BMJ Open

Investigating Skin-to-Skin Care Patterns with Extremely Preterm Infants in the NICU and Their Effect on Early Cognitive and Communication Performance

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-012985
Article Type:	Research
Date Submitted by the Author:	08-Jun-2016
Complete List of Authors:	Gonya, Jenn; The Research Institute at Nationwide Children's Hospital, Center for Perinatal Research Ray, William; The Research Institute at Nationwide Children's Hospital, Battelle Center for Mathematical Medicine Rumpf, R Wolfgang; The Research Institute at Nationwide Children's Hospital, Battelle Center for Mathematical Medicine Brock, Guy; The Ohio State University, Center for Biostatistics
Primary Subject Heading:	Intensive care
Secondary Subject Heading:	Paediatrics
Keywords:	extreme prematurity, Neonatal intensive & critical care < INTENSIVE & CRITICAL CARE, NEONATOLOGY

Investigating Skin-to-Skin Care Patterns with Extremely Preterm Infants in the NICU and Their Effect on Early Cognitive and Communication Performance

Jenn Gonya, PhD
The Research Institute at Nationwide Children's Hospital
Center for Perinatal Research
575 Children's Crossroad
RBIII WB6139
Columbus, Ohio USA 43215
jenn.gonya@nationwidechildrens.org
614-355-6653

William C. Ray, PhD
The Research Institute at Nationwide Children's Hospital
Battelle Center for Mathematical Medicine
Columbus, Ohio USA

R. Wolfgang Rumpf, PhD
The Research Institute at Nationwide Children's Hospital
Battelle Center for Mathematical Medicine
Columbus, Ohio USA

Guy Brock, PhD
The Ohio State University Department of Biomedical Informatics
Center for Biostatistics
Columbus, Ohio USA

Keywords: extremely preterm, neonatal intensive care, skin-to-skin care, neonatal neurodevelopment

Word Count: 2214

ABSTRACT

Objectives

Primary

• Identify parental skin-to-skin (SSC) patterns with extremely preterm infants during NICU hospitalization
• Investigate how SSC patterns impact infant early cognitive and communication performance

Secondary

• Explore how medical and SSC factors interact to explain outcomes in infant early cognitive and communication performance

Design

Retrospective cohort study

Setting

Level-IV all-referral neonatal intensive care unit specializing in the care of extremely preterm infants

Participants

All extremely preterm infants admitted to the unit during 2010-2011 and who completed 6- and 12-month developmental assessments in the follow-up clinic (n=97).

Outcome Measures

Bayley Scales of Infant Development, Third Edition (Bayley-III) – Cognitive and Communication Subscales

Analysis

Logistic regression, t-test, chi-squared test, and Fisher's exact test followed with network analysis using novel visual analytic software.

Results

• Mothers participate in the majority of hours of skin-to-skin care with extremely preterm infants.
• SSC hours (both total amount and frequency) decline sharply at 30 weeks corrected age, regardless of when extremely preterm infants are admitted.
• Extremely preterm infants who had higher birthweights, received antenatal steroids, and did not have IVH were least likely to participate in significant amounts of SSC.
• If fathers participated in even small amounts of SSC, infants received more weeks of SSC.
• If extremely preterm infants received more total hours of SSC at higher weekly frequency with engagement from both mothers and fathers, they were twice as likely to score >80 on the cognitive and communication scales of the Bayley-III.
• Medical and SSC factors played a parallel, non-synergistic role in contributing to early cognitive and communication performance as assessed through the Bayley-III.

Conclusion

Early and frequent skin-to-skin care with extremely preterm infants is associated with early cognitive and communication performance. Interventions aimed at increasing skin-to-skin care should include supports for fathers and emphasize the longer term developmental benefits of the practice.

ARTICLE SUMMARY

Strengths and Limitations of This Study

The study is strong in that it

- identifies natural, emergent patterns of skin-to-skin care with extremely preterm infants to reflect authentic human engagement experiences
- uses the evidence to suggest ways to target specific intervention areas for increasing skin-to-skin care
- supports current literature on the longer term benefits of skin-to-skin care

The study is limited by the fact that it

- uses one instrument to assess early cognitive and communication performance
- uses retrospective data

INTRODUCTION

The birth and subsequent hospitalization of an extremely premature infant is *a trauma event*. Unlike term infants, extremely premature infants (infants born at less than 27 weeks) spend the last trimester of their gestation ex utero, in an artificial, technology-laden neonatal intensive care (NICU) that places them at a developmental disadvantage. Monitors, tubing, and wires often create an environment that makes it difficult for authentic positive human interaction. In response, skin-to-skin care (SSC) has been incorporated into many NICU's across the world to re-establish this positive human contact.

Skin-to-skin care (SSC) is the practice of holding an infant upright on a parent's chest in a manner that provides maximum bare skin ventral contact. The practice impacts infant physiological stability, stress, and sleep as well as maternal stress and parenting behavior. SSC studies over the last twenty-five years[1-15] have collectively translated into a global acknowledgment that SSC is medically safe and has the potential to improve longer term cognitive, social, and emotional outcomes [16-18].

Despite the benefits of SSC, it is often difficult to engage some families in the practice. Findings from one of the most recent and comprehensive systematic reviews of the barriers and promoters of SSC (included in the complete package known as Kangaroo Mother Care)[19] identified multiple factors involved in integrating SSC. While current studies can help in the design of new interventions promoting SSC, they are also a reflection of participating in a highly supported and scrutinized form of SSC rather than parent practice as it naturally occurs in the NICU.

What remains unknown is how parents are actually engaging in the practice of SSC *when they are not involved in an SSC study*. A rigorous study of routine SSC across a cohort of extremely preterm infants could identify specific strategies and intervention points for care providers who aim to target their efforts at increasing parental engagement in SSC. The purpose of the current study was therefore to identify the naturalistic patterns of SSC that parents engage in with their extremely premature infants in an all-referral NICU and investigate how these patterns impact early infant cognitive and communicative performance. A secondary aim was to compare the relative effects of amount and intensity of SSC on these outcomes.

PATIENTS AND METHODS

This study was a retrospective cohort study of all infants admitted to the Small Baby Intensive Care Unit (SBICU) at Nationwide Children's Hospital (NCH) between 01/01/2010-11/30/2011. The SBICU is a specialized Level-IV all-referral unit staffed by a centralized team of nurses who provide protocol-driven care[20-22] to neonates born at a gestational age (GA) less than 27 completed weeks. All patients cared for in this unit are outborn and are transported to the SBICU for care of complications of prematurity including necrotizing enterocolitis (NEC), sepsis, surgical issues, brain injury, etc. This study was approved by the Institutional Review Board of Nationwide Children's Hospital (IRB#13-00042).

DATA

Retrospective data was extracted from the electronic medical record within three categories : a) medical b) SSC and c) cognitive and communication outcomes at follow-up. Medical record information extracted for each patient included gender, gestational age (GA) , birthweight (BW), length of hospital stay (LOS), occurrence or absence of intraventricular hemorrhage in the brain (IVH), number of days on a ventilator (IPPV days), days until first full feed by mouth (PO DOL), whether the patient was a twin, triplet, etc. (multiple births), and whether the patient received antenatal steroids.

Total hours of SSC care for each parent were recorded for each week after the baby was admitted to the NICU. Summary measures of SSC use included total hours of SSC, onset of SSC from day of admission, total hours of SSC performed by the mother and father, intensity of SSC (total number of days of SSC divided by the number of weeks of SSC), and whether the family participated in SSC after their child reached 33 weeks corrected age. To reduce the number of tested associations and aid in clinical interpretation, families were further classified as having a 'high' level of SSC participation if they were above the median in total hours, total hours per parent, and intensity of SSC. The remaining families were classified as having a 'low' level of SSC participation.

Cognitive and communication early performance outcomes were determined through the Bayley Scales of Infant Development, Third Edition (Bayley-III), a valid and reliable developmental assessment tool that is

widely used in neonatal follow-up. Assessments were performed at 6-months and 12-months by licensed professionals certified and trained in the tool (Neonatal Research Network standards REF) and scores were adjusted for prematurity. Descriptive classifications were used according to the protocol outlined by Pearson Clinical with infants scoring <80 being described as "Borderline" for developmental disability[23]. Consequently, scores were treated both as continuous variables and as dichotomized variables of scores <80 and scores ≥80.

STATISTICAL ANALYSIS

Statistical analysis was divided into three parts to address the clinical questions of interest. First, patterns of SSC participation were investigated graphically and associations between SSC measures and medical factors were tested. A logistic regression model was fit to contrast the probability of being a high vs. low SSC participant (as defined in the 'Data' section) as a function of gender, gestational age, birth weight, IVH, IPPV days, PO DOL, multiple births, and receipt of antenatal steroids. Backwards elimination was used to select a final explanatory model based on minimizing the Akaike's information criteria (AIC). Second, the association between SSC participation (high vs. low) and Bayley-III scores was evaluated. Association between continuous Bayley scores and SSC participation was investigated using boxplots and t-tests, while association between dichotomized Bayley scores and SSC participation was tested using the chi-squared test or Fisher's exact test. Associations between Bayley scores and SSC participation were additionally adjusted for confounding based on the medical factors found to be associated with SSC participation.

Patterns between medical factors and skin-to-skin care became evident and patterns of skin-to-skin care and the Bayley-III scores became evident. Consequently, for the final analysis we used our StickWRLD visual analytic software[24] to investigate potential triangulations among specific aspects of medical factors, skin-to-skin care, and the Bayley-III scores. All factors were loaded into the StickWRLD visual framework and initial two-node association patterns were set with an initial residual value[25] of 0.2. Subsequent analyses were performed incrementally at lower residual values to identify and compare associative relationships and to search for significant emerging triangular data patterns Analyses concluded when the model reached a threshold residual value corresponding to visual associative overload.

RESULTS

A total of 97 NICU patients were included in the study. Summary statistics of SSC usage (overall participation, participation by parent, SSC intensity and onset of SSC) are given in **Table 1**. Mothers represented the majority of overall SSC participation, as evidenced by **Figure 1**. Nine families were missing information on some aspect of SSC involvement. Among the remaining 88 families, 30 (34%) were classified as 'high' participants in SSC (above the median for total SSC hours, hours per parent, and SSC intensity) while the other 58 (66%) were classified as 'low' participation in SSC.

Table 1: Summary Statistics of Skin-to-Skin Care

SSC Metric	Mean (SD)	Median (IQR)	(Min, Max)
Total SSC (hours)	27.4 (29.8)	17.2 (5.1, 36.6)	(0, 129.8)
Mother SSC (hours)	22.8 (22.4)	17.2 (4.6, 30.9)	(0, 97)
Father SSC (hours)	5.8 (10.4)	1 (0, 7.5)	(0, 58)
SSC Intensity (hours / week)	2.3 (1.2)	2.2 (1.3, 3.2)	(0, 5)
SSC Onset (days)	6.2 (7.4)	4 (1.8, 8)	(0, 45)

SD = standard deviation
IQR = Inter-quartile range (25th percentile, 75th percentile)

Patterns of SSC participation between the postmenstrual ages of 23 and 40 weeks are displayed on a study-wide (total person-hours per week, **Figure 2**) and family (hours per family per week, **Figure 3**) basis. There was a steady increase in both total hours and hours per family until about 30 weeks, after which there was a corresponding precipitous decline until 40 weeks. Differences in medical factors between families with high vs. low SSC participation are given in **Table 2**. Receipt of antenatal steroids was the only significant ($p < 0.05$) finding, with 71% of children from families with high SSC participation receiving antenatal steroids and 91% of children with low family SSC participation receiving them.

Table 2: Medical Factors Influencing Skin-to-Skin Patterns

Medical Factors (categorical)		SSC Low	SSC High	p-value
Gender	Female	23 (0.4)	8 (0.27)	0.25
	Male	35 (0.6)	22 (0.73)	
Multiple Births	No	39 (0.67)	18 (0.60)	0.64
	Yes	19 (0.33)	12 (0.40)	
Antenatal Steroids	No	5 (0.09)	8 (0.29)	0.02
	Yes	53 (0.91)	20 (0.71)	
IVH	No	28 (0.48)	10 (0.33)	0.26
	Yes	30 (0.52)	20 (0.67)	
Medical Factors (continuous)		**SSC Low**	**SSC High**	**p-value**
Gestational Age (weeks)		24.9 (1)	24.4 (1.1)	0.06
BW (grams)		748.2 (164.5)	719.6 (188.5)	0.48
Length of hospital stay (days)		117.6 (46.1)	127.8 (40)	0.28
Days on ventilator		41.6 (28.6)	45 (33.2)	0.63
PO DOL (days)		106.1 (35.9)	117.7 (44.6)	0.26

Numbers in each cell are mean (std dev) for continuous and N (%) for categorical
p-value for categorical based on chi-squared, for continuous based on t-test

These factors (minus LOS, which was omitted because infants with longer LOS might be expected to have longer total SSC duration) were subsequently used to build a model to analyze the variance in SSC participation based on logistic regression with backwards elimination. The resulting model included antenatal steroids, birthweight, and IVH as predictors (**Table 3**). We investigated various cut-points for dichotomizing birth weight and found the 75th percentile to provide the best fit. Both receipt of antenatal steroids (OR = 0.136) and birth weight in the top quartile (OR = 0.152) were associated with *reduced* odds of high SSC participation, while presence of IVH was associated with increased odds (OR = 1.92).

Table 3: Odds Ratios for High Participation in Skin-to-Skin Care Based on Medical Factors

			Univariable			Multivariable		
Factor	Levels	High SSC	OR	95% CI	p-value	OR	95% CI	p-value
Antenatal Steroids	Yes	20/73 (27%)	4.16	(1.06, 18.2)	0.024	7.36	(1.67, 32.53)	0.008
	No	8/13 (62%)						
Birthweight	844+	5/24 (21%)	2.41	(0.74, 9.35)	0.13	6.59	(1.46, 29.84)	0.014
	< 844	25/64 (39%)						
IVH	Yes	20/50 (40%)	0.54	(0.19, 1.46)	0.26	0.52	(0.19, 1.43)	0.2
	No	10/38 (26%)						

Next, association between SSC participation and cognitive and communication outcomes (Bayley scores) at follow-up were investigated. **Figure 3** displays boxplots of the Bayley scores stratified by high and low SSC participation, while **Table 4** gives mean values for each exam by participation group. Communication scores at 12 months were somewhat higher in the high SSC group (p = 0.05). We then dichotomized the Bayley score at the borderline disability level (<80 vs. ≥ 80). **Table 5** displays the number and percentage of patients that fall below this borderline disability level along with univariate ORs. To account for potential confounding, ORs were further adjusted by fitting a multivariable model including the factors identified to be associated with SSC participation (BW, antenatal steroids, and IVH, **Table 5**). None of the associations (except for cognitive exam at 6 months) reached statistical significance,. However there was a relatively consistent OR of 2 for associations between each dichotomized Bayley score and SSC participation in the multivariable models. Adjusted ORs were higher than the unadjusted since SSC participation was associated with factors that were also generally associated with lower Bayley scores.

Table 4: Associations Between Low and High Participation in Skin-to-Skin Care and Bayley-III Cognitive and Communication Outcomes

Bayley-III Assessment	SSC Low	SSC High	p-value
Cognitive 6 months	92.7 (15.7)	96.3 (15.1)	0.3
Cognitive 12 months	93.1 (14.6)	93.9 (19.2)	0.84
Communication 6 months	93.1 (12.9)	96.9 (16.6)	0.28
Communication 12 months	90.7 (15.4)	98.2 (16.4)	0.05
Composite (Cog/Comm) 6 months	92.9 (12.6)	96.6 (14.4)	0.24
Composite (Cog/Comm) 12 months	91.9 (13.6)	96.1 (16.1)	0.25

Numbers in each cell are mean (std dev)

Table 5: Associations Between Low and High Participation in Skin-to-Skin Care and Borderline Disability (<80 vs. ≥80) Bayley-III Cognitive and Communication Outcomes

	Percent Borderline Developmental Disability		Univariable			Multivariable		
Bayley Exam	Low SSC	High SSC	OR	95% CI	p-value	OR	95% CI	p-value
Cognitive 6 mos	11/58 (19%)	2/30 (7%)	3.28	(0.92, 11.67)	0.07	4.46	(1.08, 18.41)	0.04
Cognitive 12 mos	8/49 (16%)	2/28 (7%)	2.54	(0.66, 9.77)	0.18	2.87	(0.62, 13.26)	0.18
Communication 6 mos	9/58 (16%)	4/30 (13%)	1.19	(0.52, 2.72)	0.67	1.72	(0.64, 4.61)	0.28
Communication 12 mos	13/49 (27%)	5/29 (17%)	1.73	(0.88, 3.42)	0.11	2.00	(0.87, 4.57)	0.10
Composite (Cog/Comm) 6 mos	8/58 (14%)	3/30 (10%)	1.44	(0.52, 3.95)	0.48	2.22	(0.68, 7.28)	0.19
Composite (Cog/Comm) 12 mos	8/49 (16%)	3/28 (11%)	1.63	(0.58, 4.53)	0.35	2.22	(0.66, 7.44)	0.20

Multivariable models include antenatal steroids, birthweight, and IVH

A final exploratory analysis of the data set was performed using StickWRLD software to identify possible emergent interactive network associations among SSC measures, medical factors, and Bayley-III scores. Network displays (**Figure 5**) indicated separate, but convergent significant associations between SSC measures and medical factors and the 12-month Bayley-III cognitive scores.

DISCUSSION

Engagement in SSC with extremely premature infants in the NICU varies among families. However, SSC patterns are evident in this population and potentially have an impact on early cognitive and communication performance. These findings are not new in that a wealth of literature has been devoted to the short- and long-term developmental benefits of SSC[26-30]. What is initially novel about our findings is that we have found a strong indication that SSC *before 30 weeks postmenstrual age* may play a crucial role in the cognitive and communication development of extremely premature infants. The overwhelming majority of SSC time in our Unit was spent before 30 weeks postmenstrual age, a period of time that is often considered developmentally marginal in that underlying brain structure and auditory/visual development are not at full capacity[31]. This elicits additional questions about why parents choose to stop at this corrected age, the underlying mechanisms of communication development in this population, and the potential added dimensional role of SSC as a communication intervention in the NICU.

A second novel finding is that extremely preterm infants who had higher birthweights, had received antenatal steroids, and who did not have IVH, were at decreased odds of receiving a 'high' level of skin-to-skin care (where high level was defined as above the median for total hours, frequency, and hours for each parent). That is, infants who were perceived as being "less sick" were at reduced odds of receiving a high level of SSC. This poses questions about how medical caregivers and parents perceive the practice of skin-to-skin care and how developmental information is being communicated between parents and the medical team.

