory cortex (10).

There is a body of evidence supporting the use of tactile (touch, holding, skin to skin), auditory (maternal voice, singing, music), visual (cycled light), kinesthetic (movement), and gustatory/olfactory (breast milk or maternal scent) stimulation for preterm infants in the NICU (7). Thus, positive and appropriate sensory exposure within the NICU is a modifiable

factor that can be used to optimize brain development and reduce the high rates of morbidity. Further, the infant's need for human contact and nurturing has long been understood. Parent involvement is also an important modifiable factor, as infants whose parents are present and engaged in the NICU demonstrate more favorable outcomes (11). Although parents can be important drivers of the early sensory environment, even when they are present in the NICU, parents may still have difficulty engaging with their infant, not knowing how or when to interact. Despite favorable evidence for positive multisensory exposures in the NICU (7), such as skin-to-skin care and music, there is significant variation in practice across different NICUs and even within the same NICU (12). The result can be months of hospitalization in a sensory-deprived environment, which can alter the long-term developmental trajectory of the infant (13).

In response to the need for improved intervention, our research team has defined a multisensory program, Supporting and Enhancing NICU Sensory Experiences (SENSE**)** (14). The SENSE program combines the need for parent engagement in the NICU environment along with the infant's daily need for positive multisensory exposures into a cohesive, evidence-based, parent-delivered guideline for consistent application of positive multisensory exposures every day in the NICU. The guideline ensures that appropriate doses of exposure are provided across all the senses. Education materials help parents understand how to implement the guideline for positive sensory exposures within the daily NICU routine and instructs them in how to apply the different sensory exposures in a unimodal (e.g. one sense at a time) or multimodal manner. The SENSE program was developed using a stepwise, rigorous, and scientific process that included evidence on sensory exposures with preterm infants, combined with expert opinion and parent input regarding developmentally appropriate and timed exposures (12, 15, 16). The SENSE program includes specific doses of tactile, auditory, vestibular, kinesthetic, olfactory, and visual exposures designed to be delivered by parents with oversight by from a neonatal therapist, nurse, or experienced staff member. In addition, the types, frequency, and duration of appropriate exposures are tailored to the infant's PMA and modified based on medical status and behavioral cues. A feasibility study demonstrated that providing the defined doses of SENSE interventions, which include substantive amounts of added positive sensory exposures, is feasible to carry out in a level IV NICU. A pilot study demonstrated that SENSE programming was related to increased parent confidence on the Maternal Confidence Questionnaire ($p<0.001$), better infant neurobehavior with less asymmetry on the NICU Network Neurobehavioral Scale ($p=0.02$; mean difference 0.90) and higher scores on the Hammersmith Neonatal Neurological Evaluation ($p=0.001$; mean difference 4) (17). This current report extends our prior published work and reports on a randomized clinical trial of the SENSE program and its effect on infant neurodevelopment as well as maternal mental health and confidence. We hypothesized that the SENSE program would relate to more maternal confidence at NICU discharge and better language outcome at one-year corrected age.

Methods.

This study was registered on clinicaltrials.gov prior to enrollment under trial #201601057. This study was approved by the Washington University Human Research Protection Office

with a Ceded Review at the University of Southern California. Parents signed informed consent.

Participants and study site.

Seventy parent-infant dyads of very preterm infants born ≤ 32 weeks estimated gestational age (EGA) were recruited within the first week of life from consecutive admissions at St. Louis Children's Hospital NICU, an 85-bed (that expanded to 132-bed during the course of the study) level IV NICU from August 2017 to June 2018. Infants were excluded if they had a suspected or confirmed congenital anomaly, were assigned to the NICU's open ward (rather than a private room), or had parents who did not speak English. They were withdrawn if they became wards of the state or were transferred to a different NICU prior to discharge home.

Power.

We defined primary outcome variables for each time point (at term equivalent age and one-year corrected age) and did a power analysis, to estimate sample size, incorporating both. The primary outcome variable at term equivalent age (35–41 weeks PMA) was the Excitability subscale score on the NICU Network Neurobehavioral Scale (NNNS). Excitability is a combination of both motor and behavioral responses, and previous work in our lab has demonstrated it to be a good predictor of later motor, cognitive and language outcomes. We estimated the variance of the Excitability subscore using data from preterm infants born < 30 weeks gestation enrolled in a longitudinal cohort from 2007–2010 and evaluated with the NNNS at term age. For this trial, a total sample of n=46 (23 in each group) will provide 80% power when the true NNNS group difference is 2.2 (2-sided test with alpha= 0.05). In a sample of typical full-term infants, the Excitability subscale score has a mean of 4.3 and a standard deviation of 2.4 (18). A group difference of 2.2 would be a difference of almost 1 standard deviation. Our primary outcome variable at one-year corrected age was the Ages and Stages Questionnaire (ASQ) Communication score. This was chosen as our primary outcome of interest, due to previous findings of poorer language outcomes in preterm infants hospitalized in low stimulation environments with poor parent engagement (5). The variance of the Communication score was estimated using a sample of preterm infants enrolled in our lab in 2011 who received the ASQ at age 3 years. A sample of n=46 provides 80% power when the true group mean ASQ difference is 9.5 (2-sided test with alpha= 0.05). In a normative sample, the Communication score on the ASQ has a mean of 52.9 with a standard deviation of 11.1 (19). A total sample of n=46 (23 in each group) would be a large enough sample to detect a difference of less than 1 standard deviation across groups at the one-year follow-up assessment. Seventy infants were enrolled to account for 15% attrition during the course of the NICU hospitalization (for n=60 at term age) and another 20% attrition by the one-year follow-up assessment (n=48 at one-year of age).

Overview of procedures.

Parent-infant dyads, enrolled within 7 days of birth, were randomized to either the standard-of-care group or SENSE multisensory program group. The randomization scheme was stratified on level of immaturity (≤ 28 weeks EGA or > 28 weeks EGA) and was uploaded

to REDCap prior to study initiation. The biostatistician, who was not involved in other study procedures, established the randomization allocation sequence. Various members of the research team (research coordinator, principal investigator, neonatal therapist) enrolled families, pulling a sealed envelope that disclosed the group assignment after enrollment. Parents with infants in the SENSE group were provided with SENSE program education and daily support by a neonatal therapist to engage in the SENSE program (described below) in addition to receiving standard-of-care. Sensory exposures were tracked on bedside logs that contained sensory exposure dose targets for each day. The monitored standard-of-care group received standard NICU care at the study site (described below) and tracked sensory exposures on bedside logs.

Standardized measures of maternal mental health and infant development were contained in a questionnaire that was completed by mothers at 35–41 weeks PMA in the NICU and at one-year corrected age. The questionnaire has been used in our longitudinal studies of preterm infants since 2007 (20) and takes approximately 30 minutes to complete.

Standard-of-care.

At the time of this study, much like other contemporary NICUs, parents were allowed to be present in the NICU 24 hours per day, with significant variability in the amount, types and timing of actual parent engagement (11, 21, 22). Infant holding was supported, provided the infant could maintain physiological and temperature stability. Infants were held while on mechanical ventilation, but holding was not encouraged when infants were on oscillatory ventilation and/or when chest tubes were in place. Nurses and therapists fostered parent participation through instruction on caregiving and developmentally appropriate interactions, but these were balanced with other priorities of medical care. No specific amount of positive sensory exposures was targeted, and practices varied based on the comfort level of nurses, the medical team, and the parents. Suboptimal parent presence, holding, and language exposure have previously been reported at the study site (4, 11). The study site is consistent with other hospitals, where there is significant variation in use of sensory based interventions and decreased parental involvement (12). The SENSE program addresses the current lack of a national standard for positive sensory exposures and the resultant inconsistency of application of these exposures across hospitalization.

SENSE multisensory program (14).

The SENSE program includes the provision of specific types and amounts of evidence-based tactile, auditory, visual, vestibular/kinesthetic, and olfactory interventions to be conducted by parents with their preterm infants, with a specific amount defined for each day of hospitalization (see Appendix 1). The program changes across PMA, and a sensory support team fills in the gaps when parents are not available. The education and parent guidance that is part of the SENSE program was overseen by a neonatal therapist (with the study using a neonatal occupational therapist and physical therapist).

SENSE program education.

Parents randomized to the SENSE group received an educational booklet for the SENSE program which informed them about the premise of the multisensory interventions, along

with identified targets in the amounts of daily multisensory exposures that are tailored to each infant's PMA. Parents could choose to provide one sensory exposure at a time or could provide multisensory interventions, based on the infant's tolerance. Parents were able to choose different types of each sensory exposure from options that have evidence to support their use and are appropriate at each PMA. The parents and medical team also opted for exposures within an infant's range of tolerance (such as using gentle human touch for an infant too sick to be transferred out of the bed to be held). Parents also received verbal education by the neonatal therapist on the research team within one week of enrollment and at least weekly thereafter to reinforce content in the booklet.

The sensory support team.

When the parents or family members were unable to reach the target doses as defined in the SENSE program, a member of the sensory support team was assigned to deliver appropriate multisensory interventions. The sensory support team consisted of trained volunteers who provided gentle human touch and language exposure to medically stable infants as directed by the research team.

Modifications to the sensory intervention based on infant factors.

The SENSE program is tailored to be responsive to each infant's cues when receiving the stimuli as well as individualized based on concurrent medical issues. The neonatal therapist on the study team assessed the infant's tolerance each week, or more often if needed, and adjusted the multisensory interventions accordingly when not tolerated. The infant assessment used for the SENSE program is part of the manualized intervention (14) and consists of infant observations, evaluation, and collaboration with the medical team. Any modifications to the structured dose and timing of the multisensory interventions were communicated to the parents, medical team, and sensory support team and documented by the research team.

Treatment fidelity/documenting sensory exposures.

To assess treatment fidelity and to ensure treatment differentiation (23), sensory exposures (conducted by parents, the medical team, or the sensory support team) were captured on bedside logs for both groups. To ensure *treatment integrity,* we measured whether the daily doses defined in the SENSE program were being met each day, with specific attention to auditory and tactile exposures, which have large dose targets and are measurable by amount of time. Continuous review of sensory exposures during the course of the study also enabled activation of the sensory support team as needed. Differences in sensory exposure in the SENSE and standard-of-care groups are reported in a previous publication (24).

Masking participants and blinding evaluators.

Parents were enrolled in this study, understanding that they would be assigned to one of two types of sensory approaches. They were masked from whether they were in the treatment group (SENSE program) or control group (standard-of-care), and the details of what we wanted them to do (within their assigned approach) were not communicated until after enrollment. All assessments in the NICU were conducted at the infant's bedside by a

certified and trained evaluator, who was blinded to treatment assignment (as well as study details).

Medical factors.

Medical factors were collected from both groups using the EPIC electronic medical record to define the characteristics of the sample and enable statistical control of other factors that can impact outcome. From these factors, a medical risk score was defined as the infant having any of these factors during the NICU hospitalization: inotropic support, patent ductus arteriosus (PDA), necrotizing enterocolitis (NEC), parenteral nutrition > 21 days, mechanical ventilation > 7 days, bronchopulmonary dysplasia, or cerebral injury (grade III or IV intraventricular hemorrhage or cystic leukomalacia) due to evidence associating them with adverse neurodevelopmental outcome.

Social factors.

Social factors were collected from EPIC as well as from the parent questionnaire. A social risk score, used in parallel research studies and modified for this study, was used to assess family environment after NICU discharge (20).

Outcomes at term equivalent age, prior to NICU discharge.

NICU Network Neurobehavioral Scale (NNNS).—Between 35–41 weeks PMA, infants were assessed at bedside with the NNNS (25) by a trained and certified evaluator blinded to treatment group. The NNNS has been used extensively with preterm infants, and has acceptable internal consistency (α =0.87–0.90), good test-retest reliability (α =0.30–0.44), and predictive validity with relationships to Bayley-II mental (p=0.011, R^2=0.295) and psychomotor (p=0.002, R^2=0.441) scores. It has also been shown to relate to ASQ scores at age 3 years. Habituation was not assessed, but the remaining 12 summary scores were used as outcomes.

Hammersmith Neonatal Neurological Evaluation.—Between 35–41 weeks PMA infants were also assessed with the Hammersmith Neonatal Neurological Evaluation (HNNE). It has excellent clinical utility as a quick assessment of neonatal neurological status with acceptable content and criterion validity (26). The interrater reliability of the assessment is good for both optimality scores and subtotal scores (ICC > 0.74 and ICC 0.6–0.74 respectively). The total score was used as an outcome variable.