Finally, our findings identify a concerning gap in skin-to-skin care from 30 weeks corrected age to term age. Numerous studies highlight the essential nature of this time period for appropriate neurodevelopment[32-36]. However, extremely preterm infants, who represent one of the highest risk categories for neurodevelopmental disability, are not receiving an intervention shown to improve neurodevelopment at a fundamental time point of their developmental trajectory.

Limitations of our study include the limited sample size (97 NICU patients) and the observational nature of the study. Confounding is thus an issue when investigating associations, however as noted previously NICU patients receiving SSC were actually associated with medical factors that were in turn associated with lower early-stage cognitive and communication scores. The study is also based on patients from a single hospital, and may not generalize to other neonatal units. While we did see a relatively consistent pattern of association (c.f. **Table 5**) between high / low SSC participation and the Bayley-III Cognitive and Communication Outcomes dichotomized at borderline disability (<80 vs. ≥80), we reiterate that none of these associations achieved statistical significance and thus can only be viewed as preliminary results in need of confirmatory analysis. If the observed associations were to hold in the population along with the same level of SSC participation and prevalence of borderline disability, then roughly 460 total subjects would be needed to achieve 80% power to detect the association in a larger study.

Our research suggests that developmental investigations into very early time points in the life of extremely premature infants is warranted and critical to understanding how to fully optimize future developmental social and cognitive processes. Additional studies, involving more comprehensive measures and analyses of the

early developmental NICU environment (22-30 weeks postmenstrual age) could help inform new designs for developmental caregiving and promotion of skin-to-skin care throughout the duration of hospitalization.

CONTRIBUTORSHIP STATEMENT

All authors contributed equally to this manuscript. Jenn Gonya and Guy Brock designed and conducted the study, analyzed the biostatistical portion, and wrote and reviewed manuscript drafts. Jenn Gonya, Will Ray, and R Wolfgang Rumpf performed visual analytics, wrote sections of the manuscript, and reviewed and refined manuscript drafts.

COMPETING INTERESTS

There are no competing interests with regard to this manuscript and project.

FUNDING

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

DATA SHARING STATEMENT

Data is stored on our internal, high security server. De-identified data set available upon request.

REFERENCES

1. Colonna F, Uxa F, daGraca AM, de Vonderweld U. The “kangaroo-mother” method: evaluation of an alternative model for care of low birth weight newborns in developing countries. *Int J Gynaecol Obstet* 1990; 31(4): 335-9.
2. de Leeuw R, Colin EM, Dunnebier EA, Mirmiran M. Physiological effects of kangaroo care in very small preterm infants. *Biol Neonate* 1991; 59(3): 149-55.
3. Ludington-Hoe SM, Thompson C, Swinth J, Hadeed AJ, Anderson GC. Kangaroo care: research results, and practice implications and guidelines. *Neonatal Netw* 1994; 13(1): 19-27.
4. Bauer K, Uhrig C, Sperling P, Pasel K, Wieland C, Versmold HT. Body temperatures and oxygen consumption during skin-to-skin (kangaroo) care in stable preterm infants weighing less than 1500 grams. *J Pediatric* 1997; 130(2): 240-4.
5. Feldman R, Eidelman AI. Intervention programs for premature infants. How and do they affect development? *Clin Perinatol* 1998; 25(3): 613-26.
6. Tornhage CJ, Stuge E, Lindberg T, Serenius F. First week kangaroo care in sick very preterm infants. *Acta Paediatr* 1999; 88(12): 1402-4.
7. Ohgi S, Fukuda M, Moriuchi H, Kusumoto T, Akiyama T, et al. Comparison of kangaroo care and standard care: behavioral organization, development, and temperament in healthy, low-birth-weight infants through 1 year. *J Perinatol* 2002; 22(5): 374-9.
8. Ludington-Hoe SM, Ferreira C, Swinth J, Ceccardi JJ. Safe criteria and procedure for kangaroo care with intubated preterm infants. *J Obstet Gynecol Neonatal Nurs* 2003; 32(5): 579-88.
9. Begum EA, Bonno M, Ohtani N, Yamashita S, Tanaka S, et al. Cerebral oxygenation responses during kangaroo care in low birth weight infants. *BMC Pediatr* 2008; 8:51.
10. Neu M, Robinson J. Maternal holding of preterm infants during the early weeks after birth and dyad interaction at six months. *J Obstet Gynecol Neonatal Nurs* 2010; 39(4): 401-14.
11. Conde-Agudelo A, Belizan JM, Diaz-Rossello J. Kangaroo mother care to reduce morbidity and mortality in low birthweight infants. *Cochrane Database Syst Rev* 2011; 3: CD002771.
12. Ludington-Hoe SM. Thirty years of kangaroo care science and practice. *Neonatal Netw* 2011; 30(5): 357-62.
13. Kaffashi F, Scher MS, Ludington-Hoe SM, Loparo KA. An analysis of the kangaroo care intervention using neonatal EEG complexity: a preliminary study. *Clin Neurophysiol* 2013; 124(2): 238-46.
14. Conde-Agudelo A, Diaz-Rossello J. Kangaroo mother care to reduce morbidity and mortality in low birthweight infants. *Cochrane Database Syst Rev* 2014;4: CD002771.
15. Morelius E, Ortenstran A, Theodorsson E, Frostell A. A randomized trial of continuous skin-to-skin contact after preterm birth and the effects on salivary cortisol, parental stress, depression, and breastfeeding. *Early Hum Dev* 2015; 91(1): 63-70.
16. Boundy EO, Dastjerdi R, Spegelman D, Fawzi WW, Missmer SA, et al. Kangaroo mother care and neonatal outcomes: a meta-analysis. *Pediatrics* 2016; 137(1).
17. Flackin R, Lehtnonen L, Thomson G, Axelin A, Moran VH, et al. Closeness and separation in neonatal intensive care. *Acta Paediatr* 2012; 101(10): 1032-7.
18. Feldman R, Rosenthal Z, Eidelman AI. Maternal-preterm skin-to-skin contact enhances child physiologic organization and cognitive control across the first 10 years of life. *Biol Psychiatry* 2014; 75(1): 56-64.
19. Seidman G, Unnikrishnan S, Kenny E, Myslinski S, Cairns-Smith S, et al. Barriers and enablers of kangaroo mother care practice: a systematic review. *PLoS One* 2015; 10(5): e0125643.

20. Nankervis CA, Martin EM, Crane ML, Samson KS, Welty SE, Nelin LD. Implementation of a multidisciplinary guideline-driven approach to the care of the extremely premature infant improved hospital outcomes. *Acta Paediatr* 2010; 99: 188-93.
21. Martin E., McGregor S, Gonya J, Foor, N, Shepherd, E, Nelin, L. The effect of developing a small baby program on outcomes in extremely preterm infants born at <27 weeks gestation. Poster presentation at the national conference of the Pediatric Academic Society. 2015; April, San Diego, California.
22. Shepherd E, Calvert T, Martin E, Hitchner J, Welty, S, Nelin, L. Outcomes of extremely premature infants admitted to a children's hospital depends on referring hospital. *J Neonat Perinat Med* 2011; 4: 45-53.
23. Pearson Education. Bayley scales of infant development (third edition). Pearson Clinical 2008 Training.
24. Ray WC. MAVL and StickWRLD: visually exploring relationships in nucleic acid sequence alignments. *Nucleic Acids Res* 2004; 32: 59-63.
25. Ray WC, Wolock SL, Li N, Bartlett CW. StickWRLD: Interactive visualization of massive parallel contingency data for personalized analysis to facilitate precision medicine. Proceedings of the 3rd annual Workshop on Visual Analytics in Healthcare, in conjunction with the American Medical Informatics Symposium. 2013; November.
26. Silva MG, Barros MC, Pessoa UM, Guinsburg R. Kangaroo-mother care method and neurobehavior of preterm infants. *Early Hum Dev* 2016; 95: 55-9.
27. Feldman R, Eidelman AI. Skin-to-skin contact (kangaroo care) accelerates autonomic and neurobehavioural maturation in preterm infants. *Dev Med Child Neurol* 2003; 45(4): 274-81.
28. Feldman R, Eidelman AI, Sirota, Weller A. Comparison of skin-to-skin (kangaroo) and traditional care: parenting outcomes and preterm infant development. *Pediatrics* 2002; 110: 16-26.
29. Feldman R. From biological rhythms to social rhythms: physiological precursors of mother-infant synchrony. *Dev Psychol* 2006; 42(1) 175-88.
30. Key APF, Lambert EW, Aschner JL, Maitre NL. Influence of gestational age and postnatal age on speech sound processing in NICU infants. *Psychophys* 2012; 49: 720-731.
31. Fetal Development: Research on Brain and Behavior, Environmental Influences, and Emerging Technologies. Reissland N, Kisilevsky BS (Eds.) Switzerland: Springer International 2016.
32. Thomason ME, Grove L, Lozon TA, Vila AM, Ye Y, et al. Age related increases in long-range connectivity in fetal functional neural connectivity networks in utero. *Developmental Cog Neurosci* 2015; 11: 96-104.
33. Krueger C, Garvan C. Emergence and retention of learning in early fetal development. *Infant Behavior and Dev* 2014; 37(2): 162-173.
34. Pearson J, Tarabulsy GM, Bussieres E. Foetal programming and cortisol secretion in early childhood: a metal-analysis of different programming variables. *Infant Behavior and Dev* 2015; 40: 204-215.
35. Fetal Growth and Development. Harding R, Bocking AD (Eds.) 2001. United Kingdom: Cambridge University Press.

FIGURES AND LEGENDS

FIGURE 1 – Overall and Parent Specific SSC Participation: Boxplots displaying the distribution of overall SSe participation and by parent. Thick horizontal lines give medians while boxes display the middle 50% of the data (25th and 75th percentiles). Points beyond the whiskers represent outliers.

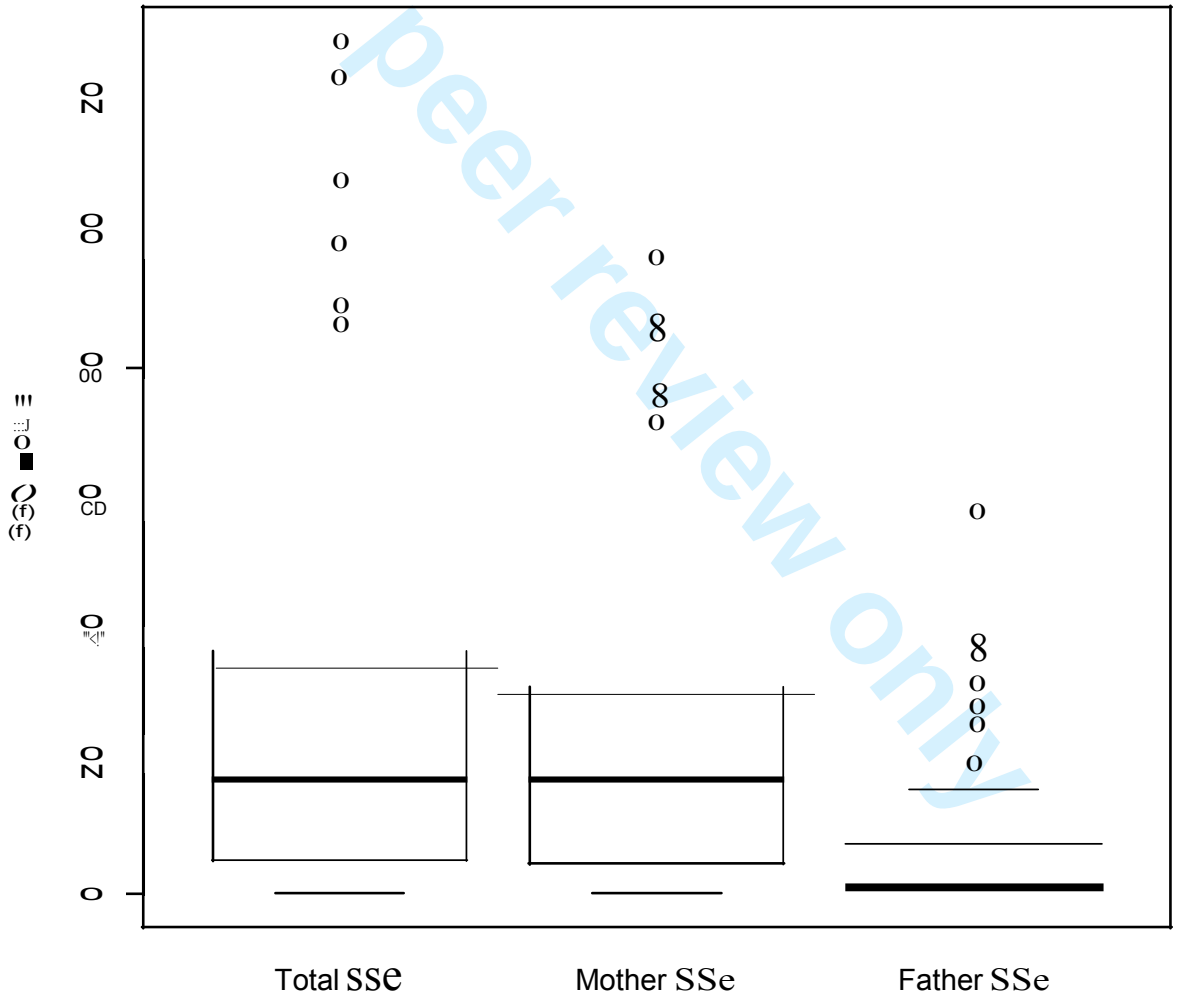


FIGURE 2 – Total SSC hours per week: Blue line displays the total number of SSC hours per week for all families in the study, by postmenstrual age (PMA). Since the unit is an all-referral unit, the pink line indicates the total number of extremely preterm infants in the cohort hospitalized in the NICU at the given PMA. All infants were admitted before 30 weeks PMA.

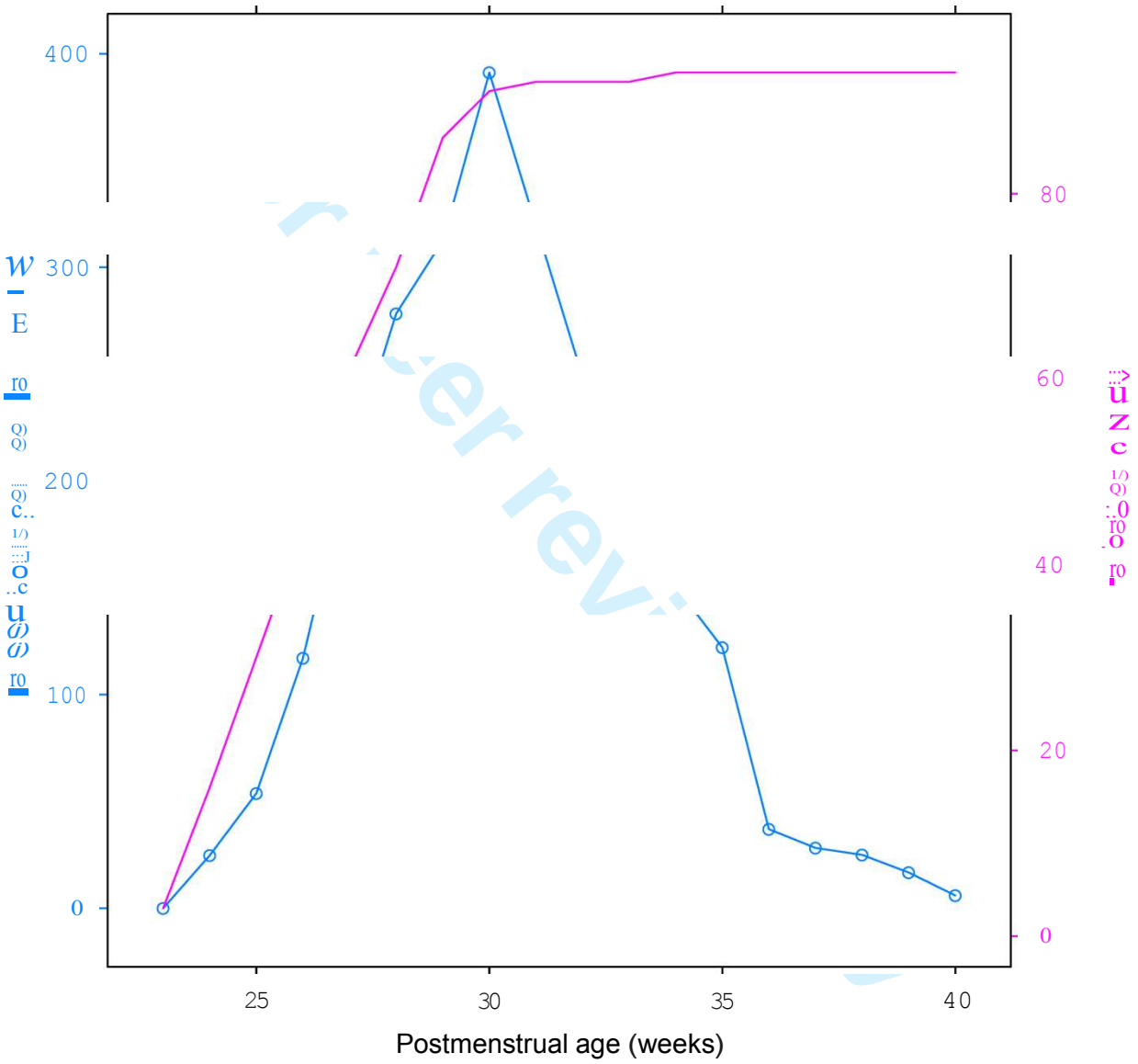


FIGURE 3 – SSe intensity (hours per week per family): Blue line displays the average SSe intensity (hours per family per week) by postmenstrual age. Again, since the unit is an all-referral unit, the pink line indicates the total number of extremely preterm infants in the cohort hospitalized in the NICU at the given PMA.