Sensory processing.—The questionnaire included the Sensory Profile 2 (short form) (27). It is used in clinical practice and research and has good test-retest reliability (α=0.81–0.90), validity, and internal consistency (α =0.83). Summary scores for Tactile Sensitivity, Taste/Smell Sensitivity, Movement Sensitivity, Auditory Filtering, Under Responsiveness/ Seeks Sensation, Low Energy/Weak, and Visual/Auditory Sensitivity were used as outcomes.

Maternal mental health outcome.—The questionnaire included the State Trait Anxiety Inventory (STAI) (28), the Edinburgh Postnatal Depression Scale (EPDS) (29), the Life Stress Subscale of the Parenting Stress Index (PSI) (30), the Perinatal Post-Traumatic

Stress Disorder Questionnaire (PPQ) (31), the Parental Stressor Scale: NICU (PSS-NICU) (32), the Maternal Confidence Questionnaire (MCQ) (33), and the Infant Characteristics Questionnaire (ICQ) (34). The STAI is the most widely used self-report assessment of anxiety in adults. Internal consistency coefficients range from 0.86–0.95, and test-retest reliability ranges from 0.65–0.89. The STAI has good construct and concurrent validity. The EPDS measures and has cut-offs for diagnosis of clinical depression. The EPDS has fair validity (specificity of 49–100%, sensitivity of 65%−100%, 83% predictive value). The scale has good test retest reliability of 0.92, split half reliability of 0.88 with a standardized α coefficient of 0.87. The PSI (4th ed) screens for stress in the parent-child relationship and has good reliability, internal consistency with α=0.96, and is useful across diverse populations. The PPQ is a measure of post-traumatic stress symptoms in the perinatal population and has good internal consistency (coefficient α=0.85) and test-retest reliability (r=0.92). The PSS NICU measures parental perception of stressors arising from the physical and psychosocial environment of the NICU and has acceptable internal consistency (Cronbach's alpha >0.7 for all scales) and good construct validity across all scales (r=0.45, p<0.05). The MCQ measures maternal confidence in parenting and has fair test-retest reliability (0.69) and good internal consistency with Cronbach's alpha between 0.86 to 0.93. The ICQ measures perceptions about ability and competence in providing infant care and has good internal consistency (Cronbach's alpha from 0.39 to 0.79) and test-retest reliability (Pearson's r between 0.47 −0.70).

Outcomes at one-year corrected age.

Developmental outcome.—At one-year corrected age, the parents completed the ASQ, a parent-report measure of developmental outcome (35), which can be used for children from 2 months to 5 years. Scores were obtained for: Communication, Gross Motor, Fine Motor, Problem Solving, and Personal-Social. The ASQ has good validity (combined validity 86%, 73%−100%) and reliability (test-retest reliability α =0.75–0.82, interrater reliability α =0.43–0.69).

Sensory *processing:* Sensory processing was also measured at one-year corrected age using the Sensory Profile-2 (short form).

Maternal mental health.—The STAI, PSI, modified PPQ, ICQ, and MCQ were also administered at 1-year corrected age. While the EPDS was used to determine maternal depression at term age, the Beck Depression Inventory II (BDI-II) was used to determine maternal depression at 1 year corrected age. The BDI-II has good validity, internal consistency with Cronbach's α coefficient 0.83 to 0.96 and good reliability (test retest r= 0.73 to 0.96).

Feeding outcomes at one-year of age.—Feeding was assessed with the Pediatric Eating Assessment Tool (PediEat) and the Behavioral Pediatric Feeding Assessment Scale (BPFAS). The PediEAT measures symptoms of feeding problems in infants and children aged 6 months to 7 years. It has excellent internal consistency with Cronbach's α coefficient 0.83 to 0.92, good to excellent test-retest reliability (ICC=0.95), and established construct validity. The BPFAS defines patterns of mealtime and feeding behaviors in young children

aged 9 months to 7 years. It has good test-retest reliability (ICC=0.91), internal consistency with Cronbach's α coefficient 0.71 to 0.81, and established content and concurrent validity.

Statistical analysis.

Descriptive statistics were used to report characteristics of the sample. Differences in medical and sociodemographic factors across groups were explored using independent samples t-tests, chi-square analyses, regression models, and nonparametrics. All factors that were different across groups ($p<0.05$ and $r>0.30$) were considered for inclusion in the statistical model as a covariate, as long as they were not already represented in the social risk or medical risk scores.

First, mixed random effects models were used to investigate group differences in NNNS, ASQ, and other outcomes. Correlation between siblings, who are multiples, were modeled by using mother-infant dyad as a random effect. PMA at the time of assessment was controlled for due to its previously reported relation to neurobehavioral outcome (36). To further explore group differences, a second analysis was conducted, controlling for baseline covariates of social risk score and medical risk score. In addition, a final analysis was conducted to understand the potential impact of parent-driven, compared to sensory support driven, sensory interventions. An interaction between parent engagement (50% of interventions done by the parents) and treatment group was investigated in a factorial model. Other analyses of outcomes included mixed effects repeated measures ANOVA for continuous measures across time and using logistic regression for categorical outcomes of measures conducted at one point in time. The threshold of significance was $p=0.05$.

Results.

Among 70 infants who were randomized, 3 expired, 5 withdrew, and 10 were transferred to another NICU. Among 52 infants who were evaluated at term age prior to NICU discharge, one expired after discharge, and 12 did not complete the one-year assessments, leaving 39 infants at the one-year follow-up (21 in the standard-of-care group and 18 in the SENSE group). There were no differences in attrition, based on group assignment or infant and family characteristics. See enrollment diagram in Figure 1.

The groups were homogenous, except younger mothers ($p<0.003$), lower household income ($p=0.02$) and more social risk ($p=0.049$) were observed in the SENSE group. See Table 1 for sample descriptives and differences across groups.

There were more sensory interventions conducted with infants in the SENSE program ($p=0.001$) with a greater percentage of infants receiving 100% of the doses defined in the SENSE program ($p=0.01$). See Appendix 2 for factors related to treatment fidelity/ differentiation.

Infants who received the SENSE program had more lethargy on the NNNS ($p=0.05$), even after controlling for medical and social risk ($p=0.043$). Infants who received the SENSE program had significantly higher Communication scores on the ASQ ($p=0.04$), but this relationship failed to reach significance after controlling for medical and social

risk (p=0.12). Higher scores on the MCQ and lower scores on the PSI dysfunctional interaction subscore observed in the SENSE group failed to reach significance (p=0.07 and 0.13 respectively) even after controlling for medical and social risk (p=0.097 and 0.052 respectively). There were no other significant relationships related to maternal or infant outcomes at term or one-year. See Table 2, Table 3, Table 4, and Table 5 for differences in outcome across groups.