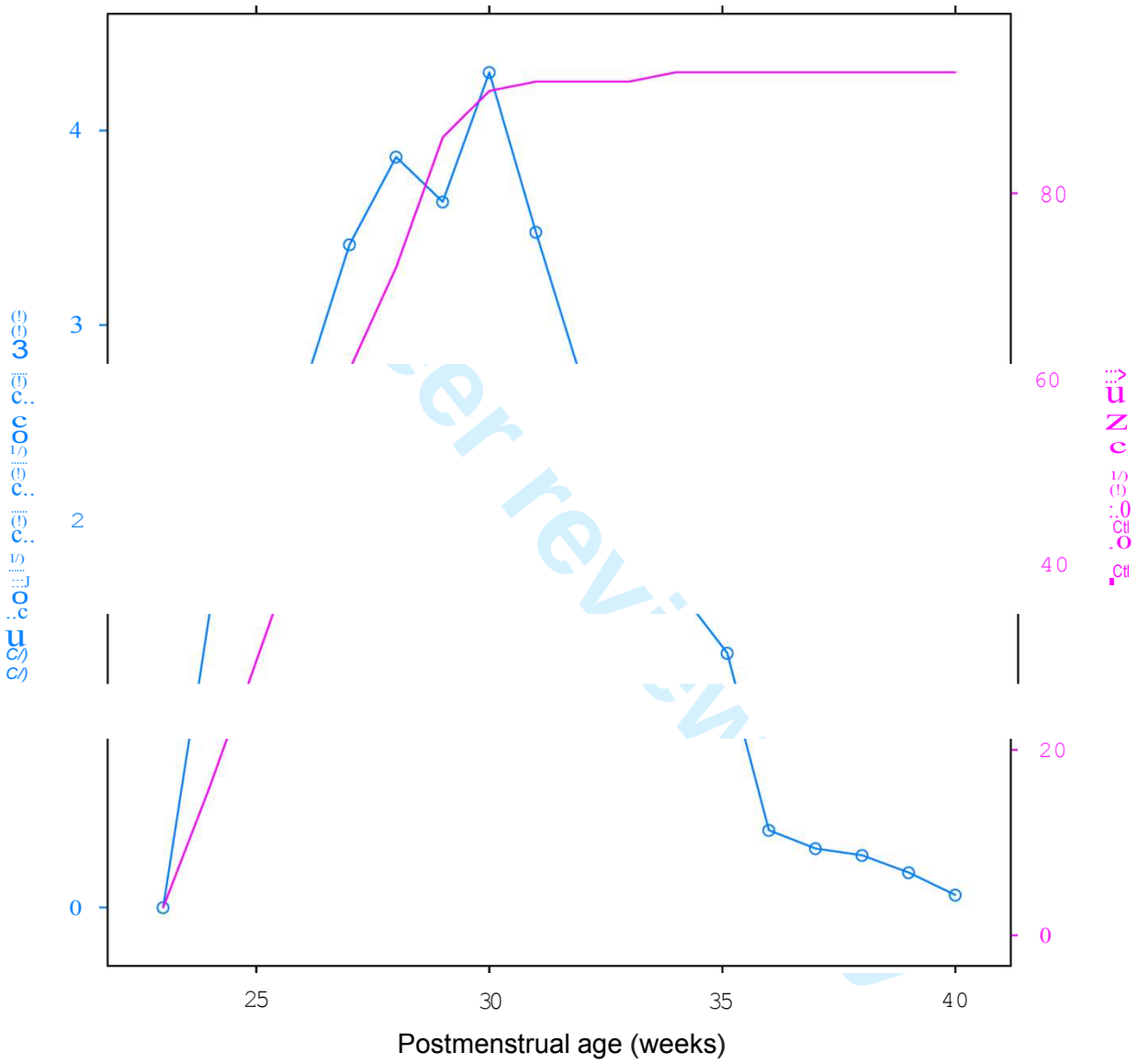


FIGURE 4 – Bayley Cognitive and Communication scores by SSC participation: Boxplots displaying the distribution of Bayley cognitive, communication, and combined cognitive-communication (Cog-Comm) scores at 6 and 12 months by SSC participation (high vs. low). High SSC participation was defined as having above the median participation for total SSC hours, mother SSC hours, father SSC hours, and SSC intensity (see text for details). Thick horizontal lines give medians while boxes display the middle 50% of the data (25th and 75th percentiles). Points beyond the whiskers represent outliers.

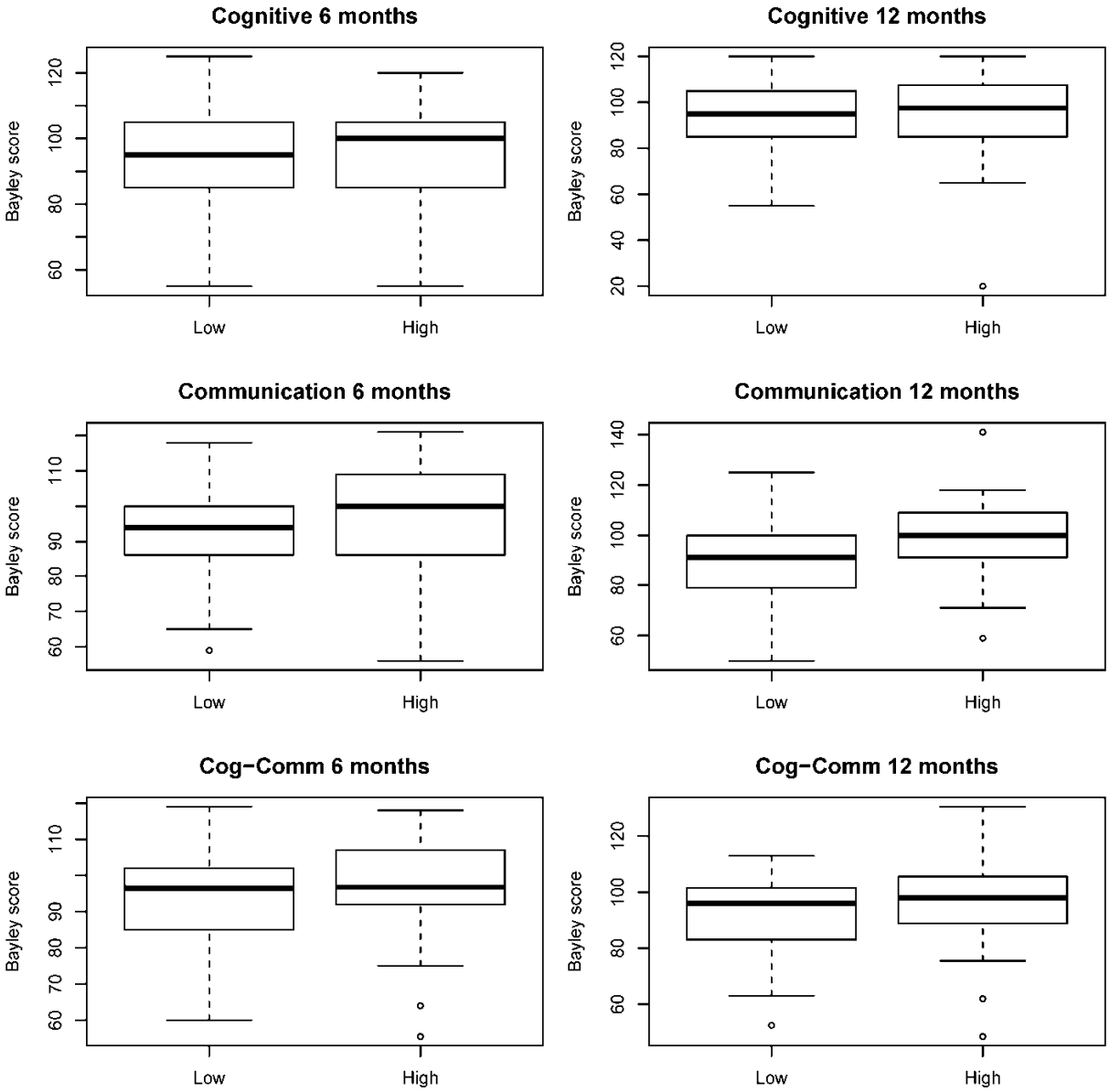
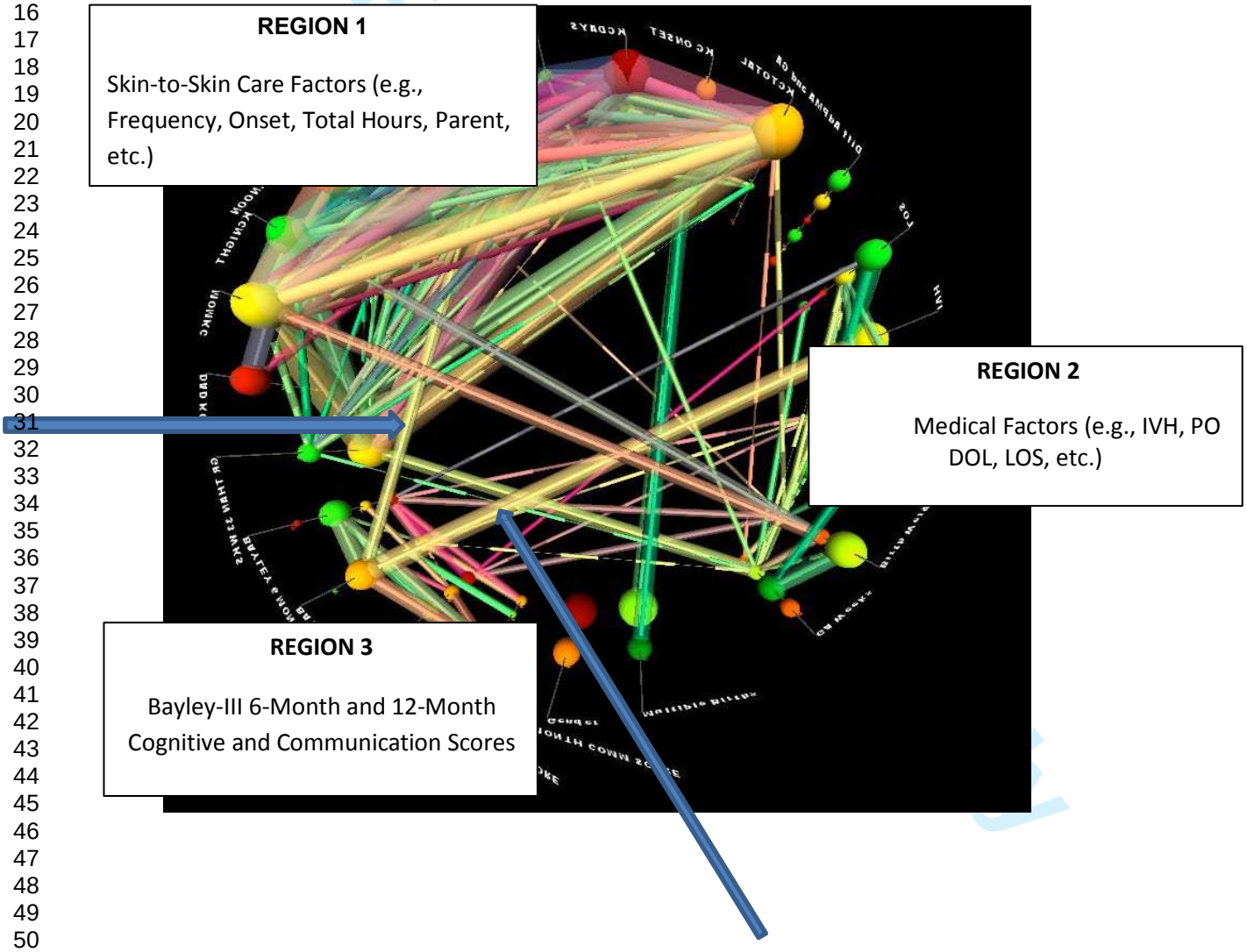


FIGURE 5 – Visual Analytical Display from StickWRLD Software. The visual space is divided into three main regions: Medical Factors, Skin-to-Skin Factors, and Bayley-III Scores. Each line represents a significant correlation between factors with stronger correlations represented by lines that are thicker in diameter. Within region correlations are evident and expected. Two blue arrows indicate two unexpected strong correlations (one from each region) that converge on the Bayley-III 12-Month Cognitive Score, highlighting **Skin-to Skin Care Frequency** and presence or absence of **Intraventricular Hemmorhage (IVH)** as parallel, but non-interactive factors impacting the score.



STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	p.1
		p.2
Introduction		
Background/rationale	2	p.4
Objectives	3	p.1 and p.4
Methods		
Study design	4	p.5
Setting	5	p.5
Participants	6	p.5
Variables	7	pp.5-6
Data sources/ measurement	8*	pp.5-6
Bias	9	p. na Retrospective Study
Study size	10	p. na All infants in cohort included
Quantitative variables	11	p. 5
Statistical methods	12	p. 6

Continued on next page

Results		
Participants	13*	p.7
Descriptive data	14*	p. 7
Outcome data	15*	pp. 7-10
Main results	16	pp.7-10
Other analyses	17	p. 10
Discussion		
Key results	18	pp. 10-12
Limitations	19	p. 11
Interpretation	20	pp. 10-12
Generalisability	21	p. 11
Other information		
Funding	22	p. 12

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Investigating Skin-to-Skin Care Patterns with Extremely Preterm Infants in the NICU and Their Effect on Early Cognitive and Communication Performance

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-012985.R1
Article Type:	Research
Date Submitted by the Author:	05-Oct-2016
Complete List of Authors:	Gonya, Jenn; The Research Institute at Nationwide Children's Hospital, Center for Perinatal Research Ray, William; The Research Institute at Nationwide Children's Hospital, Battelle Center for Mathematical Medicine Rumpf, R Wolfgang; The Research Institute at Nationwide Children's Hospital, Battelle Center for Mathematical Medicine Brock, Guy; The Ohio State University, Center for Biostatistics
Primary Subject Heading:	Intensive care
Secondary Subject Heading:	Paediatrics
Keywords:	extreme prematurity, Neonatal intensive & critical care < INTENSIVE & CRITICAL CARE, NEONATOLOGY

Investigating Skin-to-Skin Care Patterns with Extremely Preterm Infants in the NICU and Their Effect on Early Cognitive and Communication Performance

Jenn Gonya, PhD
The Research Institute at Nationwide Children's Hospital
Center for Perinatal Research
575 Children's Crossroad
RBIII WB6139
Columbus, Ohio USA 43215
jenn.gonya@nationwidechildrens.org
614-355-6653

William C. Ray, PhD
The Research Institute at Nationwide Children's Hospital
Battelle Center for Mathematical Medicine
Columbus, Ohio USA

R. Wolfgang Rumpf, PhD
The Research Institute at Nationwide Children's Hospital
Battelle Center for Mathematical Medicine
Columbus, Ohio USA

Guy Brock, PhD
The Ohio State University Department of Biomedical Informatics
Center for Biostatistics
Columbus, Ohio USA

Keywords: extremely preterm, neonatal intensive care, skin-to-skin care, neonatal neurodevelopment

Word Count: 3142

ABSTRACT

Objectives

Primary

- Identify skin-to-skin patterns that parents engage in with their extremely preterm infant during hospitalization in the neonatal intensive care unit
- Investigate how patterns of skin-to-skin care impact infant early cognitive and communication performance

Secondary

- Explore how medical and skin-to-skin factors interact to explain outcomes in infant early cognitive and communication performance

Design

This was a retrospective cohort study.

Setting

This study took place in a Level-IV all-referral neonatal intensive care unit in the Midwest specializing in the care of extremely preterm infants.

Participants

Data was collected from the electronic medical records of all extremely preterm infants (gestational age < 27 weeks) admitted to the unit during 2010-2011 and who completed 6- and 12-month developmental assessments in the follow-up clinic (n=97).

Outcome Measures

- Bayley Scales of Infant Development, Third Edition (Bayley-III) – Cognitive and Communication Subscales
- Skin-to-Skin Care Patterns: Total Hours of Maternal and Paternal Participation Throughout Hospitalization,Total Duration in Weeks, Frequency (Hours per Week)

Analysis

Extracted data was analyzed through a multi-step process of logistic regressions, t-tests, chi-squared tests, and Fisher's exact tests followed with exploratory network analysis using novel visual analytic software.

Results

- Mothers provide the majority of skin-to-skin care with extremely preterm infants.
- Skin-to-skin care hours (both total amount and frequency) decline sharply at 30 weeks corrected age, regardless of when extremely preterm infants are admitted.
- Extremely preterm infants who had higher birthweights, received antenatal steroids, and who did not have IVH were less likely to participate in significant amounts of skin-to-skin care.
- Extremely preterm infants who received above the sample median in total hours, weekly frequency, and total hours from mothers *and* fathers of skin-to-skin care were more likely to score ≥80 on the cognitive and communication scales of the Bayley-III (odds ratios of roughly two for each of the dichotomized scores, after adjustment for BW, antenatal steroids, and IVH). However the results were not statistically significant (p>0.05).
- Exploratory network analysis suggests that medical and skin-to-skin factors play a parallel, non-synergistic role in contributing to early cognitive and communication performance as assessed through the Bayley-III.

Conclusion

This study presents suggestive results concerning the association between early and frequent skin-to-skin care with extremely preterm infants and early cognitive and communication performance. However the results were not statistically significant and a larger study is needed to validate these initial findings. Interventions aimed at increasing skin-to-skin care should include supports for fathers and emphasize the potential longer term developmental benefits of the practice.

ARTICLE SUMMARY

Strengths and Limitations of This Study

The study is strong in that it

- identifies natural, emergent patterns of skin-to-skin care with extremely preterm infants to reflect authentic human engagement experiences
- uses the evidence to suggest ways to target specific intervention areas for increasing skin-to-skin care
- supports current literature on the longer term benefits of skin-to-skin care

The study is limited by the fact that it

- uses one instrument to assess early cognitive and communication performance
- uses retrospective data

INTRODUCTION

The birth and subsequent hospitalization of an extremely preterm infant is *a trauma event*. Unlike term infants, extremely preterm infants (infants born at less than 27 weeks) spend the last trimester of their gestation ex utero, in an artificial, technology-laden neonatal intensive care (NICU) that places them at a developmental disadvantage. Monitors, tubing, and wires often create an environment that makes it difficult for authentic positive human interaction. In response, skin-to-skin care (SSC) has been incorporated into many NICU's across the world to re-establish this positive human contact.

Skin-to-skin care (SSC) is the practice of holding an infant upright on a parent's chest in a manner that provides maximum bare skin ventral contact. The practice impacts infant physiological stability, stress, and sleep as well as maternal stress and parenting behavior. SSC studies over the last twenty-five years[1-15] have collectively translated into a global acknowledgment that SSC is medically safe and significantly affects longer term neurodevelopmental cognitive, social, and emotional outcomes [16-22].

Despite the benefits of SSC, it is often difficult to engage some families in the practice. Findings from one of the most recent and comprehensive systematic reviews of the barriers and promoters of SSC (included in the complete package known as Kangaroo Mother Care)[23] identified over thirty-five factors involved in integrating SSC into the NICU environment. The top three barriers to SSC were issues with the NICU physical facility, negative impressions by the staff about the practice, and fear of injuring the infant during SSC. In contrast, SSC increased when mothers felt attached to their infants, felt confident in their parenting role, and received support from family, friends, or other mothers. While current studies, such as those found in the systematic review, can help in the design of new interventions promoting SSC, many are a reflection of participating in a highly supported and scrutinized form of SSC rather than parent practice as it naturally occurs in the NICU.

What remains unknown is how parents are actually engaging in the practice of SSC in an all referral NICU setting in the United States *when they are not involved in an SSC study*. A rigorous study of routine SSC across a cohort of extremely preterm infants could identify specific strategies and intervention points for care providers who aim to target their efforts at increasing parental engagement in SSC. Therefore, the purpose of the current study was to identify the naturalistic patterns of SSC that parents engage in with their extremely preterm infants in an all-referral NICU and investigate how these patterns impact early infant cognitive and communicative

performance. A secondary aim was to compare the relative effects of amount and intensity of SSC on these outcomes.

PATIENTS AND METHODS

This study was a retrospective cohort study of all infants admitted to the Small Baby Intensive Care Unit (SBICU) at Nationwide Children's Hospital (NCH) between 01/01/2010-11/30/2011. The SBICU is a specialized Level-IV all-referral unit staffed by a centralized team of nurses who provide protocol-driven care[23-25] to neonates born at a gestational age (GA) less than 27 completed weeks. These protocols, organized within the Small Baby Guidelines, outline how to specifically address the medical and developmental needs of extremely preterm infants. Skin-to-skin care is specifically designated as a critical practice for medical stability and neurodevelopmental outcomes and is described as a care piece that should be strongly encouraged whenever possible, as long as possible. All patients cared for in this unit are outborn and are transported to the SBICU for care of complications of prematurity including necrotizing enterocolitis (NEC), sepsis, surgical issues, brain injury, etc. This study was approved by the Institutional Review Board of Nationwide Children's Hospital (IRB#13-00042) as an exempt study.

DATA

Retrospective data was extracted from the electronic medical record within three categories : a) medical b) SSC and c) cognitive and communication outcomes at follow-up. Medical record information extracted for each patient included gender, gestational age (GA) , birthweight (BW), length of hospital stay (LOS), occurrence or absence of intraventricular hemorrhage in the brain (IVH), number of days on a ventilator (IPPV days), days until first full feed by mouth (PO DOL), whether the patient was a twin, triplet, etc. (multiple births), and whether the patient received antenatal steroids. These variables were selected based on the outcome trajectories calculator developed by the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network.[26]

Total hours of SSC care for each parent were recorded for each day after the baby was admitted to the NICU until discharge. Hours were documented by the nursing staff in the patient medical record. (Audits performed comparing parental report and nurse report of SSC time indicated 89% consistency.) Summary measures of SSC use included total hours of SSC, the number of days between the day of admission and the first onset of SSC, total hours of SSC performed by the mother and father, intensity of SSC (average days of

SSC per week), and whether the family participated in SSC after their child reached 33 weeks corrected age, a critical period of auditory development .[27] To reduce the number of tested associations and aid in clinical interpretation, families were further classified as having a 'high' level of SSC participation if they were above the median in total hours, total hours for mother and total hours for father, and frequency of SSC (that is, above the median for each of the four variables). The remaining families were classified as having a 'low' level of SSC participation.

Cognitive and communication early performance outcomes were determined through the Bayley Scales of Infant Development, Third Edition (Bayley-III), a valid and reliable developmental assessment tool that is widely used in neonatal follow-up. Assessments were performed at 6-months and 12-months by licensed professionals certified and trained in the tool[28] and scores were adjusted for prematurity. Descriptive classifications were used according to the protocol outlined by Pearson Clinical with infants scoring <80 being described as "Borderline" for developmental disability.[29] Consequently, scores were treated both as continuous variables and as dichotomized variables of scores <80 and scores ≥80.

STATISTICAL ANALYSIS

Statistical analysis was divided into three parts to address the clinical questions of interest. First, since the study is observational in nature patterns of SSC participation ('high' vs. 'low', as defined in the 'Data' section) were investigated graphically and associations between SSC measures and medical factors were tested. These associations were considered to explore for potential factors associated with SSC participation and to account for potential confounding of SSC with these other clinical / medical variables. A logistic regression model was fit to contrast the probability of being a high vs. low SSC participant (as defined in the 'Data' section) as a function of gender, gestational age, birth weight, IVH, IPPV days, PO DOL, multiple births, and receipt of antenatal steroids. Backwards elimination was used to select a final explanatory model based on minimizing the Akaike's information criteria (AIC). Second, the association between SSC participation (high vs. low) and Bayley-III scores was evaluated. Strength of association between raw Bayley scores and SSC participation (high vs. low) was quantified and tested using point biserial correlations (r_{pb}, tested against a null that the correlation was zero). Bayley scores dichotomized at the borderline disability level (<80 vs. ≥ 80) were tested for association with SSC participation using the chi-squared test or Fisher's exact test. Associations between dichotomized Bayley scores and SSC participation were additionally adjusted for confounding based on the

medical factors found to be associated with SSC participation.

Patterns between medical factors and skin-to-skin care became evident and patterns of skin-to-skin care and the Bayley-III scores became evident. Consequently, for the final analysis we used our StickWRLD visual analytic software[30-31] to investigate potential triangulations among specific aspects of medical factors, skin-to-skin care, and the Bayley-III scores. All factors were loaded into the StickWRLD visual framework and initial two- node association patterns were set with an initial residual value[32] of 0.2. Subsequent analyses were performed incrementally at lower residual values to identify and compare associative relationships and to search for significant emerging triangular data patterns. Analyses concluded when the model reached a threshold residual value corresponding to visual associative overload.

RESULTS

A total of 97 NICU patients were included in the study. The gestational age ranged from 22 weeks to 26 weeks with an overall median of 25 weeks. Summary statistics of SSC usage (overall participation, participation by parent, SSC intensity and onset of SSC) are given in **Table 1**. Mothers represented the majority of overall SSC participation, as evidenced by **Figure 1**. Nine families were missing information on some aspect of SSC involvement. Among the remaining 88 families, 30 (34%) were classified as 'high' participants in SSC (above the median for total SSC hours, hours per parent, and SSC intensity) while the other 58 (66%) were classified as 'low' participation in SSC.

Table 1: Summary Statistics of Skin-to-Skin Care from admission to 40 weeks postmenstrual age

SSC Metric	Mean (SD)	Median (IQR)	(Min, Max)
Total SSC (hours)	27.4 (29.8)	17.2 (5.1, 36.6)	(0, 129.8)
Mother SSC (hours)	22.8 (22.4)	17.2 (4.6, 30.9)	(0, 97)
Father SSC (hours)	5.8 (10.4)	1 (0, 7.5)	(0, 58)
SSC Frequency (days / week)	2.3 (1.2)	2.2 (1.3, 3.2)	(0, 5)
SSC Onset (days)	6.2 (7.4)	4 (1.8, 8)	(0, 45)

SD = standard deviation
IQR = Inter-quartile range (25th percentile, 75th percentile)

Patterns of intensity and total hours of SSC participation between the postmenstrual ages of 23 and 40 weeks are displayed on a study- wide (total person-hours per week, **Figure 2**) and family (hours per family per week, **Figure 3**) basis. There was a steady increase in both total hours and hours per family until about 30 weeks,

after which there was a corresponding precipitous decline until 40 weeks. Differences in medical factors between families with high vs. low SSC participation are given in **Table 2**. Receipt of antenatal steroids was the only significant ($p < 0.05$) finding, with 71% of children from families with high SSC participation receiving antenatal steroids and 91% of children with low family SSC participation receiving them.

Table 2: Medical Factors Influencing Skin-to-Skin Patterns

Medical Factors (categorical)		SSC Low	SSC High	p-value
Gender	Female	23 (0.4)	8 (0.27)	0.25
	Male	35 (0.6)	22 (0.73)	
Multiple Births	No	39 (0.67)	18 (0.60)	0.64
	Yes	19 (0.33)	12 (0.40)	
Antenatal Steroids	No	5 (0.09)	8 (0.29)	0.02
	Yes	53 (0.91)	20 (0.71)	
IVH	No	28 (0.48)	10 (0.33)	0.26
	Yes	30 (0.52)	20 (0.67)	
Medical Factors (continuous)		**SSC Low**	**SSC High**	**p-value**
Gestational Age (weeks)		24.9 (1)	24.4 (1.1)	0.06
BW (grams)		748.2 (164.5)	719.6 (188.5)	0.48
Length of hospital stay (days)		117.6 (46.1)	127.8 (40)	0.28
Days on ventilator		41.6 (28.6)	45 (33.2)	0.63
PO DOL (days)		106.1 (35.9)	117.7 (44.6)	0.26

Numbers in each cell are mean (std dev) for continuous and N (%) for categorical
p-value for categorical based on chi-squared, for continuous based on t-test

These factors (minus LOS, which was omitted because infants with longer LOS might be expected to have longer total SSC duration) were subsequently used to build a model to analyze the variance in SSC participation based on logistic regression with backwards elimination. The resulting model included antenatal steroids, birthweight, and IVH as predictors (**Table 3**). We investigated various cut-points for dichotomizing birth weight and found the 75th percentile to provide the best fit. Both receipt of antenatal steroids (OR = 0.136) and birth weight in the top quartile (OR = 0.152) were associated with *reduced* odds of high SSC participation, while presence of IVH was associated with increased odds (OR = 1.92).

Table 3: Odds Ratios for High Participation in Skin-to-Skin Care Based on Medical Factors

			Univariable			Multivariable		
Factor	Levels	High SSC	OR	95% CI	p-value	OR	95% CI	p-value
Antenatal Steroids	Yes	20/73 (27%)	4.16	(1.06, 18.2)	0.024	7.36	(1.67, 32.53)	0.008
	No	8/13 (62%)						
Birthweight	844+	5/24 (21%)	2.41	(0.74, 9.35)	0.13	6.59	(1.46, 29.84)	0.014
	< 844	25/64 (39%)						
IVH	Yes	20/50 (40%)	0.54	(0.19, 1.46)	0.26	0.52	(0.19, 1.43)	0.2
	No	10/38 (26%)						

Next, association between SSC participation and cognitive and communication outcomes (Bayley scores) at follow-up were investigated. **Figure 4** displays boxplots of the Bayley scores stratified by high and low SSC participation, while **Table 4** gives mean values for each exam by participation group. Communication scores at 12 months were somewhat higher in the high SSC group (p = 0.05). We then dichotomized the Bayley score at the borderline disability level (<80 vs. ≥ 80). **Table 5** displays the number and percentage of patients that fall below this borderline disability level along with univariate ORs. To account for potential confounding, ORs were further adjusted by fitting a multivariable model including the factors identified to be associated with SSC participation (BW, antenatal steroids, and IVH, **Table 5**). None of the associations (except for cognitive exam at 6 months) reached statistical significance. However there was a relatively consistent OR of 2 for associations between each dichotomized Bayley score and SSC participation in the multivariable models. Adjusted ORs were higher than the unadjusted because SSC participation was associated with factors that were also generally associated with lower Bayley scores.

Table 4: Point biserial correlations (r_{pb}) between Low and High Participation in Skin-to-Skin Care and Bayley-III Cognitive and Communication Outcomes

Bayley-III Assessment	SSC Low[1]	SSC High[1]	r_{pb}	p-value[2]
Cognitive 6 months	92.7 (15.7)	96.3 (15.1)	0.11	0.30
Cognitive 12 months	93.1 (14.6)	93.9 (19.2)	0.03	0.82
Communication 6 months	93.1 (12.9)	96.9 (16.6)	0.13	0.24
Communication 12 months	90.7 (15.4)	98.2 (16.4)	0.23	0.05
Composite (Cog/Comm) 6 months	92.9 (12.6)	96.6 (14.4)	0.13	0.21
Composite (Cog/Comm) 12 months	91.9 (13.6)	96.1 (16.1)	0.14	0.22

[1] Numbers in each cell are mean (std dev)

[2] P-values are from test that point biserial correlations are different from zero

Table 5: Associations Between Low and High Participation in Skin-to-Skin Care and Borderline Disability (<80 vs. ≥80) Bayley-III Cognitive and Communication Outcomes

	Percent Borderline Developmental Disability		Univariable			Multivariable		
Bayley Exam	Low SSC	High SSC	OR	95% CI	p-value	OR	95% CI	p-value
Cognitive 6 mos	11/58 (19%)	2/30 (7%)	3.28	(0.92, 11.67)	0.07	4.46	(1.08, 18.41)	0.04
Cognitive 12 mos	8/49 (16%)	2/28 (7%)	2.54	(0.66, 9.77)	0.18	2.87	(0.62, 13.26)	0.18
Communication 6 mos	9/58 (16%)	4/30 (13%)	1.19	(0.52, 2.72)	0.67	1.72	(0.64, 4.61)	0.28
Communication 12 mos	13/49 (27%)	5/29 (17%)	1.73	(0.88, 3.42)	0.11	2.00	(0.87, 4.57)	0.10
Composite (Cog/Comm) 6 mos	8/58 (14%)	3/30 (10%)	1.44	(0.52, 3.95)	0.48	2.22	(0.68, 7.28)	0.19
Composite (Cog/Comm) 12 mos	8/49 (16%)	3/28 (11%)	1.63	(0.58, 4.53)	0.35	2.22	(0.66, 7.44)	0.20

Multivariable models include antenatal steroids, birthweight, and IVH

A final exploratory analysis of the data set was performed using StickWRLD software to identify possible emergent interactive network associations among SSC measures, medical factors, and Bayley-III scores. Network displays (**Figure 5**) indicated separate, but convergent significant associations between SSC measures and medical factors and the 12-month Bayley-III cognitive scores.

DISCUSSION

Engagement in SSC with extremely preterm infants in the NICU varies among families. However, SSC patterns are evident in this population and potentially have an impact on early cognitive and communication performance. These findings are not new in that numerous studies[11-22] have been devoted to the short- and long- term developmental benefits of SSC. What is initially novel about our findings is that we have found a strong indication that SSC *before 30 weeks postmenstrual age* may play a crucial role in the cognitive and communication development of extremely preterm infants. The period of time before 32 weeks is often considered a developmentally marginal time period in communication and language development. Underlying brain structure and auditory/visual development are not at full capacity[33] and preterm infants are not yet prepared to vocalize or discern formal speech sounds.[34-35] However, studies in neurobiology indicate that social development does occur during this time[36-39] and could possibly represent an early foundational stage in the developmental continuum of communication and language.

A second novel finding is that extremely preterm infants who had higher birthweights, had received antenatal steroids, and who did not have IVH, were at decreased odds of receiving a 'high' level of skin-to-skin care (where high level was defined as above the median for total hours, frequency, and hours for each parent). One possible explanation is that infants who were perceived as being "less sick" were at reduced odds of receiving a high level of SSC. This poses questions about how medical caregivers and parents perceive the practice of skin-to-skin care and how developmental information is being communicated between parents and the medical team.

Finally, our findings identify a concerning gap in skin-to-skin care from 30 weeks corrected age to term age. Numerous studies highlight the essential nature of this time period for appropriate neurodevelopment.[40-44] However, extremely preterm infants, who represent one of the highest risk categories for neurodevelopmental disability, are not receiving an SSC intervention shown to improve neurodevelopment at a fundamental time point of their developmental trajectory. This elicits additional questions about why parents choose to stop at this corrected age, the underlying mechanisms of communication development in this population, and the potential added dimensional role of SSC as a communication intervention in the NICU.

Limitations of our study include the limited sample size (97 NICU patients) and the retrospective nature of the study, which excludes additional factors shown to impact neonatal neurodevelopment (e.g., maternal education, socioeconomic status, etc.). Confounding is thus an issue when investigating associations, however as noted previously NICU patients receiving SSC were actually associated with medical factors that were in turn associated with lower early-stage cognitive and communication scores. The study is also based on patients from a single hospital, and may not generalize to other neonatal units especially because our unit is a Level 4 all referral unit with high acuity infants and geographically distant parents. While we did see a relatively consistent pattern of association (c.f. **Table 5**) between high / low SSC participation and the Bayley-III Cognitive and Communication Outcomes dichotomized at borderline disability (<80 vs. ≥80), we reiterate that none of these associations achieved statistical significance and thus can only be viewed as suggestive results in need of confirmatory analysis. If the observed associations were to hold in the population along with the same level of SSC participation and prevalence of borderline disability, then roughly 460 total subjects would be needed to achieve 80% power to detect the association in a larger study.

Our research suggests that developmental investigations into very early time points in the life of extremely preterm infants is warranted and critical to understanding how to fully optimize future developmental social and cognitive processes. Additional studies, involving more comprehensive measures and analyses of the early developmental NICU environment (22-40 weeks postmenstrual age) could help inform new designs for developmental caregiving and promotion of skin-to-skin care throughout the duration of hospitalization.

CONTRIBUTORSHIP STATEMENT

All authors contributed equally to this manuscript. Jenn Gonya and Guy Brock designed and conducted the study, analyzed the biostatistical portion, and wrote and reviewed manuscript drafts. Jenn Gonya, Will Ray, and R Wolfgang Rumpf performed visual analytics, wrote sections of the manuscript, and reviewed and refined manuscript drafts.

COMPETING INTERESTS

There are no competing interests with regard to this manuscript and project.

FUNDING

This project was supported by Award Number UL1TR001070 from the National Center for Advancing Translational Sciences. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Center for Advancing Translational Sciences or the National Institutes of Health.

ACKNOWLEDGMENTS

We would like to thank Dr. Leif Nelin and the Small Baby Program for their continual advocacy and advancement toward the highest standard of developmentally appropriate care of extremely preterm infants.

DATA SHARING STATEMENT

Data are stored on our internal, high security server. De-identified data set available upon request.