We also tested for the effects of parent-driven interventions (50% or more of interventions done by the parents), and they did not impact the results.

Discussion.

The key findings of this study were that infants randomized to the SENSE program demonstrated more lethargy at term equivalent age, but had better language outcome at one-year of age. However, when controlling for social risk and medical risk, relationships with lethargy remained, but relationships between SENSE programming and language outcome were no longer observed. We also did not observe relationships between SENSE programming and maternal confidence.

The SENSE program was developed to address the role of the sensory environment on appropriate brain development (37–39). As the SENSE program was developed by combining available evidence, stakeholder input, and expert guidance (16), our current findings parallel other studies investigating positive sensory exposures such as skin-to-skin care and language exposure (15). Similar to previous findings showing relationships between quiet and low-stimulation private rooms and poorer language outcomes, we were able to demonstrate an effect of the multisensory SENSE program on better language outcomes at one-year of age on univariate analysis. Due to multifactorial influences on language outcomes (40), we conducted a secondary multivariate analysis. We were not able to demonstrate relationships between SENSE programming and language outcome on multivariate analysis. The randomized clinical trial design aims to balance out confounding factors across groups within the assignment of groups, and stratification on EGA was further employed to aid in group homogeneity. The multivariate analysis enables additional attention to the significant number of confounding conditions that preterm infants experience which can impact the results. An issue with adding more variables to control for in a multivariate model is that it increases the risk of a Type II error and becomes unclear if inadequate power affects the ability to detect differences across groups. This concern is also magnified by a sample size at follow-up that is lower than the original univariate power calculation. Due to these complex issues, we have chosen to include all the results of both analyses to enable clinicians to make their own interpretation of the results.

In this project, the SENSE program was related to more lethargy at term equivalent age, even after controlling for PMA at the time of testing, sibling effect, medical risk, and social risk. This parallels previous work that has found more lethargy among infants whose parents were present more often. Although lethargy is largely depicted as a negative marker of neurobehavioral performance, there are some obscurities worth mentioning. Other studies have demonstrated that lethargy scores have marked reductions across PMA (41), and

lethargy scores have been observed to decrease from birth to one month of age (42), which could make it more difficult to isolate an effect as a response to an intervention. Further, lethargy may correlate with sleep, making our findings consistent with studies that have identified better electroencephalographic sleep-wake cycle organization and sleep behaviors among infants who received skin-to-skin care (43). Therefore, it remains unclear if increased activity or multisensory stimulation being associated with lethargy and sleep is a positive or negative sign.

We were unable to demonstrate an impact of the SENSE program on maternal mental health and confidence. Although positive trends in the data can be interpreted cautiously, we were unable to demonstrate the same improvements in maternal confidence that were previously observed among mother-infant dyads receiving the SENSE program during a pilot study (17). Our pilot study demonstrated a positive increase in maternal confidence among mothers receiving the SENSE program (17), which is consistent with other educational and intervention-based studies that target parents to engage with their infants with demonstrated improvements in confidence and mother-child interaction, as well as reductions in stress (44–47). This study was not powered to investigate differences in maternal mental health and confidence, and therefore, it remains unclear if a larger sample size may have resulted in different findings.

Limitations

There were several limitations to this randomized clinical trial. More infants than expected were transferred to other NICUs after enrollment, leading to a smaller sample size than planned (10 fewer infants). This could have impacted the findings, particularly multivariate results. This study was not powered on all outcome variables. The assumption of homogeneity across groups due to randomization could not fully be appreciated in this study of preterm infants with multiple social and medical confounds that could impact the results. We attempted to address this statistically, but fully untangling these factors to isolate the effect of an intervention remains complex and imperfect, especially with a small sample size. While excluding infants with significant co-morbidities would address this issue in future studies, it is important that the impact of the SENSE program is evaluated on the medically complex infants it is designed for.

There could have been bias and suggestion introduced due to the way that parents were approached for enrollment. Parents were approached very early after birth and informed that this was a study of sensory exposures in high-risk infants. They were told each parent-infant dyad would be randomized to one of two approaches to sensory stimuli (standard-of-care or the SENSE program). This could have been suggestive of the importance of sensory exposures and led to heightened awareness of the need to provide positive sensory exposures, resulting in parents providing more sensory exposures than they would have otherwise, impacting the ability to observe differences across groups. In addition, parents in the control group also had log sheets at the bedside to document their infant’s sensory exposures, which could also have been suggestive and led to increased provision of sensory exposures. Some parents in the control group (1/4 of the sample) achieved the full doses identified in the SENSE program without receiving the specific information and education

related to the SENSE program. The use of statistical interactions to assess the effect of the SENSE program in the midst of different levels of parent engagement could aid in evaluating this, however, a much larger sample size would be needed to establish power. There were times within the complex, level IV NICU when sensory interventions had to be put on hold (24). While 100% of infants in the SENSE group received >75% of the SENSE program doses, only 65% received 100% or more of the dosage across all of hospitalization. Untangling the impact of this necessary hold on sensory exposures and assessing the impact of medical instability is complex.

The study site NICU is the location of previous work that identified lower language scores in infants hospitalized in private NICU rooms. These findings, as well as research conducted after it, could have impacted clinical interventions and behavior just prior to and during the trial, impacting the results of this study. It is also unknown how the transition from an 85-bed to 132-bed NICU during the study time period may have impacted behavior and the results of this study.

Early neurobehavioral assessments are impacted by the PMA at the time of assessment in addition to concurrent medical factors (36), which adds nuance to their interpretation. We also had multiple measures across different constructs over time (infant behavior, one-year child outcome, maternal mental health, maternal confidence), which can increase the risk of a Type I error. In addition to the measures reported here, we video recorded infant movement, feeding, and parent-infant interaction in the NICU and attempted to evaluate these constructs using standard measures from the videotapes. Immediate interpretation was limited due to issues with the camera angle, the length of the video, and other perspectives about the environment that are missing from a video clip. Further analysis is underway.