REFERENCES

1. Colonna F, Uxa F, daGraca AM, de Vonderweld U. The “kangaroo-mother” method: evaluation of an alternative model for care of low birth weight newborns in developing countries. *Int J Gynaecol Obstet* 1990; 31(4): 335-9.
2. de Leeuw R, Colin EM, Dunnebier EA, Mirmiran M. Physiological effects of kangaroo care in very small preterm infants. *Biol Neonate* 1991; 59(3): 149-55.
3. Ludington-Hoe SM, Thompson C, Swinth J, Hadeed AJ, Anderson GC. Kangaroo care: research results, and practice implications and guidelines. *Neonatal Netw* 1994; 13(1): 19-27.
4. Bauer K, Uhrig C, Sperling P, Pasel K, Wieland C, Versmold HT. Body temperatures and oxygen consumption during skin-to-skin (kangaroo) care in stable preterm infants weighing less than 1500 grams. *J Pediatric* 1997; 130(2): 240-4.
5. Feldman R, Eidelman AI. Intervention programs for premature infants. How and do they affect development? *Clin Perinatol* 1998; 25(3): 613-26.
6. Tornhage CJ, Stuge E, Lindberg T, Serenius F. First week kangaroo care in sick very preterm infants. *Acta Paediatr* 1999; 88(12): 1402-4.
7. Ohgi S, Fukuda M, Moriuchi H, Kusumoto T, Akiyama T, et al. Comparison of kangaroo care and standard care: behavioral organization, development, and temperament in healthy, low-birth-weight infants through 1 year. *J Perinatol* 2002; 22(5): 374-9.
8. Ludington-Hoe SM, Ferreira C, Swinth J, Ceccardi JJ. Safe criteria and procedure for kangaroo care with intubated preterm infants. *J Obstet Gynecol Neonatal Nurs* 2003; 32(5): 579-88.
9. Begum EA, Bonno M, Ohtani N, Yamashita S, Tanaka S, et al. Cerebral oxygenation responses during kangaroo care in low birth weight infants. *BMC Pediatr* 2008; 8:51.
10. Neu M, Robinson J. Maternal holding of preterm infants during the early weeks after birth and dyad interaction at six months. *J Obstet Gynecol Neonatal Nurs* 2010; 39(4): 401-14.
11. Conde-Agudelo A, Belizan JM, Diaz-Rossello J. Kangaroo mother care to reduce morbidity and mortality in low birthweight infants. *Cochrane Database Syst Rev* 2011; 3: CD002771.
12. Ludington-Hoe SM. Thirty years of kangaroo care science and practice. *Neonatal Netw* 2011; 30(5): 357-62.
13. Kaffashi F, Scher MS, Ludington-Hoe SM, Loparo KA. An analysis of the kangaroo care intervention using neonatal EEG complexity: a preliminary study. *Clin Neurophysiol* 2013; 124(2): 238-46.
14. Conde-Agudelo A, Diaz-Rossello J. Kangaroo mother care to reduce morbidity and mortality in low birthweight infants. *Cochrane Database Syst Rev* 2014;4: CD002771.
15. Morelius E, Ortenstran A, Theodorsson E, Frostell A. A randomized trial of continuous skin-to-skin contact after preterm birth and the effects on salivary cortisol, parental stress, depression, and breastfeeding. *Early Hum Dev* 2015; 91(1): 63-70.
16. Boundy EO, Dastjerdi R, Spegelman D, Fawzi WW, Missmer SA, et al. Kangaroo mother care and neonatal outcomes: a meta-analysis. *Pediatrics* 2016; 137(1).
17. Flacking R, Lehtnonen L, Thomson G, Axelin A, Ahlqvist S, et al. Closeness and separation in neonatal intensive care. *Acta Paediatr* 2012; 101(10): 1032-7.
18. Feldman R, Rosenthal Z, Eidelman AI. Maternal-preterm skin-to-skin contact enhances child physiologic organization and cognitive control across the first 10 years of life. *Biol Psychiatry* 2014; 75(1): 56-64.
19. Roberts KL, Paynter C, McEwan B. A comparison of kangaroo mother care and conventional cuddling care. *Neonatal Netw* 2000; 19(4): 31-5.
20. Rojas MA, Kaplan M, Quevedo M, Sherwonit E, Foster LB, Ehrenkranz RA, Mayes L. Somatic growth of preterm infants during skin-to-skin care versus traditional holding: a randomized, controlled trial. *J Dev Behav Pediatr* 2003; 24(3): 163-8.
21. Schneider C, Charpak N, Ruiz-Pelaez JG, Tessier R. Cerebral motor function in very premature-at-birth adolescents: a brain stimulation exploration of kangaroo mother care effects. *Acta Paediatr* 2012; 101(10): 1045-53.

22. Scher MS, Ludington-Hoe S, Kaffashi F, Johnson MW, Holditch-Davis D, Loparo KA. Neurophysiologic assessment of brain maturation after an 8-week trial of skin-to-skin contact on preterm infants. *Clin Neurophysiol* 2009; 120(10) 1812-8.
23. Seidman G, Unnikrishnan S, Kenny E, Myslinski S, Cairns-Smith S, et al. Barriers and enablers of kangaroo mother care practice: a systematic review. *PLoS One* 2015; 10(5): e0125643.
24. Nankervis CA, Martin EM, Crane ML, Samson KS, Welty SE, Nelin LD. Implementation of a multidisciplinary guideline-driven approach to the care of the extremely premature infant improved hospital outcomes. *Acta Paediatr* 2010; 99: 188-93.
25. Shepherd E, Calvert T, Martin E, Hitchner J, Welty, S, Nelin, L. Outcomes of extremely premature infants admitted to a children's hospital depends on referring hospital. *J Neonat Perinat Med* 2011; 4: 45-53.
26. Ambalavanan N, Carlo WA, Tyson JE, Langer JC, Walsh MC, Parikh NA, et.al. Outcome trajectories in extremely preterm infants. *Pediatrics* 2012; 130(1): e115-25.
27. McMahon E, Wintermark P, Lahav A. Auditory brain development in premature infants: the importance of early Experience. *Ann N Y Acad Sci* 2012; 1252: 17-24.
28. National Institute of Child Health and Human Development Neonatal Research Network. Follow-up program. 2013; Retrieved from https://neonatal.rti.org/about/fu_background.cfm
29. Pearson Education. Bayley scales of infant development (third edition). Pearson Clinical 2008 Training.
30. Ray WC. MAVL and StickWRLD: visually exploring relationships in nucleic acid sequence alignments. *Nucleic Acids Res* 2004; 32: 59-63.
31. Rumpf RW, Gonya J, Ray W. Visual hypothesis and correlation discovery for precision medicine. AMIA workshop on visual analytics in healthcare conference paper 2014.
32. Ray WC, Wolock SL, Li N, Bartlett CW. StickWRLD: Interactive visualization of massive parallel contingency data for personalized analysis to facilitate precision medicine. Proceedings of the 3rd annual Workshop on Visual Analytics in Healthcare, in conjunction with the American Medical Informatics Symposium. 2013; November.
33. Key APF, Lambert EW, Aschner JL, Maitre NL. Influence of gestational age and postnatal age on speech sound processing in NICU infants. *Psychophys* 2012; 49: 720-731.
34. Caskey M, Stephens B, Tucker R, Vohr B. Importance of parent talk on the development of preterm infant vocalizations. *Pediatrics* 2011; 128(5): 910-6.
35. Caskey M, Stephens B, Tucker R, Vohr B. Adult talk in the NICU with preterm infants and developmental outcomes. *Pediatrics* 2014; 133(3): 578-84.
36. Silva MG, Barros MC, Pessoa UM, Guinsburg R. Kangaroo-mother care method and neurobehavior of preterm infants. *Early Hum Dev* 2016; 95: 55-9.
37. Feldman R, Eidelman AI. Skin-to-skin contact (kangaroo care) accelerates autonomic and neurobehavioural maturation in preterm infants. *Dev Med Child Neurol* 2003; 45(4): 274-81.
38. Feldman R, Eidelman AI, Sirota, Weller A. Comparison of skin-to-skin (kangaroo) and traditional care: parenting outcomes and preterm infant development. *Pediatrics* 2002; 110: 16-26.
39. Feldman R. From biological rhythms to social rhythms: physiological precursors of mother-infant synchrony. *Dev Psychol* 2006; 42(1) 175-88.
40. Fetal Development: Research on Brain and Behavior, Environmental Influences, and Emerging Technologies. Reissland N, Kisilevsky BS (Eds.) Switzerland: Springer International 2016.
41. Thomason ME, Grove L, Lozon TA, Vila AM, Ye Y, et al. Age related increases in long-range connectivity in fetal functional neural connectivity networks in utero. *Developmental Cog Neurosci* 2015; 11: 96-104.
42. Krueger C, Garvan C. Emergence and retention of learning in early fetal development. *Infant Behavior and Dev* 2014; 37(2): 162-173.
43. Pearson J, Tarabulsy GM, Bussieres E. Foetal programming and cortisol secretion in early childhood: a metal-analysis of different programming variables. *Infant Behavior and Dev* 2015; 40: 204-215.
44. Fetal Growth and Development. Harding R, Bocking AD (Eds.) 2001. United Kingdom: Cambridge University Press.

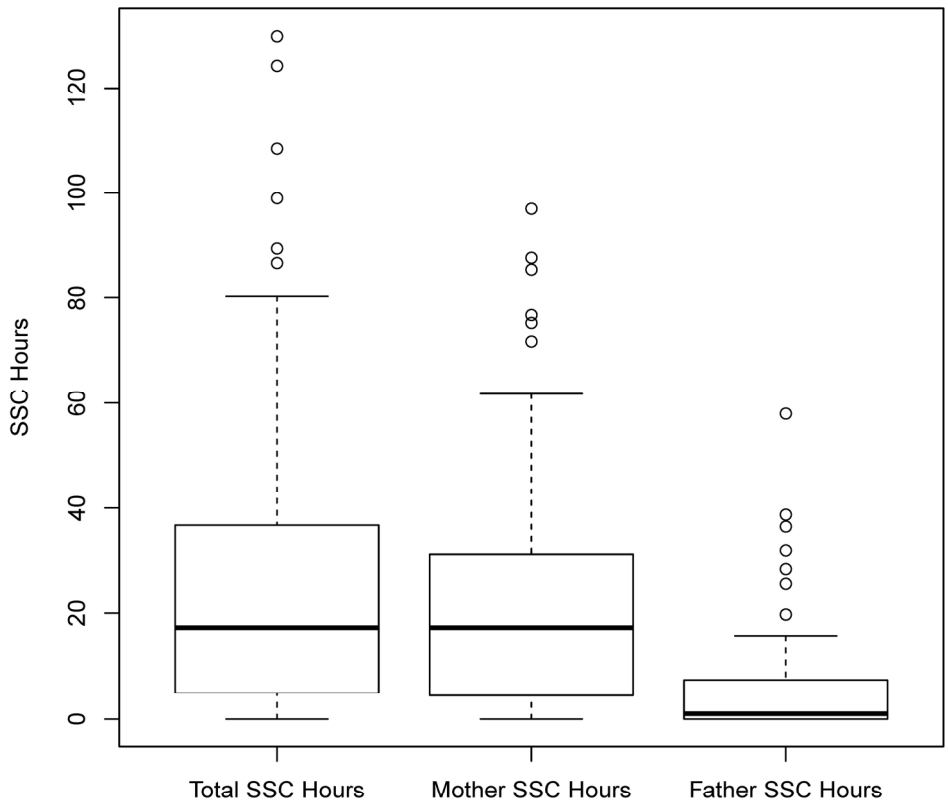


FIGURE 1 – Overall and Parent Specific SSC Participation: Boxplots displaying the distribution of overall SSC participation and by parent. Thick horizontal lines give medians while boxes display the middle 50% of the data (25th and 75th percentiles). Whiskers extend to no more than 1.5 times the interquartile range (IQR = difference between 75th and 25th percentiles) from the edge of the box. Points beyond the whiskers represent outliers.

177x177mm (300 x 300 DPI)

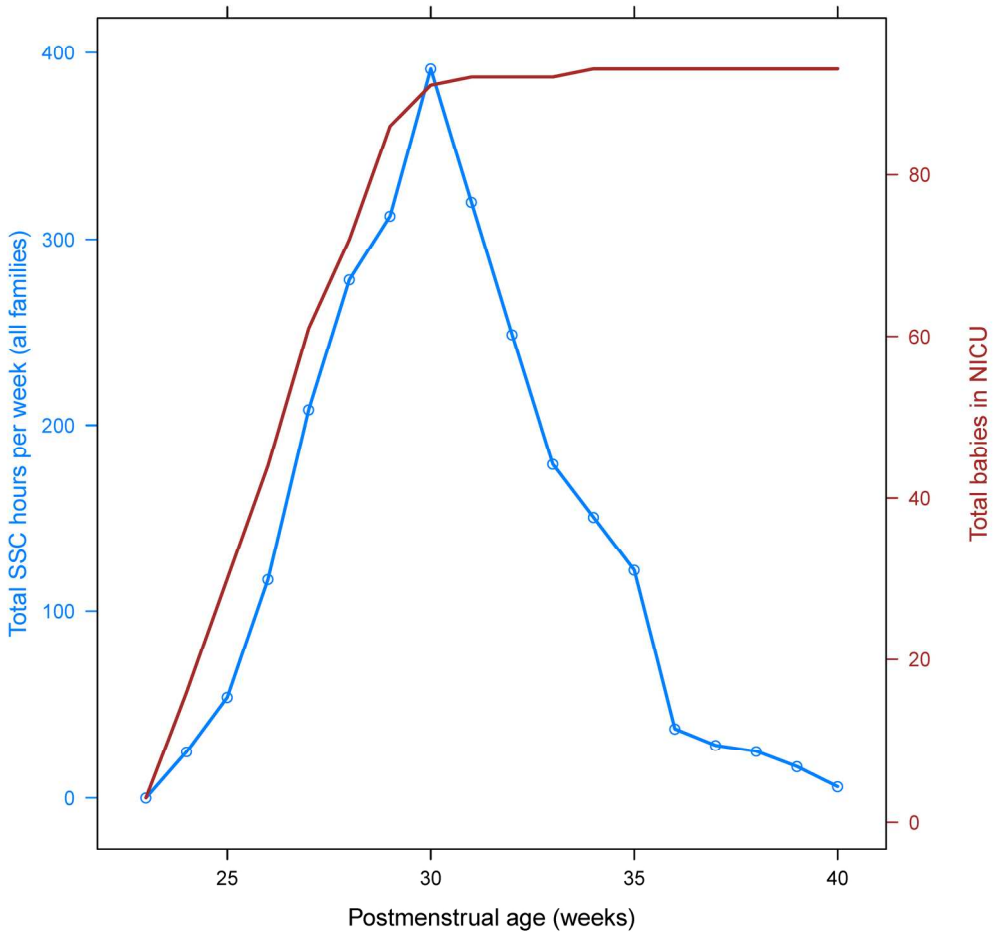


FIGURE 2 – Total SSC hours per week: Blue line displays the total number of SSC hours per week for all families in the study, by postmenstrual age. Red line gives the total number of babies in the NICU for the given week.

177x177mm (300 x 300 DPI)

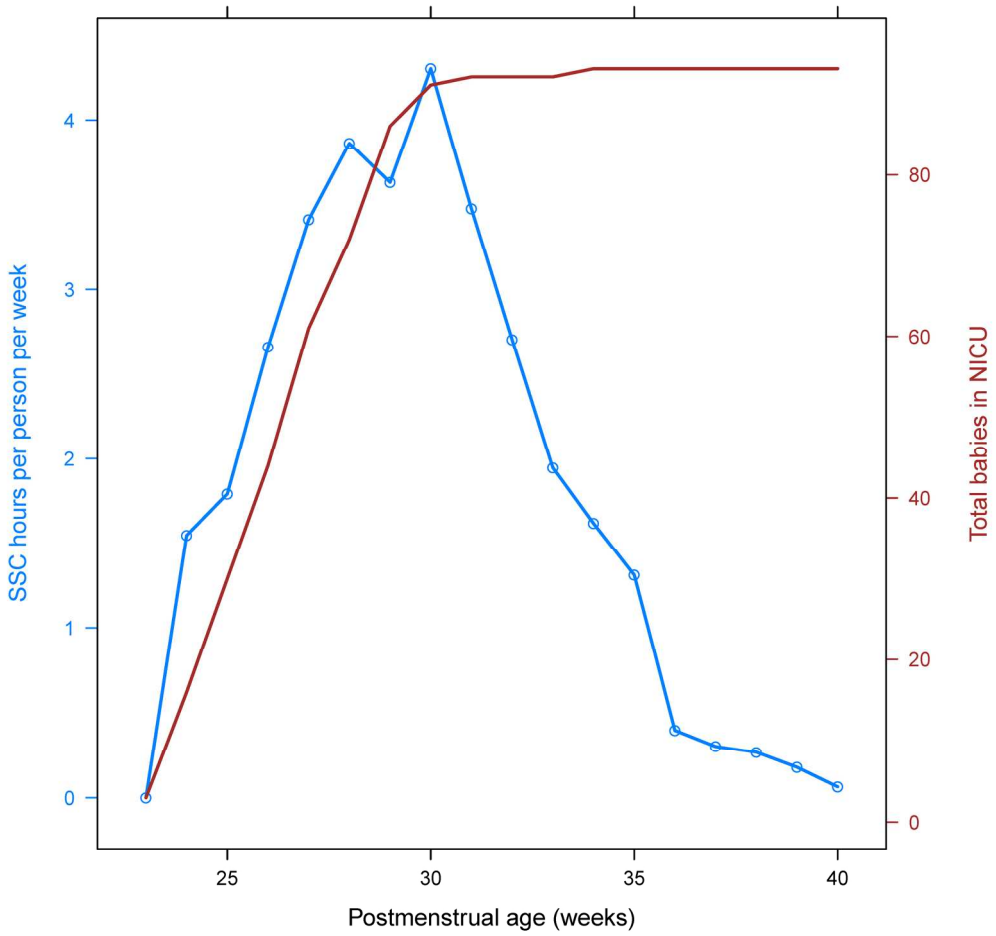


FIGURE 3 – SSC intensity (hours per week per family): Blue line displays the average SSC intensity (hours per family per week) by postmenstrual age. Red line gives the total number of babies in the NICU for the given week.