Conclusions

The SENSE program was developed using a systematic and scientific process to enable a strategy that reflects best practice in tailoring the sensory environment, and this randomized clinical trial provides more evidence to support the SENSE program. However, clinical practice continues to change as new evidence emerges. Therefore, it will be important to update the SENSE program, based on current evidence and/or to continue to evaluate its efficacy, including whether and how efficacy is altered in different types of NICU environments (e.g. open ward vs. private room). Further consideration of the unique contribution of each type of sensory exposure (tactile, auditory, olfactory/gustatory, visual, kinesthetic/vestibular) could also benefit from further inquiry. The relative contribution of each sensory modality could be assessed with the Multiphasic Optimization Strategy, which ultimately could lead to further optimization the SENSE program. Additional research regarding implementation, at the individual and organizational level, would help determine how adaptations made in real-world practice impact the administration of the program across different NICUs. Despite the need for more research, the SENSE program continues to be adopted by NICUs worldwide and its implementation is another step in optimizing the early sensory environment and providing neuroprotective care to fragile infants who start their lives in the NICU.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

(NICU)	neonatal intensive care unit
(SENSE)	Supporting and Enhancing NICU Sensory Experiences
(PMA)	program, postmenstrual age
(NNNS)	NICU Network Neurobehavioral Scale
(ASQ)	Ages and Stages Questionnaire
(EGA)	estimated gestational age
(CRIB score)	Clinical Risk Index for Babies
(NEC)	necrotizing enterocolitis
(IVH)	intraventricular hemorrhage
(PVL)	periventricular leukomalacia
(PDA)	patent ductus arteriosus
(STAI)	State Trait Anxiety Inventory
(EPDS)	Edinburgh Post Natal Depression Scale
(PSI)	Parenting Stress Index
(BDI-II)	Beck Depression Inventory II
(Pedi-Eat)	Pediatric Eating Assessment Tool
(BPFAS)	Behavioral Pediatric Feeding Assessment Scale
(MCQ)	Maternal Confidence Questionnaire

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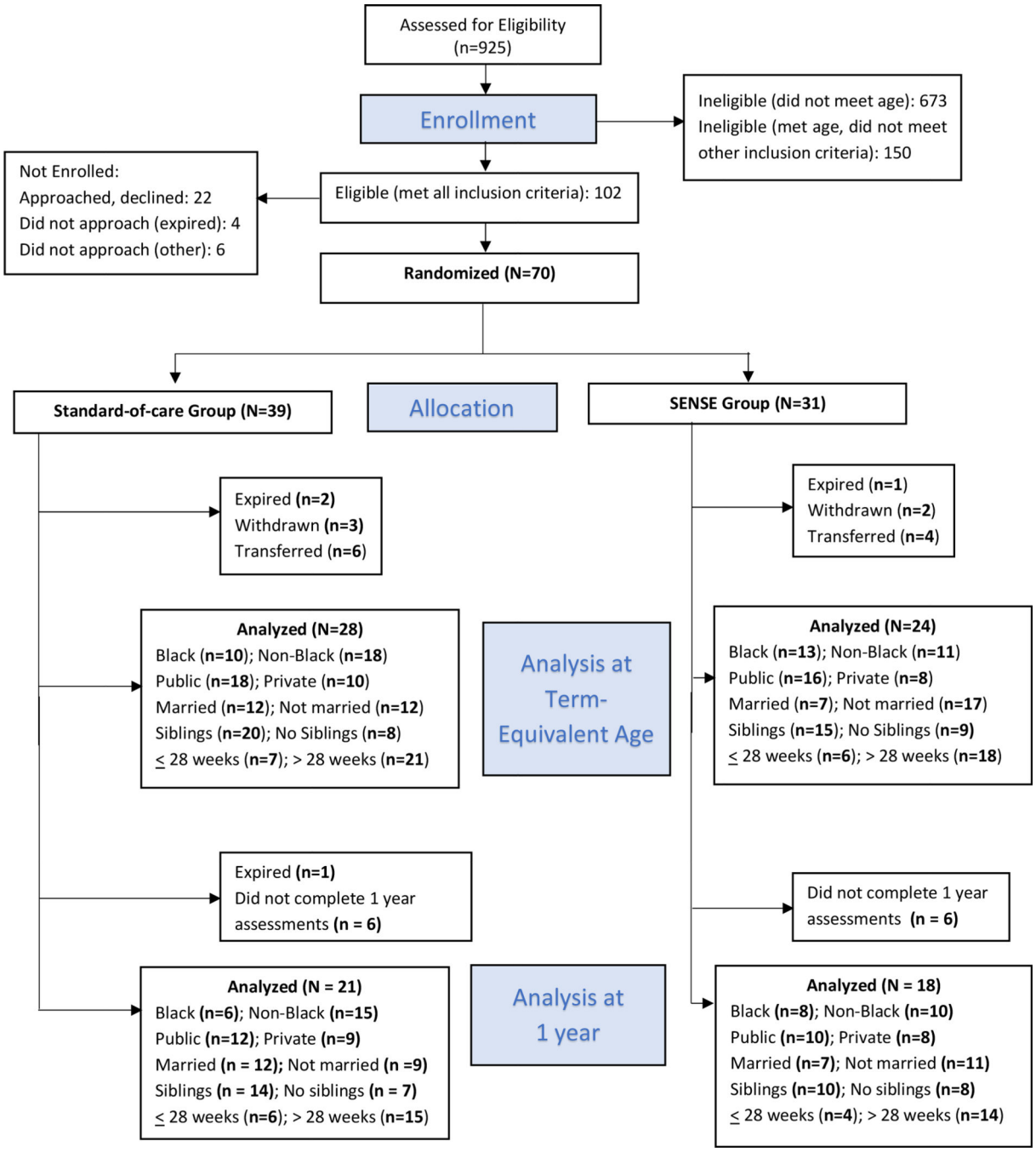

Figure 1.
Participant Flow Diagram

Table 1.

Sample characteristics.

Factor (n=52, unless otherwise specified)	Total Mean±SD or N (%), Median (IQR)	Standard-of-care Group Mean±SD or N (%), Median (IQR)	SENSE Group Mean±SD or N (%), Median (IQR)	P Value* (Differences between groups)
Medical Factors				
Estimated gestational age at birth (weeks)	29.6 ± 2.5	29.5 ± 2.5	29.7 ± 2.6	0.73
Birthweight (g)	1453.2 ± 492.9	1418.2 ± 486.5	1494.0 ± 507.6	0.59
CRIB Score	5.2 ± 5.6	4.3 ± 4.5	6.3 ± 6.7	0.21
Infant received inotropic support	11 (21%)	6 (21%)	5 (21%)	0.96
Multiple birth	19 (37%)	13 (46%)	6 (25%)	0.11
Infant sex (Male)	23 (44%)	11 (39%)	12 (50%)	0.44
Presence of NEC n = 51	3 (6%)	2 (7%)	1 (4%)	0.67
Presence of Severe Brain Injury (Grade III or IV IVH or PVL)	3 (6%)	2 (7%)	1 (4%)	0.65
Presence of PDA	11 (21%)	6 (21%)	5 (21%)	0.96
Presence of Sepsis	8 (15%)	5 (18%)	3 (13%)	0.59
Apgars at 1 minute	4.5 ± 2.7	4.9 ± 2.5	4.0 ± 2.9	0.24
Apgars at 5 minutes	6.4 ± 2.2	6.5 ± 2.1	6.2 ± 2.4	0.60
# Days of endotracheal intubation n=52	1.0 (0.0–7.8)	1.0 (0.0–7.8)	1.0 (0.3–9.5)	0.76
# Days on NIMV (CPAP, SiPAP) n = 51	6.0 (2.0–15.0)	6.0 (2.0–19.0)	5.5 (1.3–10.3)	0.58
BPD	16 (31%)	10 (36%)	6 (25%)	0.40
PMA of infant when transitioned to room air	33.6 ± 3.2	34.1 ± 3.3	33.0 ± 3.0	0.25
# days on TPN	5.0 (0.0–8.3)	4.5 (0.0–7.5)	5.0 (0.0–8.8)	0.58
Post-menstrual age at discharge (weeks)	40.2 ± 8.4	39.9 ± 5.9	40.5 ± 10.8	0.78
Length of stay (days)	77.0 ± 67.3	75.8 ± 55.4	78.4 ± 80.2	0.89
Medical risk score indicating higher medical risk**	28 (54%)	15 (54%)	13 (54%)	0.97
Social Factors				
Maternal age (years)	28.6 ± 6.8	31.1 ± 7.2	25.6 ± 5.0	**0.003**
Insurance type (public)	34 (65%)	18 (64%)	16 (67%)	0.86
Infant race (Black)	23 (44%)	10 (36%)	13 (54%)	0.18
# of siblings	1.4 ± 1.7	1.8 ± 2.1	1.1 ± 1.1	0.17
Education level (some college) n = 46	32 (70%)	15 (68%)	17 (71%)	0.85
Income level (< $25,000/year) n = 46	23 (50%)	7 (32%)	16 (67%)	**0.02**
Living situation (Child living with both mother and father) n = 47	32 (68%)	17 (74%)	15 (63%)	0.40

Factor (n=52, unless otherwise specified)	Total Mean±SD or N (%), Median (IQR)	Standard-of-care Group Mean±SD or N (%), Median (IQR)	SENSE Group Mean±SD or N (%), Median (IQR)	P Value* (Differences between groups)
Maternal marital status (married) n = 48	19 (40%)	12 (50%)	7 (29%)	0.14
Social risk score*** n = 46	3.7 ± 2.8	2.8 ± 2.7	4.4 ± 2.6	**0.049**

Abbreviations: CRIB-Clinical Risk Index for Babies score, NEC-necrotizing enterocolitis, PDA-patent ductus arteriosus, NIMV-noninvasive mechanical ventilation, IVH-intraventricular hemorrhage, PVL-periventricular leukomalacia, TPN-total parenteral nutrition, BPD-Bronchopulmonary dysplasia (oxygen requirement at 36 weeks PMA), PMA-postmenstrual age

*P-value is from investigating differences across groups using independent samples t-tests, chi-square analyses, regression models, or non-parametrics.

**A medical risk score (0 = lower risk, 1 = higher risk) was assigned to each infant. Medical risk was defined as the infant having any of these factors during the NICU hospitalization: inotropic support, PDA, NEC, parenteral nutrition > 21 days, mechanical ventilation > 7 days, oxygen requirement at 36 weeks PMA, or cerebral injury (grade III or IV intraventricular hemorrhage or cystic leukomalacia).

***A social risk score, used in parallel research studies and modified for this study, was used to assess family environment after NICU discharge (1). Social risk scores range from 0 (minimal risk) to 10 (high risk). Language spoken at home was removed, as English language was an inclusion criteria for this study. Due to having information about family income and not family employment status and occupation of primary income earner, family income was weighted to represent both of those variables which were previously part of the social risk score. Variables that contributed to the social risk score for this study then included: family structure (0 points: child living with both parents, 1 point: separated/dual custody or cared for by other family such as grandparents, 2 points: single caregiver or foster care), education of primary caregiver (0 points: college education, 1 point: completed year 11 or 12 of high school, 2 points: completed < year 11 of high school), family income (0 points: > $50,000, 2 points: $25,000–50,000, 4 points: < $25,000), and maternal age at infant birth (0 points: > 21 years, 1 point: 18–21 years, 2 points: < 18 years). Income level was weighed heaviest due to its ties to employment, education level, as well as living situation.

Table 2.

Relationships between group assignment and outcomes at term equivalent age.