177x177mm (300 x 300 DPI)

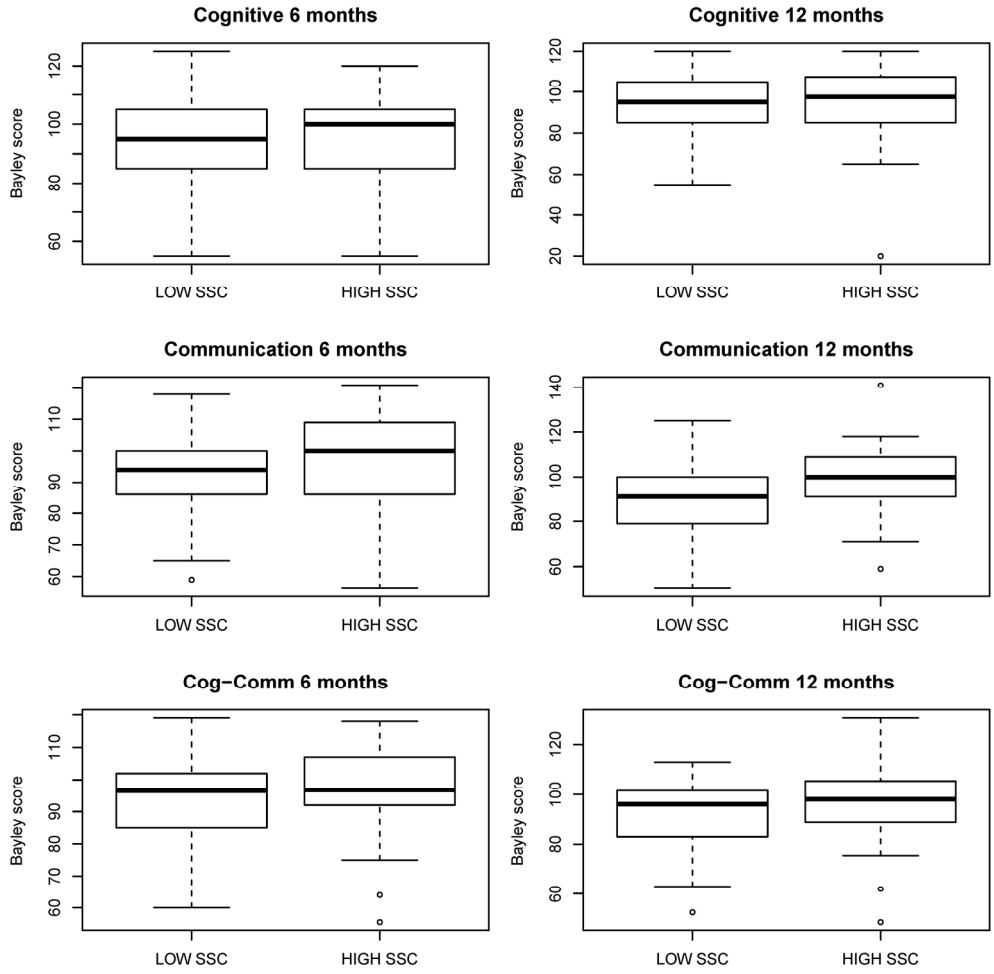


FIGURE 4 – Bayley Cognitive and Communication scores by SSC participation: Boxplots displaying the distribution of Bayley cognitive, communication, and combined cognitive-communication (Cog-Comm) scores at 6 and 12 months by SSC participation (high vs. low). High SSC participation was defined as having above the median participation for total SSC hours, mother SSC hours, father SSC hours, and SSC intensity (see text for details). Thick horizontal lines give medians while boxes display the middle 50% of the data (25th and 75th percentiles). Whiskers extend to no more than 1.5 times the interquartile range (IQR = difference between 75th and 25th percentiles) from the edge of the box. Points beyond the whiskers represent outliers.

177x177mm (300 x 300 DPI)

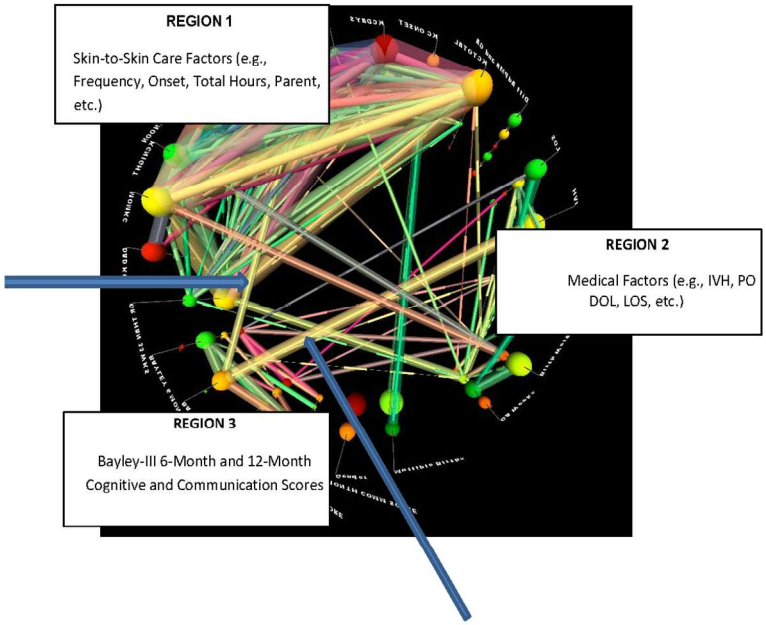


FIGURE 5 – Visual Analytical Display from StickWRLD Software. The visual space is divided into three main regions: Medical Factors, Skin-to-Skin Factors, and Bayley-III Scores. Each line represents a significant correlation between factors with stronger correlations represented by lines that are thicker in diameter. Within region correlations are evident and expected. Two blue arrows indicate two unexpected strong correlations (one from each region) that converge on the Bayley-III 12-Month Cognitive Score, suggesting Skin-to Skin Care Frequency and presence or absence of Intraventricular Hemmorhage (IVH) as parallel, but non-interactive factors impacting the score.

215x279mm (157 x 166 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	p.1
		p.2
Introduction		
Background/rationale	2	p.4
Objectives	3	p.1 and p.4
Methods		
Study design	4	p.5
Setting	5	p.5
Participants	6	p.5
Variables	7	pp.5-6
Data sources/ measurement	8*	pp.5-6
Bias	9	p. na Retrospective Study
Study size	10	p. na All infants in cohort included
Quantitative variables	11	p. 5
Statistical methods	12	p. 6

Continued on next page

Results		
Participants	13*	p.7
Descriptive data	14*	p. 7
Outcome data	15*	pp. 7-10
Main results	16	pp.7-10
Other analyses	17	p. 10
Discussion		
Key results	18	pp. 10-12
Limitations	19	p. 11
Interpretation	20	pp. 10-12
Generalisability	21	p. 11
Other information		
Funding	22	p. 12

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Investigating Skin-to-Skin Care Patterns with Extremely Preterm Infants in the NICU and Their Effect on Early Cognitive and Communication Performance: a retrospective cohort study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-012985.R2
Article Type:	Research
Date Submitted by the Author:	09-Dec-2016
Complete List of Authors:	Gonya, Jenn; The Research Institute at Nationwide Children's Hospital, Center for Perinatal Research Ray, William; The Research Institute at Nationwide Children's Hospital, Battelle Center for Mathematical Medicine Rumpf, R Wolfgang; The Research Institute at Nationwide Children's Hospital, Battelle Center for Mathematical Medicine Brock, Guy; The Ohio State University, Center for Biostatistics
Primary Subject Heading:	Intensive care
Secondary Subject Heading:	Paediatrics
Keywords:	extreme prematurity, Neonatal intensive & critical care < INTENSIVE & CRITICAL CARE, NEONATOLOGY

Investigating Skin-to-Skin Care Patterns with Extremely Preterm Infants in the NICU and Their Effect on Early Cognitive and Communication Performance: a retrospective cohort study

Jenn Gonya, PhD
The Research Institute at Nationwide Children's Hospital
Center for Perinatal Research
575 Children's Crossroad
RBIII WB6139
Columbus, Ohio USA 43215
jenn.gonya@nationwidechildrens.org
614-355-6653

William C. Ray, PhD
The Research Institute at Nationwide Children's Hospital
Battelle Center for Mathematical Medicine
Columbus, Ohio USA

R. Wolfgang Rumpf, PhD
The Research Institute at Nationwide Children's Hospital
Battelle Center for Mathematical Medicine
Columbus, Ohio USA

Guy Brock, PhD
The Ohio State University Department of Biomedical Informatics
Center for Biostatistics
Columbus, Ohio USA

Keywords: extremely preterm, neonatal intensive care, skin-to-skin care, neonatal neurodevelopment

Word Count: 3224

ABSTRACT

Objectives
The primary objective of the study was to investigate how patterns of skin-to-skin care might impact infant early cognitive and communication performance

Design
This was a retrospective cohort study.

Setting
This study took place in a Level-IV all-referral neonatal intensive care unit in the Midwest United States specializing in the care of extremely preterm infants.

Participants
Data was collected from the electronic medical records of all extremely preterm infants (gestational age < 27 weeks) admitted to the unit during 2010-2011 and who completed 6- and 12-month developmental assessments in the follow-up clinic (n=97).

Outcome Measures
Outcome measures included the cognitive and communication subscales of the Bayley Scales of Infant Development, Third Edition (Bayley-III); and skin-to-skin patterns including: total hours of maternal and paternal participation throughout hospitalization, total duration in weeks, and frequency (hours per week).

Analysis
Extracted data was analyzed through a multi-step process of logistic regressions, t-tests, chi-squared tests, and Fisher's exact tests followed with exploratory network analysis using novel visual analytic software.

Results
Infants who received above the sample median in total hours, weekly frequency, and total hours from mothers *and* fathers of skin-to-skin care were more likely to score ≥80 on the cognitive and communication scales of the Bayley-III. However, the results were not statistically significant ($p>0.05$). Mothers provided the majority of skin-to-skin care with a sharp decline at 30 weeks corrected age, regardless of when extremely preterm infants were admitted. Additional exploratory network analysis suggests that medical and skin-to-skin factors play a parallel, non-synergistic role in contributing to early cognitive and communication performance as assessed through the Bayley-III.

Conclusion
This study suggests an association between early and frequent skin-to-skin care with extremely preterm infants and early cognitive and communication performance.

ARTICLE SUMMARY

Strengths and Limitations of This Study

The study is strong in that it

- identifies natural, emergent patterns of skin-to-skin care with extremely preterm infants to reflect authentic human engagement experiences
- uses the evidence to suggest ways to target specific intervention areas for increasing skin-to-skin care
- supports current literature on the longer term benefits of skin-to-skin care

The study is limited by the fact that it

- uses one instrument to assess early cognitive and communication performance
- uses retrospective data which excludes variables known to impact neonatal neurodevelopment

INTRODUCTION

The birth and subsequent hospitalization of an extremely preterm infant is *a trauma event*. Unlike term infants, extremely preterm infants (infants born at less than 27 weeks) spend the last trimester of their gestation ex utero, in an artificial, technology-laden neonatal intensive care (NICU) that places them at a developmental disadvantage. Monitors, tubing, and wires often create an environment that makes it difficult for authentic positive human interaction. In response, skin-to-skin care (SSC) has been incorporated into many NICU's across the world to re-establish this positive human contact.

Skin-to-skin care (SSC) is the practice of holding an infant upright on a parent's chest in a manner that provides maximum bare skin ventral contact. The practice impacts infant physiological stability, stress, and sleep as well as maternal stress and parenting behavior. SSC studies over the last twenty-five years[1-15] have collectively translated into a global acknowledgment that SSC is medically safe and significantly affects longer term neurodevelopmental cognitive, social, and emotional outcomes [16-22].

Despite the benefits of SSC, it is often difficult to engage some families in the practice. Findings from one of the most recent and comprehensive systematic reviews of the barriers and promoters of SSC (included in the complete package known as Kangaroo Mother Care)[23] identified over thirty-five factors involved in integrating SSC into the NICU environment. The top three barriers to SSC were issues with the NICU physical facility, negative impressions by the staff about the practice, and fear of injuring the infant during SSC. In contrast, SSC increased when mothers felt attached to their infants, felt confident in their parenting role, and received support from family, friends, or other mothers. While current studies, such as those found in the systematic review, can help in the design of new interventions promoting SSC, many are a reflection of participating in a highly supported and scrutinized form of SSC rather than parent practice as it naturally occurs in the NICU.

What remains unknown is how parents are actually engaging in the practice of SSC in an all referral NICU setting in the United States *when they are not involved in an SSC study*. A rigorous study of routine SSC across a cohort of extremely preterm infants could identify specific strategies and intervention points for care providers to target their efforts at increasing parental engagement in SSC. Therefore, the purpose of the current study was to identify the naturalistic patterns of SSC that parents engage in with their extremely preterm infants in an all-referral NICU and investigate how these patterns impact early infant cognitive and communicative performance. A secondary aim was to compare the relative effects of amount and intensity of SSC on these outcomes.

PATIENTS AND METHODS

This study was a retrospective cohort study of all infants admitted to the Small Baby Intensive Care Unit (SBICU) at Nationwide Children's Hospital (NCH) between 01/01/2010-11/30/2011. The SBICU is a specialized Level-IV all-referral unit staffed by a centralized team of nurses who provide protocol-driven care[23-25] to neonates born at a gestational age (GA) less than 27 completed weeks. These protocols, organized within the Small Baby Guidelines, outline how to specifically address the medical and developmental needs of extremely preterm infants. Skin-to-skin care is specifically designated as a critical practice for medical stability and neurodevelopmental outcomes and is described as a care piece that should be strongly encouraged whenever possible, as long as possible. All patients cared for in this unit are outborn and are transported to the SBICU for care of complications of prematurity including necrotizing enterocolitis (NEC), sepsis, surgical issues, brain injury, etc. This study was approved by the Institutional Review Board of Nationwide Children's Hospital (IRB#13-00042) as an expedited study that meets the criteria for waiver of authorization.

DATA

Retrospective data was extracted from the electronic medical record within three categories : a) medical b) SSC and c) cognitive and communication outcomes at follow-up. Medical record information extracted for each patient included gender, gestational age (GA) , birthweight (BW), length of hospital stay (LOS), occurrence or absence of intraventricular hemorrhage in the brain (IVH), number of days on a ventilator (IPPV days), days until first full feed by mouth (PO DOL), whether the patient was a twin, triplet, etc. (multiple births), and whether the patient received antenatal steroids. These variables were selected based on the outcome trajectories calculator developed by the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network.[26]

Total hours of SSC care for each parent were recorded for each day after the baby was admitted to the NICU until discharge. Hours were documented by the nursing staff in the patient medical record. (Audits performed comparing parental report and nurse report of SSC time indicated 89% consistency.) Summary measures of SSC use included total hours of SSC, the number of days between the day of admission and the first onset of SSC, total hours of SSC performed by the mother and father, intensity of SSC (average days of SSC per week), and whether the family participated in SSC after their child reached 33 weeks corrected age, a critical period of auditory development .[27] To reduce the number of tested associations and aid in clinical interpretation, families were further classified as having a 'high' level of SSC participation if they were above the

median in total hours, total hours for mother and total hours for father, and frequency of SSC (that is, above the median for each of the four variables). The remaining families were classified as having a 'low' level of SSC participation.

Cognitive and communication early performance outcomes were determined through the Bayley Scales of Infant Development, Third Edition (Bayley-III), a valid and reliable developmental assessment tool that is widely used in neonatal follow-up. Assessments were performed at 6-months and 12-months by licensed professionals certified and trained in the tool[28] and scores were adjusted for prematurity. Descriptive classifications were used according to the protocol outlined by Pearson Clinical with infants scoring <80 being described as "Borderline" for developmental disability.[29] Consequently, scores were treated both as continuous variables and as dichotomized variables of scores <80 and scores ≥80.

STATISTICAL ANALYSIS

Statistical analysis was divided into three parts to address the clinical questions of interest. First, since the study is observational in nature patterns of SSC participation ('high' vs. 'low', as defined in the 'Data' section) were investigated graphically and associations between SSC measures and medical factors were tested. These associations were considered to explore for potential factors associated with SSC participation and to account for potential confounding of SSC with these other clinical / medical variables. A logistic regression model was fit to contrast the probability of being a high vs. low SSC participant (as defined in the 'Data' section) as a function of gender, gestational age, birth weight, IVH, IPPV days, PO DOL, multiple births, and receipt of antenatal steroids. Backwards elimination was used to select a final explanatory model based on minimizing the Akaike's information criteria (AIC). Second, the association between SSC participation (high vs. low) and Bayley-III scores was evaluated. Strength of association between raw Bayley scores and SSC participation (high vs. low) was quantified and tested using point biserial correlations (r_{pb}, tested against a null that the correlation was zero). Bayley scores dichotomized at the borderline disability level (<80 vs. ≥ 80) were tested for association with SSC participation using the chi-squared test or Fisher's exact test. Associations between dichotomized Bayley scores and SSC participation were additionally adjusted for confounding based on the medical factors found to be associated with SSC participation.

Patterns between medical factors and skin-to-skin care became evident and patterns of skin-to-skin care and the Bayley-III scores became evident. Consequently, for the final analysis we used our StickWRLD visual analytic software[30-31] to investigate potential triangulations among specific aspects of medical factors, skin-to-skin care, and the Bayley-III scores. All factors were loaded into the StickWRLD visual framework and initial two- node association patterns were set with an initial residual value[32] of 0.2. Subsequent analyses were performed incrementally at lower residual values to identify and compare associative relationships and to search for significant emerging triangular data patterns. Analyses concluded when the model reached a threshold residual value corresponding to visual associative overload.

RESULTS

A total of 97 NICU patients were included in the study. The gestational age ranged from 22 weeks to 26 weeks with an overall median of 25 weeks. Summary statistics of SSC usage (overall participation, participation by parent, SSC intensity and onset of SSC) are given in **Table 1**. Mothers represented the majority of overall SSC participation, as evidenced by **Figure 1**. Nine families were missing information on some aspect of SSC involvement. Among the remaining 88 families, 30 (34%) were classified as 'high' participants in SSC (above the median for total SSC hours, hours per parent, and SSC intensity) while the other 58 (66%) were classified as 'low' participation in SSC.

Table 1: Summary Statistics of Skin-to-Skin Care from admission to 40 weeks postmenstrual age

SSC Metric	Mean (SD)	Median (IQR)	(Min, Max)
Total SSC (hours)	27.4 (29.8)	17.2 (5.1, 36.6)	(0, 129.8)
Mother SSC (hours)	22.8 (22.4)	17.2 (4.6, 30.9)	(0, 97)
Father SSC (hours)	5.8 (10.4)	1 (0, 7.5)	(0, 58)
SSC Frequency (days / week)	2.3 (1.2)	2.2 (1.3, 3.2)	(0, 5)
SSC Onset (days)	6.2 (7.4)	4 (1.8, 8)	(0, 45)

SD = standard deviation
IQR = Inter-quartile range (25th percentile, 75th percentile)

Patterns of intensity and total hours of SSC participation between the postmenstrual ages of 23 and 40 weeks are displayed on a study- wide (total person-hours per week, **Figure 2**) and family (hours per family per week, **Figure 3**) basis. There was a steady increase in both total hours and hours per family until about 30 weeks, after which there was a corresponding precipitous decline until 40 weeks. Differences in medical factors

between families with high vs. low SSC participation are given in **Table 2**. Receipt of antenatal steroids was the only significant ($p < 0.05$) finding, with 71% of children from families with high SSC participation receiving antenatal steroids and 91% of children with low family SSC participation receiving them.