	Total Mean ± SD	Standard-of-care Group Mean ± SD	SENSE Group Mean ± SD	P Value*	P Value**
HNNE *higher = better* n = 50	21.8 ± 3.9	22.8 ± 4.0	20.6 ± 3.4	0.15	0.95
HNNE - Tone n = 50	6.7 ± 2.1	7.0 ± 1.9	6.2 ± 2.3	0.28	0.76
HNNE - Tone Pattern n = 50	4.1 ± 0.9	4.2 ± 1.0	4.0 ± 0.8	0.40	0.86
HNNE - Reflexes n = 50	4.3 ± 0.9	4.3 ± 1.0	4.3 ± 0.8	0.91	0.80
HNNE - Movement n = 50	1.5 ± 0.9	1.6 ± 1.0	1.4 ± 0.8	0.49	0.83
HNNE - Abnormal Signs n = 50	1.8 ± 0.7	1.9 ± 0.6	1.8 ± 0.8	0.52	0.67
HNNE - Orientation Behavior n = 50	3.4 ± 1.5	3.7 ± 1.4	3.0 ± 1.5	0.20	0.69
NNNS Orientation *higher = better* n = 41	4.6 ± 1.3	4.9 ± 1.1	4.3 ± 1.5	0.27	0.88
NNNS Handling *higher = better* n = 45	0.5 ± 0.3	0.5 ± 0.3	0.5 ± 0.3	0.89	0.55
NNNS Quality of Movement *higher = better* n = 50	4.1 ± 0.7	4.1 ± 0.7	4.0 ± 0.8	0.76	0.35
NNNS Self-regulation *higher = better* n = 50	4.9 ± 1.0	5.0 ± 1.0	4.9 ± 1.0	0.94	0.34
NNNS Suboptimal reflexes *higher = worse* n = 50	6.8 ± 2.1	6.5 ± 2.2	7.0 ± 1.8	0.37	0.86
NNNS Stress *higher = worse* n = 49	0.2 ± 0.1	0.2 ± 0.1	0.3 ± 0.1	0.66	0.56
NNNS Arousal *higher = better* n = 50	4.0 ± 0.8	4.1 ± 0.8	3.8 ± 0.8	0.44	0.54
NNNS Hypertonia *higher = worse* n = 50	0.4 ± 0.9	0.6 ± 1.1	0.2 ± 0.5	0.33	0.19
NNNS Hypotonia *higher = worse* n = 50	0.8 ± 0.7	0.6 ± 0.6	1.0 ± 0.8	0.11	0.37
NNNS Asymmetry *higher = worse* n = 50	2.3 ± 1.8	2.5 ± 1.8	2.1 ± 1.8	0.49	0.34
NNNS Excitability *higher = worse* n = 50	4.2 ± 2.4	4.4 ± 2.7	4.1 ± 2.2	0.79	0.39
NNNS Lethargy *higher = worse* n = 50	6.1 ± 3.2	4.7 ± 2.0	7.7 ± 3.6	**0.005**	**0.043**
Sensory Profile - Touch *Higher = possible dysfunction* n = 32	4.6 ± 2.0	4.3 ± 1.8	4.8 ± 2.1	0.26	0.31
Sensory Profile -Auditory *Higher = possible dysfunction* n = 32	8.6 ± 3.3	9.2 ± 3.7	8.1 ± 3.4	0.39	0.55
Sensory Profile - Visual *Higher = possible dysfunction* n = 32	6.1 ± 3.4	6.7 ± 4.0	5.6 ± 2.8	0.35	0.36
Sensory Profile -Movement *Higher = possible dysfunction* n = 32	7.9 ± 2.2	8.0 ± 2.0	7.9 ± 2.4	0.78	0.98
Sensory Profile - Oral *Higher = possible dysfunction* n = 32	4.4 ± 1.8	4.6 ± 1.9	4.2 ± 1.7	0.28	0.61
Sensory Profile - General *Higher = possible dysfunction* n = 32	14.6 ± 5.5	14.1 ± 5.7	14.9 ± 5.6	0.69	0.18

*P value is from investigating relationships between assigned group and outcomes at term equivalent age using mixed random effects models, controlling for the PMA at the time of testing and sibling effect from multiple birth.

**P value is from investigating relationships between assigned group and outcomes at term equivalent age using mixed random effects models, controlling for the PMA at the time of testing and sibling effect from multiple birth in addition to social risk and medical risk.

Abbreviations: HNNE-Hammersmith Neonatal Neurological Evaluation; NNNS-NICU Network Neurobehavioral Scale

Table 3.

Relationship of group assignment to maternal confidence and mental health at NICU discharge.

n = 40, unless otherwise specified	**Total Mean ± SD or Median (IQR)**	**Standard-of-care Group Mean ± SD or Median (IQR)**	**SENSE Group Mean ± SD or Median (IQR)**	**Mean Difference**	**P Value***	**P Value****
PSI-Defensive Responding *Higher = more dysfunction*	13.1 ± 5.7	13.3 ± 5.4	13.0 ± 6.1	0.26	0.89	0.98
PSI-Parental Distress *Higher = more dysfunction*	22.7 ± 8.9	22.7 ± 7.7	22.6 ± 10.0	0.17	0.95	0.91
PSI-Parent-Child Dysfunctional Interaction *Higher = more dysfunction* n = 39	19.1 ± 6.5	19.6 ± 5.4	18.7 ± 7.5	0.98	0.64	0.30
PSI-Difficult Child *Higher = more dysfunction* n = 39	17.7 ± 5.4	18.2 ± 5.2	17.4 ± 5.7	0.81	0.65	0.56
PSI- Stress Score Total *Higher = more dysfunction* n = 39	59.4 ± 17.4	60.5 ± 13.7	58.4 ± 20.7	2.18	0.70	0.56
Edinburgh Postnatal Depression Scale *Higher = possible depression*	8.7 ± 5.1	9.0 ± 4.7	8.5 ± 5.5	0.47	0.77	0.93
Parental Stressor Scale - NICU *Higher = more stress*	2.8 ± 1.1	3.1 ± 1.2	2.5 ± 1.0	0.63	0.08	0.28
STAI- State Anxiety *Higher = more anxiety*	36.7 ± 15.2	38.5 ± 11.9	35.1 ± 17.9	3.33	0.50	0.62
STAI- Trait Anxiety *Higher = more anxiety*	35.8 ± 13.1	37.0 ± 11.5	34.8 ± 14.7	2.19	0.61	0.70
Maternal Confidence Questionnaire *Higher = increased confidence*	46.8 ± 8.6	44.2 ± 9.0	49.1 ± 7.6	−4.99	**0.07**	**0.097**
ICQ- Mom & Baby *Higher = better care*	4.3 ± 0.7	4.3 ± 0.5	4.3 ± 0.8	0.01	0.95	1.0
ICQ- Emotionality *Higher = better care*	4.2 ± 0.9	4.2 ± 0.9	4.3 ± 0.9	−0.09	0.76	0.72
ICQ- Responsiveness *Higher = better care*	3.9 ± 0.9	3.7 ± 0.8	4.1 ± 0.9	−0.35	0.20	0.24
Modified Perinatal Post-traumatic Stress Disorder Questionnaire *Higher = more stress*	9.5 (2.3–22.0)	12.0 (4.0–24.5)	8.0 (1.5–20.5)			0.96

*P value is from investigating relationships between assigned group and maternal outcomes at term equivalent age using mixed random effects models, controlling for sibling effect from multiple birth

**P value is from investigating relationships between assigned group and maternal outcomes at term equivalent age using mixed random effects models, controlling for sibling effect from multiple birth in addition to social risk and medical risk.

Abbreviations: PSI - Parenting Stress Index, STAI - State-Trait Anxiety Inventory for Adults, ICQ - Infant Care

Questionnaire

Table 4.

Relationships of group assignment to outcome at one-year of age.

n = 39, unless otherwise specified	**Total Mean ± SD**	**Standard-of-care Group Mean ± SD**	**SENSE Group Mean ± SD**	**P Value***	**P Value****
ASQ-Communication *Higher = more milestones achieved*	43.2 ± 15.7	38.6 ± 18.1	48.6 ± 10.3	**0.04**	0.12
ASQ-Problem Solving *Higher = more milestones achieved* n = 38	38.3 ± 17.7	35.8 ± 20.4	41.1 ± 14.2	0.22	0.27
ASQ-Gross Motor *Higher = more milestones achieved*	38.1 ± 21.4	34.1 ± 22.6	42.8 ± 19.6	0.22	0.34
ASQ-Fine Motor *Higher = more milestones achieved* n = 38	47.1 ± 12.1	46.5 ± 10.4	47.8 ± 14.0	0.68	0.46
ASQ-Personal-Social *Higher = more milestones achieved* n = 38	38.0 ± 17.1	36.0 ± 17.8	40.3 ± 16.4	0.41	0.55
Sensory profile-Touch *Higher = more dysfunction*	18.2 ± 5.5	16.9 ± 6.2	19.7 ± 4.3	0.13	0.31
Sensory profile-Auditory *Higher = more dysfunction*	9.7 ± 4.7	9.7 ± 4.6	9.7 ± 5.0	0.79	0.94
Sensory profile-Visual *Higher = more dysfunction*	21.8 ± 4.2	22.0 ± 4.3	21.6 ± 4.2	0.78	0.90
Sensory profile-Movement Processing *Higher = more dysfunction*	19.5 ± 3.5	18.8 ± 3.8	20.3 ± 2.9	0.17	0.30
Sensory profile- Oral *Higher = more dysfunction*	11.0 ± 4.5	11.4 ± 4.7	10.6 ± 4.4	0.57	0.55
Sensory profile- General *Higher = more dysfunction*	14.1 ± 6.3	14.2 ± 6.6	13.9 ± 6.1	0.75	0.76
Sensory profile-Behavior *Higher = more dysfunction*	10.9 ± 4.6	10.6 ± 5.3	11.2 ± 3.6	0.75	0.87
Pediatric Eating Assessment Tool *Higher = more concern* n = 38	57.3 ± 30.2	54.1 ± 31.6	61.2 ± 28.7	0.42	0.64
Behavioral Pediatrics Feeding Assessment Scale *Higher = More mealtime behavior problems* n = 38	53.4 ± 16.1	55.4 ± 16.2	51.0 ± 16.1	0.53	0.32

*P value is from investigating relationships between assigned group and one-year outcomes using mixed random effects models, controlling for sibling effect from multiple birth

**P value is from investigating relationships between assigned group and one-year outcomes using mixed random effects models, controlling for sibling effect from multiple birth in addition to social risk and medical risk.

Abbreviations: ASQ – Ages and Stages Questionnaire

Table 5.

Relationship of group assignment to maternal outcomes at one-year of age,

n = 39, unless otherwise specified	**Total Mean ± SD or Median (IQR)**	**Standard-of-care Group Mean ± SD or Median (IQR)**	**SENSE Group Mean ± SD or Median (IQR)**	**Mean Difference**	**P Value***	**P Value****
PSI-Defensive Responding *Higher = more dysfunction* n = 33	13.1 ± 5.7	11.9 ± 4.4	11.7 ± 7.0	−0.20	0.95	0.72
PSI-Parental Distress *Higher = more dysfunction* n = 33	22.7 ± 8.9	20.8 ± 7.8	20.6 ± 11.6	−0.19	0.91	0.79
PSI-Parent-Child Dysfunctional Interaction *Higher = more dysfunction* n = 33	19.1 ± 6.5	17.8 ± 6.2	14.3 ± 6.0	−3.5	0.13	**0.052**
PSI-Difficult Child *Higher = more dysfunction* n = 32	17.7 ± 5.4	20.1 ± 6.3	17.8 ± 8.1	−2.4	0.50	0.31
PSI-Stress Score Total *Higher = more dysfunction* n = 33	59.4 ± 17.4	57.0 ± 19.6	52.7 ± 24.0	−4.3	0.73	0.44
Beck Depression Inventory *Higher = more depression*	3.7 ± 5.0	3.6 ± 4.1	3.9 ± 5.9	0.3	0.96	0.83
STAI- State Anxiety *Higher = more anxious*	31.5 ± 9.5	33.7 ± 9.6	28.9 ± 9.0	−4.8	0.89	0.48
STAI- Trait Anxiety *Higher = more anxious*	32.5 ± 11.6	35.8 ± 9.3	28.8 ± 13.1	−7.0	0.29	0.20
Maternal Confidence Questionnaire *Higher = increased confidence*	51.9 ± 4.4	51.4 ± 5.2	52.4 ± 3.2	1.1	0.41	0.54
ICQ- Mom & Baby *Higher = better care*	4.3 ± 0.8	4.2 ± 0.9	4.3 ± 0.9	0.1	0.59	0.75
ICQ- Emotionality *Higher = better care*	3.9 ± 1.3	4.1 ± 0.9	3.8 ± 1.7	−0.3	0.89	0.63
ICQ- Responsiveness *Higher = better care*	4.5 ± 1.0	4.5 ± 1.0	4.6 ± 1.1	0.1	0.72	0.67
Modified Perinatal Post-traumatic Stress Disorder Questionnaire *Higher = more stress* n = 33	12.0 (1.5–26.5)	13.0 (1.0–29.0)	10.5 (5.3–25.5)	−2.5	0.63	0.79

*P value is from investigating relationships between assigned group and one-year outcomes using mixed random effects models, controlling for sibling effect from multiple birth

**P value is from investigating relationships between assigned group and one-year outcomes using mixed random effects models, controlling for sibling effect from multiple birth in addition to social risk and medical risk.

Abbreviations: PSI – Parenting Stress Index, STAI – State-Trait Anxiety Inventory for Adults, ICQ – Infant Care Questionnaire