Table 2: Medical Factors Influencing Skin-to-Skin Patterns

Medical Factors (categorical)		SSC Low	SSC High	p-value
Gender	Female	23 (0.4)	8 (0.27)	0.25
	Male	35 (0.6)	22 (0.73)	
Multiple Births	No	39 (0.67)	18 (0.60)	0.64
	Yes	19 (0.33)	12 (0.40)	
Antenatal Steroids	No	5 (0.09)	8 (0.29)	0.02
	Yes	53 (0.91)	20 (0.71)	
IVH	No	28 (0.48)	10 (0.33)	0.26
	Yes	30 (0.52)	20 (0.67)	
Medical Factors (continuous)		**SSC Low**	**SSC High**	**p-value**
Gestational Age (weeks)		24.9 (1)	24.4 (1.1)	0.06
BW (grams)		748.2 (164.5)	719.6 (188.5)	0.48
Length of hospital stay (days)		117.6 (46.1)	127.8 (40)	0.28
Days on ventilator		41.6 (28.6)	45 (33.2)	0.63
PO DOL (days)		106.1 (35.9)	117.7 (44.6)	0.26

Numbers in each cell are mean (std dev) for continuous and N (%) for categorical
p-value for categorical based on chi-squared, for continuous based on t-test

These factors (minus LOS, which was omitted because infants with longer LOS might be expected to have longer total SSC duration) were subsequently used to build a model to analyze the variance in SSC participation based on logistic regression with backwards elimination. The resulting model included antenatal steroids, birthweight, and IVH as predictors (**Table 3**). We investigated various cut-points for dichotomizing birth weight and found the 75th percentile to provide the best fit. Both receipt of antenatal steroids (OR = 0.136) and birth weight in the top quartile (OR = 0.152) were associated with *reduced* odds of high SSC participation, while presence of IVH was associated with increased odds (OR = 1.92).

Table 3: Odds Ratios for High Participation in Skin-to-Skin Care Based on Medical Factors

			Univariable			Multivariable		
Factor	Levels	High SSC	OR	95% CI	p-value	OR	95% CI	p-value
Antenatal Steroids	Yes	20/73 (27%)	4.16	(1.06, 18.2)	0.024	7.36	(1.67, 32.53)	0.008
	No	8/13 (62%)						
Birthweight	844+	5/24 (21%)	2.41	(0.74, 9.35)	0.13	6.59	(1.46, 29.84)	0.014
	< 844	25/64 (39%)						
IVH	Yes	20/50 (40%)	0.54	(0.19, 1.46)	0.26	0.52	(0.19, 1.43)	0.2
	No	10/38 (26%)						

Next, association between SSC participation and cognitive and communication outcomes (Bayley scores) at follow-up were investigated. **Figure 4** displays boxplots of the Bayley scores stratified by high and low SSC participation, while **Table 4** gives mean values for each exam by participation group. Communication scores at 12 months were somewhat higher in the high SSC group (p = 0.05). We then dichotomized the Bayley score at the borderline disability level (<80 vs. ≥ 80). **Table 5** displays the number and percentage of patients that fall below this borderline disability level along with univariate ORs. To account for potential confounding, ORs were further adjusted by fitting a multivariable model including the factors identified to be associated with SSC participation (BW, antenatal steroids, and IVH, **Table 5**). None of the associations (except for cognitive exam at 6 months) reached statistical significance. However there was a relatively consistent OR of 2 for associations between each dichotomized Bayley score and SSC participation in the multivariable models. Adjusted ORs were higher than the unadjusted because SSC participation was associated with factors that were also generally associated with lower Bayley scores.

Table 4: Point biserial correlations (r_{pb}) between Low and High Participation in Skin-to-Skin Care and Bayley-III Cognitive and Communication Outcomes

Bayley-III Assessment	SSC Low[1]	SSC High[1]	r_{pb}	p-value[2]
Cognitive 6 months	92.7 (15.7)	96.3 (15.1)	0.11	0.30
Cognitive 12 months	93.1 (14.6)	93.9 (19.2)	0.03	0.82
Communication 6 months	93.1 (12.9)	96.9 (16.6)	0.13	0.24
Communication 12 months	90.7 (15.4)	98.2 (16.4)	0.23	0.05
Composite (Cog/Comm) 6 months	92.9 (12.6)	96.6 (14.4)	0.13	0.21
Composite (Cog/Comm) 12 months	91.9 (13.6)	96.1 (16.1)	0.14	0.22

[1] Numbers in each cell are mean (std dev)

[2] P-values are from test that point biserial correlations are different from zero

Table 5: Associations Between Low and High Participation in Skin-to-Skin Care and Borderline Disability (<80 vs. ≥80) Bayley-III Cognitive and Communication Outcomes

	Percent Borderline Developmental Disability		Univariable			Multivariable		
Bayley Exam	Low SSC	High SSC	OR	95% CI	p-value	OR	95% CI	p-value
Cognitive 6 mos	11/58 (19%)	2/30 (7%)	3.28	(0.92, 11.67)	0.07	4.46	(1.08, 18.41)	0.04
Cognitive 12 mos	8/49 (16%)	2/28 (7%)	2.54	(0.66, 9.77)	0.18	2.87	(0.62, 13.26)	0.18
Communication 6 mos	9/58 (16%)	4/30 (13%)	1.19	(0.52, 2.72)	0.67	1.72	(0.64, 4.61)	0.28
Communication 12 mos	13/49 (27%)	5/29 (17%)	1.73	(0.88, 3.42)	0.11	2.00	(0.87, 4.57)	0.10
Composite (Cog/Comm) 6 mos	8/58 (14%)	3/30 (10%)	1.44	(0.52, 3.95)	0.48	2.22	(0.68, 7.28)	0.19
Composite (Cog/Comm) 12 mos	8/49 (16%)	3/28 (11%)	1.63	(0.58, 4.53)	0.35	2.22	(0.66, 7.44)	0.20

Multivariable models include antenatal steroids, birthweight, and IVH

A final exploratory analysis of the data set was performed using StickWRLD software to identify possible emergent interactive network associations among SSC measures, medical factors, and Bayley-III scores. Network displays (**Figure 5**) indicated separate, but convergent significant associations between SSC measures and medical factors and the 12-month Bayley-III cognitive scores.

DISCUSSION

Engagement in SSC with extremely preterm infants in the NICU varies among families. However, SSC patterns are evident in this population and potentially have an impact on early cognitive and communication performance. These findings are not new in that numerous studies[11-22] have been devoted to the short- and long- term developmental benefits of SSC. What is initially novel about our findings is that we have found a strong indication that SSC *before 30 weeks postmenstrual age* may play a role in the cognitive and communication development of extremely preterm infants. The period of time before 32 weeks is often considered a developmentally marginal time period in communication and language development. Underlying brain structure and auditory/visual development are not at full capacity[33] and preterm infants are not yet prepared to vocalize or discern formal speech sounds.[34-35] However, studies in neurobiology indicate that social development does occur during this time[36-39] and could possibly represent an early foundational stage in the developmental continuum of communication and language.

A second novel finding is that extremely preterm infants who had higher birthweights, had received antenatal steroids, and who did not have IVH, were at decreased odds of receiving a 'high' level of skin-to-skin care (where high level was defined as above the median for total hours, frequency, and hours for each parent). One possible explanation is that infants who were perceived as being "less sick" were at reduced odds of receiving a high level of SSC. This poses questions about how medical caregivers and parents perceive the practice of skin-to-skin care and how developmental information is being communicated between parents and the medical team.

Finally, our findings identify a concerning gap in skin-to-skin care from 30 weeks corrected age to term age. Numerous studies highlight the essential nature of this time period for appropriate neurodevelopment.[40-44] However, extremely preterm infants, who represent one of the highest risk categories for neurodevelopmental disability, are not receiving an SSC intervention shown to improve neurodevelopment at a fundamental time point of their developmental trajectory. This elicits additional questions about why parents choose to stop at this corrected age, the underlying mechanisms of communication development in this population, and the potential added dimensional role of SSC as a communication intervention in the NICU.

One important limitation of our study is that it is retrospective in nature within an all-referral hospital system in the United States, which impedes our ability to capture and analyze additional factors shown to impact neonatal neurodevelopment. Consequently, we could not explore the effects of maternal health, socioeconomic status, or education, which are shown to significantly influence neonatal developmental outcome. However, the intent of our study was to investigate if patterns of parental skin-to-skin behavior should be considered in the overall discussion of mesosystemic variables contributing to longer term outcomes.

The study is also limited by sample size and possible confounding, which is inherently an issue when investigating associations. However as noted previously, NICU patients receiving SSC were actually associated with medical factors that were in turn associated with lower early-stage cognitive and communication scores. The study is also based on patients from a single hospital, and may not generalize to other neonatal units especially because our unit is a Level 4 all referral unit with high acuity infants and geographically distant parents. While we did see a relatively consistent pattern of association (c.f. **Table 5**)

between high / low SSC participation and the Bayley-III Cognitive and Communication Outcomes dichotomized at borderline disability (<80 vs. ≥80), we reiterate that none of these associations achieved statistical significance and thus can only be viewed as suggestive results in need of confirmatory analysis. If the observed associations were to hold in the population along with the same level of SSC participation and prevalence of borderline disability, then roughly 460 total subjects would be needed to achieve 80% power to detect the association in a larger study.

Our research suggests that developmental investigations into very early time points in the life of extremely preterm infants that incorporates both medical and behavioral components is warranted and critical to understanding how to fully optimize future developmental social and cognitive processes. Further prospective studies, involving more comprehensive measures and analyses of the early developmental NICU environment (22-40 weeks postmenstrual age) could help inform new designs for developmental caregiving and promotion of skin-to-skin care throughout the duration of hospitalization.

CONTRIBUTORSHIP STATEMENT

All authors contributed equally to this manuscript. Jenn Gonya and Guy Brock designed and conducted the study, analyzed the biostatistical portion, and wrote and reviewed manuscript drafts. Jenn Gonya, Will Ray, and R Wolfgang Rumpf performed visual analytics, wrote sections of the manuscript, and reviewed and refined manuscript drafts.

COMPETING INTERESTS

There are no competing interests with regard to this manuscript and project.

FUNDING

This project was supported by Award Number UL1TR001070 from the National Center for Advancing Translational Sciences. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Center for Advancing Translational Sciences or the National Institutes of Health.

ACKNOWLEDGMENTS

We would like to thank Dr. Leif Nelin and the Small Baby Program for their continual advocacy and advancement toward the highest standard of developmentally appropriate care of extremely preterm infants.

DATA SHARING STATEMENT

Data are stored on our internal, high security server. De-identified data set available upon request.

REFERENCES

1. Colonna F, Uxa F, daGraca AM, de Vonderweld U. The “kangaroo-mother” method: evaluation of an alternative model for care of low birth weight newborns in developing countries. *Int J Gynaecol Obstet* 1990; 31(4): 335-9.
2. de Leeuw R, Colin EM, Dunnebier EA, Mirmiran M. Physiological effects of kangaroo care in very small preterm infants. *Biol Neonate* 1991; 59(3): 149-55.
3. Ludington-Hoe SM, Thompson C, Swinth J, Hadeed AJ, Anderson GC. Kangaroo care: research results, and practice implications and guidelines. *Neonatal Netw* 1994; 13(1): 19-27.
4. Bauer K, Uhrig C, Sperling P, Pasel K, Wieland C, Versmold HT. Body temperatures and oxygen consumption during skin-to-skin (kangaroo) care in stable preterm infants weighing less than 1500 grams. *J Pediatric* 1997; 130(2): 240-4.
5. Feldman R, Eidelman AI. Intervention programs for premature infants. How and do they affect development? *Clin Perinatol* 1998; 25(3): 613-26.
6. Tornhage CJ, Stuge E, Lindberg T, Serenius F. First week kangaroo care in sick very preterm infants. *Acta Paediatr* 1999; 88(12): 1402-4.
7. Ohgi S, Fukuda M, Moriuchi H, Kusumoto T, Akiyama T, et al. Comparison of kangaroo care and standard care: behavioral organization, development, and temperament in healthy, low-birth-weight infants through 1 year. *J Perinatol* 2002; 22(5): 374-9.
8. Ludington-Hoe SM, Ferreira C, Swinth J, Ceccardi JJ. Safe criteria and procedure for kangaroo care with intubated preterm infants. *J Obstet Gynecol Neonatal Nurs* 2003; 32(5): 579-88.
9. Begum EA, Bonno M, Ohtani N, Yamashita S, Tanaka S, et al. Cerebral oxygenation responses during kangaroo care in low birth weight infants. *BMC Pediatr* 2008; 8:51.
10. Neu M, Robinson J. Maternal holding of preterm infants during the early weeks after birth and dyad interaction at six months. *J Obstet Gynecol Neonatal Nurs* 2010; 39(4): 401-14.
11. Conde-Agudelo A, Belizan JM, Diaz-Rossello J. Kangaroo mother care to reduce morbidity and mortality in low birthweight infants. *Cochrane Database Syst Rev* 2011; 3: CD002771.
12. Ludington-Hoe SM. Thirty years of kangaroo care science and practice. *Neonatal Netw* 2011; 30(5): 357-62.
13. Kaffashi F, Scher MS, Ludington-Hoe SM, Loparo KA. An analysis of the kangaroo care intervention using neonatal EEG complexity: a preliminary study. *Clin Neurophysiol* 2013; 124(2): 238-46.
14. Conde-Agudelo A, Diaz-Rossello J. Kangaroo mother care to reduce morbidity and mortality in low birthweight infants. *Cochrane Database Syst Rev* 2014;4: CD002771.
15. Morelius E, Ortenstran A, Theodorsson E, Frostell A. A randomized trial of continuous skin-to-skin contact after preterm birth and the effects on salivary cortisol, parental stress, depression, and breastfeeding. *Early Hum Dev* 2015; 91(1): 63-70.
16. Boundy EO, Dastjerdi R, Spegelman D, Fawzi WW, Missmer SA, et al. Kangaroo mother care and neonatal outcomes: a meta-analysis. *Pediatrics* 2016; 137(1).
17. Flacking R, Lehtnonen L, Thomson G, Axelin A, Ahlqvist S, et al. Closeness and separation in neonatal intensive care. *Acta Paediatr* 2012; 101(10): 1032-7.
18. Feldman R, Rosenthal Z, Eidelman AI. Maternal-preterm skin-to-skin contact enhances child physiologic organization and cognitive control across the first 10 years of life. *Biol Psychiatry* 2014; 75(1): 56-64.
19. Roberts KL, Paynter C, McEwan B. A comparison of kangaroo mother care and conventional cuddling care. *Neonatal Netw* 2000; 19(4): 31-5.
20. Rojas MA, Kaplan M, Quevedo M, Sherwonit E, Foster LB, Ehrenkranz RA, Mayes L. Somatic growth of preterm infants during skin-to-skin care versus traditional holding: a randomized, controlled trial. *J Dev Behav Pediatr* 2003; 24(3): 163-8.
21. Schneider C, Charpak N, Ruiz-Pelaez JG, Tessier R. Cerebral motor function in very premature-at-birth adolescents: a brain stimulation exploration of kangaroo mother care effects. *Acta Paediatr* 2012; 101(10): 1045-53.

22. Scher MS, Ludington-Hoe S, Kaffashi F, Johnson MW, Holditch-Davis D, Loparo KA. Neurophysiologic assessment of brain maturation after an 8-week trial of skin-to-skin contact on preterm infants. *Clin Neurophysiol* 2009; 120(10) 1812-8.
23. Seidman G, Unnikrishnan S, Kenny E, Myslinski S, Cairns-Smith S, et al. Barriers and enablers of kangaroo mother care practice: a systematic review. *PLoS One* 2015; 10(5): e0125643.
24. Nankervis CA, Martin EM, Crane ML, Samson KS, Welty SE, Nelin LD. Implementation of a multidisciplinary guideline-driven approach to the care of the extremely premature infant improved hospital outcomes. *Acta Paediatr* 2010; 99: 188-93.
25. Shepherd E, Calvert T, Martin E, Hitchner J, Welty, S, Nelin, L. Outcomes of extremely premature infants admitted to a children's hospital depends on referring hospital. *J Neonat Perinat Med* 2011; 4: 45-53.
26. Ambalavanan N, Carlo WA, Tyson JE, Langer JC, Walsh MC, Parikh NA, et.al. Outcome trajectories in extremely preterm infants. *Pediatrics* 2012; 130(1): e115-25.
27. McMahon E, Wintermark P, Lahav A. Auditory brain development in premature infants: the importance of early Experience. *Ann N Y Acad Sci* 2012; 1252: 17-24.
28. National Institute of Child Health and Human Development Neonatal Research Network. Follow-up program. 2013; Retrieved from https://neonatal.rti.org/about/fu_background.cfm
29. Pearson Education. Bayley scales of infant development (third edition). Pearson Clinical 2008 Training.
30. Ray WC. MAVL and StickWRLD: visually exploring relationships in nucleic acid sequence alignments. *Nucleic Acids Res* 2004; 32: 59-63.
31. Rumpf RW, Gonya J, Ray W. Visual hypothesis and correlation discovery for precision medicine. AMIA workshop on visual analytics in healthcare conference paper 2014.
32. Ray WC, Wolock SL, Li N, Bartlett CW. StickWRLD: Interactive visualization of massive parallel contingency data for personalized analysis to facilitate precision medicine. Proceedings of the 3rd annual Workshop on Visual Analytics in Healthcare, in conjunction with the American Medical Informatics Symposium. 2013; November.
33. Key APF, Lambert EW, Aschner JL, Maitre NL. Influence of gestational age and postnatal age on speech sound processing in NICU infants. *Psychophys* 2012; 49: 720-731.
34. Caskey M, Stephens B, Tucker R, Vohr B. Importance of parent talk on the development of preterm infant vocalizations. *Pediatrics* 2011; 128(5): 910-6.
35. Caskey M, Stephens B, Tucker R, Vohr B. Adult talk in the NICU with preterm infants and developmental outcomes. *Pediatrics* 2014; 133(3): 578-84.
36. Silva MG, Barros MC, Pessoa UM, Guinsburg R. Kangaroo-mother care method and neurobehavior of preterm infants. *Early Hum Dev* 2016; 95: 55-9.
37. Feldman R, Eidelman AI. Skin-to-skin contact (kangaroo care) accelerates autonomic and neurobehavioural maturation in preterm infants. *Dev Med Child Neurol* 2003; 45(4): 274-81.
38. Feldman R, Eidelman AI, Sirota, Weller A. Comparison of skin-to-skin (kangaroo) and traditional care: parenting outcomes and preterm infant development. *Pediatrics* 2002; 110: 16-26.
39. Feldman R. From biological rhythms to social rhythms: physiological precursors of mother-infant synchrony. *Dev Psychol* 2006; 42(1) 175-88.
40. Fetal Development: Research on Brain and Behavior, Environmental Influences, and Emerging Technologies. Reissland N, Kisilevsky BS (Eds.) Switzerland: Springer International 2016.
41. Thomason ME, Grove L, Lozon TA, Vila AM, Ye Y, et al. Age related increases in long-range connectivity in fetal functional neural connectivity networks in utero. *Developmental Cog Neurosci* 2015; 11: 96-104.
42. Krueger C, Garvan C. Emergence and retention of learning in early fetal development. *Infant Behavior and Dev* 2014; 37(2): 162-173.
43. Pearson J, Tarabulsy GM, Bussieres E. Foetal programming and cortisol secretion in early childhood: a metal-analysis of different programming variables. *Infant Behavior and Dev* 2015; 40: 204-215.
44. Fetal Growth and Development. Harding R, Bocking AD (Eds.) 2001. United Kingdom: Cambridge University Press.

Figure Legends

FIGURE 1 – Overall and Parent Specific SSC Participation: Boxplots displaying the distribution of overall SSC participation and by parent. Thick horizontal lines give medians while boxes display the middle 50% of the data (25th and 75th percentiles). Whiskers extend to no more than 1.5 times the interquartile range (IQR = difference between 75th and 25th percentiles) from the edge of the box. Points beyond the whiskers represent outliers.

FIGURE 2 – Total SSC hours per week: ***Blue line*** displays the total number of SSC hours per week for all families in the study, by postmenstrual age. ***Red line*** gives the total number of babies in the NICU for the given week.

FIGURE 3 – SSC intensity (hours per week per family): ***Blue line*** displays the average SSC intensity (hours per family per week) by postmenstrual age. ***Red line*** gives the total number of babies in the NICU for the given week.

FIGURE 4 – Bayley Cognitive and Communication scores by SSC participation: Boxplots displaying the distribution of Bayley cognitive, communication, and combined cognitive-communication (Cog-Comm) scores at 6 and 12 months by SSC participation (high vs. low). High SSC participation was defined as having above the median participation for total SSC hours, mother SSC hours, father SSC hours, and SSC intensity (see text for details). Thick horizontal lines give medians while boxes display the middle 50% of the data (25th and 75th percentiles). Whiskers extend to no more than 1.5 times the interquartile range (IQR = difference between 75th and 25th percentiles) from the edge of the box. Points beyond the whiskers represent outliers.

FIGURE 5 – Visual Analytical Display from StickWRLD Software. The visual space is divided into three main regions: Medical Factors, Skin-to-Skin Factors, and Bayley-III Scores. Each line represents a significant correlation between factors with stronger correlations represented by lines that are thicker in diameter. ***Line colors are assigned randomly and are used only to aid in visual comparisons of associations***. Within region correlations are evident and expected. Two blue arrows indicate two unexpected strong correlations (one from each region) that converge on the Bayley-III 12-Month Cognitive Score, suggesting Skin-to Skin Care Frequency and presence or absence of Intraventricular Hemmorhage (IVH) as parallel, but non-interactive factors impacting the score.

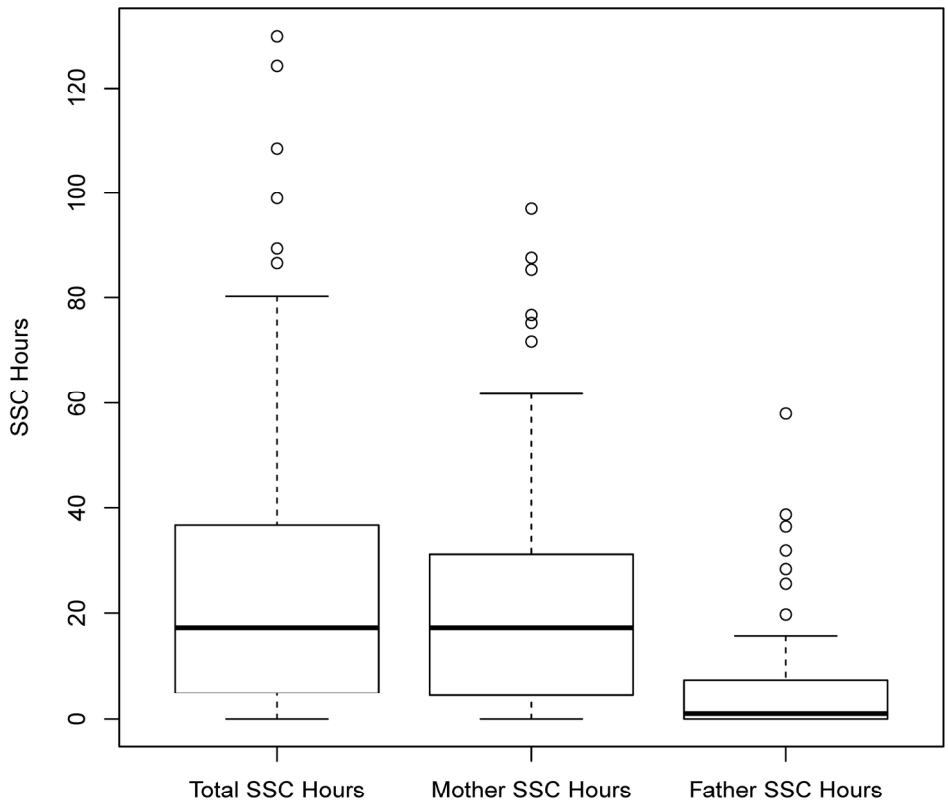


FIGURE 1 – Overall and Parent Specific SSC Participation: Boxplots displaying the distribution of overall SSC participation and by parent. Thick horizontal lines give medians while boxes display the middle 50% of the data (25th and 75th percentiles). Whiskers extend to no more than 1.5 times the interquartile range (IQR = difference between 75th and 25th percentiles) from the edge of the box. Points beyond the whiskers represent outliers.

177x177mm (300 x 300 DPI)

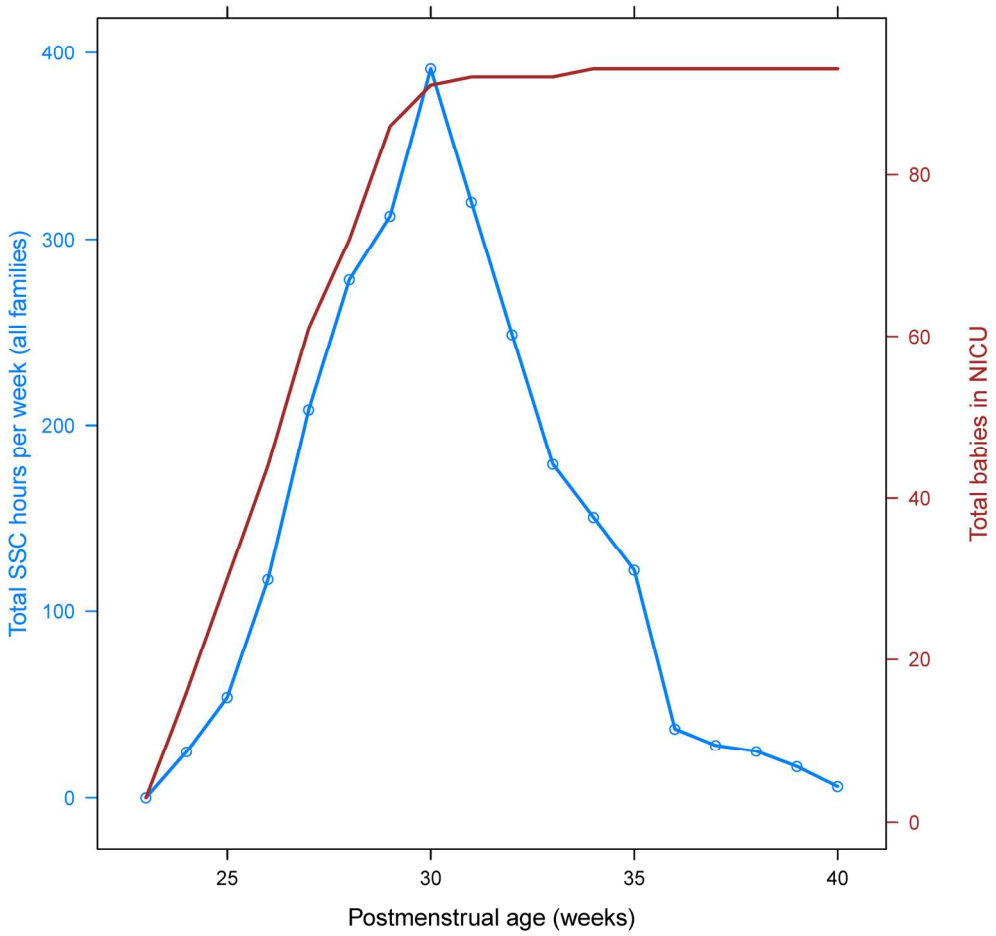


FIGURE 2 – Total SSC hours per week: Blue line displays the total number of SSC hours per week for all families in the study, by postmenstrual age. Red line gives the total number of babies in the NICU for the given week.

177x177mm (300 x 300 DPI)

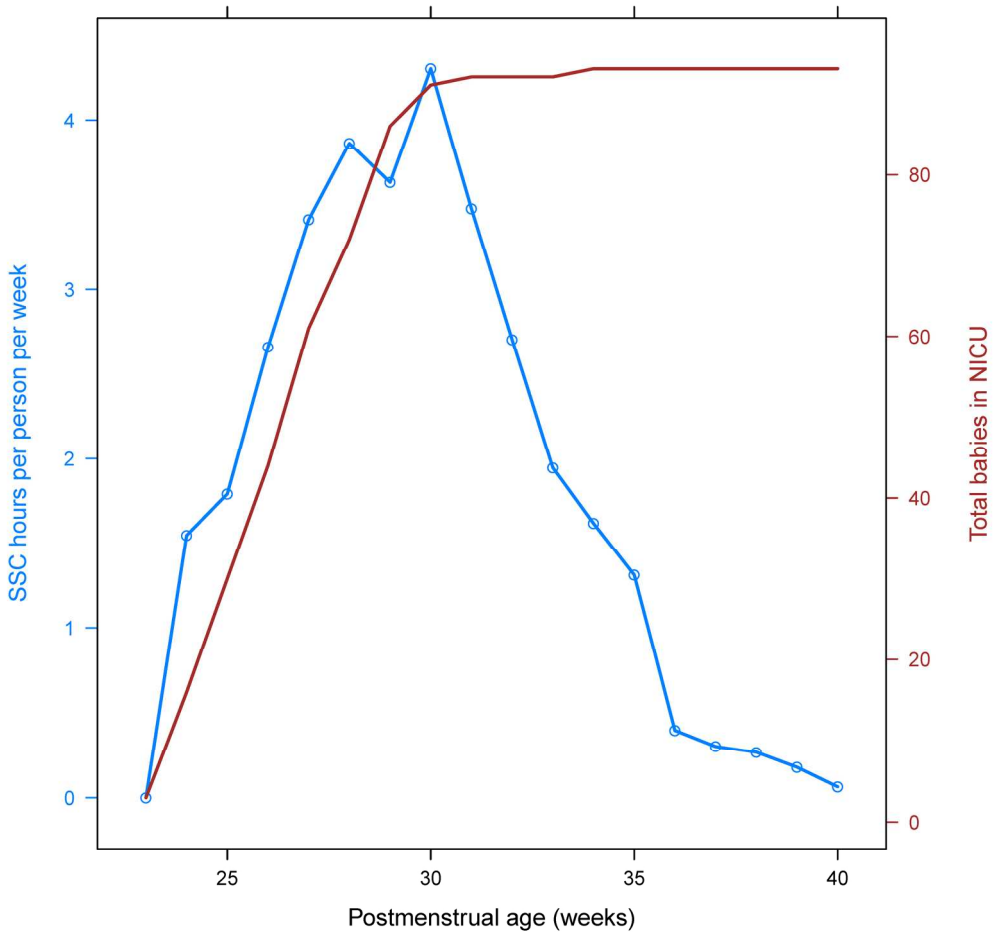


FIGURE 3 – SSC intensity (hours per week per family): Blue line displays the average SSC intensity (hours per family per week) by postmenstrual age. Red line gives the total number of babies in the NICU for the given week.

177x177mm (300 x 300 DPI)

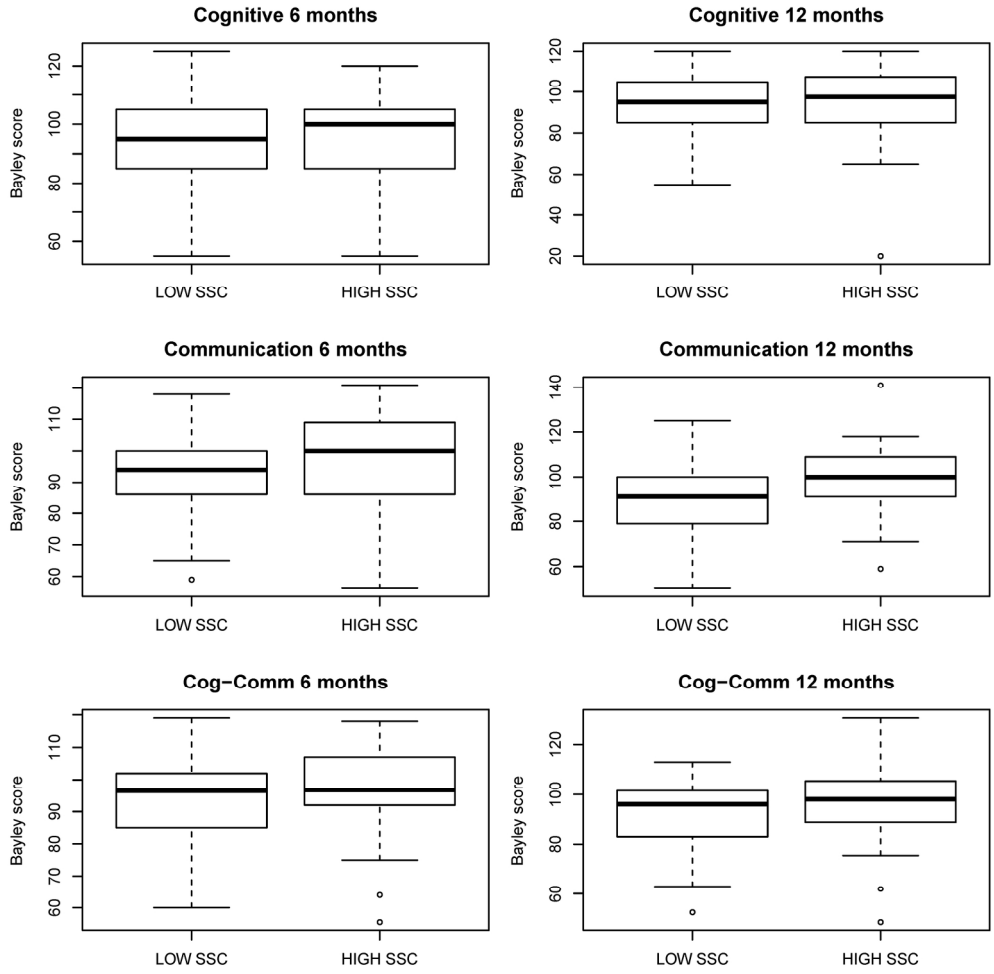


FIGURE 4 – Bayley Cognitive and Communication scores by SSC participation: Boxplots displaying the distribution of Bayley cognitive, communication, and combined cognitive-communication (Cog-Comm) scores at 6 and 12 months by SSC participation (high vs. low). High SSC participation was defined as having above the median participation for total SSC hours, mother SSC hours, father SSC hours, and SSC intensity (see text for details). Thick horizontal lines give medians while boxes display the middle 50% of the data (25th and 75th percentiles). Whiskers extend to no more than 1.5 times the interquartile range (IQR = difference between 75th and 25th percentiles) from the edge of the box. Points beyond the whiskers represent outliers.

177x177mm (300 x 300 DPI)

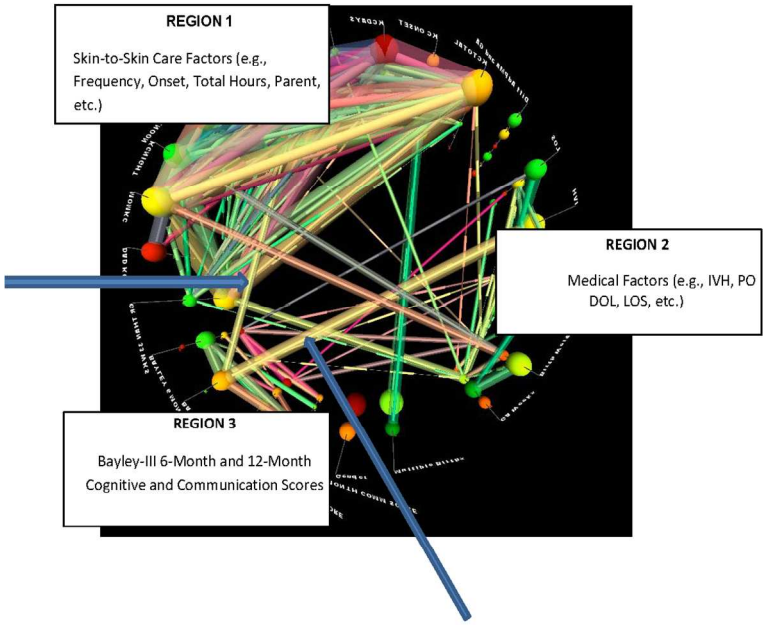


FIGURE 5 – Visual Analytical Display from StickWRLD Software. The visual space is divided into three main regions: Medical Factors, Skin-to-Skin Factors, and Bayley-III Scores. Each line represents a significant correlation between factors with stronger correlations represented by lines that are thicker in diameter. Line colors are assigned randomly and are used only to aid in visual comparisons of associations. Within region correlations are evident and expected. Two blue arrows indicate two unexpected strong correlations (one from each region) that converge on the Bayley-III 12-Month Cognitive Score, suggesting Skin-to Skin Care Frequency and presence or absence of Intraventricular Hemmorhage (IVH) as parallel, but non-interactive factors impacting the score.

215x279mm (157 x 166 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	p.1
		p.2
Introduction		
Background/rationale	2	p.4
Objectives	3	p.1 and p.4
Methods		
Study design	4	p.5
Setting	5	p.5
Participants	6	p.5
Variables	7	pp.5-6
Data sources/ measurement	8*	pp.5-6
Bias	9	p. na Retrospective Study
Study size	10	p. na All infants in cohort included
Quantitative variables	11	p. 5
Statistical methods	12	p. 6

Continued on next page

Results		
Participants	13*	p.7
Descriptive data	14*	p. 7
Outcome data	15*	pp. 7-10
Main results	16	pp.7-10
Other analyses	17	p. 10
Discussion		
Key results	18	pp. 10-12
Limitations	19	p. 11
Interpretation	20	pp. 10-12
Generalisability	21	p. 11
Other information		
Funding	22	p. 12

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.