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ORIGINAL ARTICLE

Language outcomes at 36 months in prematurely born children is associated with the quality of developmental care in NICUs

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OBJECTIVE: The aim of this study was to examine the relationship between the quality levels of NICU developmental care (DC) and language skills at 36 months in very preterm (VPT) children.
STUDY DESIGN: Language skills of 78 VPT children from 19 NICUs and 90 full-term controls was assessed using a standardized language test. We compared children' language task performance by splitting NICUs into units with high- and low-quality of DC according to two main factors: (1) *infant centered care* (ICC), and (2) *infant pain management* (IPM).
RESULTS: VPT children from low-care units with respect to ICC obtained lower scores in sentence comprehension, compared to children from high-care units. No differences were found between preterm children from high-quality ICC NICUs and full-term children.
CONCLUSIONS: Findings suggest that higher quality of DC related to infant centered care can mitigate delays in language skills at 36 months in children born VPT.

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INTRODUCTION

Several studies have documented that preterm birth has a long-term impact on neurodevelopment,[1] including language skills.[2] Difficulties in specific linguistic competences, such as vocabulary and grammar are reported in preschool age children.[3–7] Interestingly, impaired languages skills were found in children born preterm without severe clinical complications in the perinatal period, even after controlling for general cognitive level (e.g., intelligence quotient) at 36 months of age.[8] These long-lasting effects of preterm birth on language skills underscore the relationship between early experience and development outcomes beyond the first years of life. Indeed, it has been suggested that language difficulties might be, at least partially, associated with less than optimal neonatal auditory and communicative experiences,[9,10] which in turn suggests the importance of the quality of care during the NICU stay.

Early experience has profound effect on the developing brain,[11] so that early interventions effectively support neurodevelopment and improve health, cognition and social outcomes.[12] Studies suggest that development care (DC) interventions improve infants' neurodevelopment in both short-term[13–16] and long-term.[17] DC includes a broad category of interventions designed to minimize the effects of NICU stress exposure,[18] such as: control of external stimuli (e.g., auditory, visual, tactile), kangaroo care and parental involvement (e.g., breastfeeding, the policies of NICUs toward parental visiting, promoting infant-parent bonding), developmental activities of daily living (i.e., nesting, swaddling, prone position) and infant pain management.[19,20] As result, apart from specific protocols, such as for example the Newborn Individualized Developmental Care and Assessment Program (NIDCAP;[21]) or the Wee Care Neuroprotective NICU program,[22] NICUs have increasingly incorporated DC practices (or a set of DC procedures) in their daily routine management of the infants. Although the beneficial effects of DC practices on infant development have been documented,[23] a critical point is that the utilization of DC practices is not yet uniformly applied in NICUs and multicenter research offers unique insight about the variability between units.[24] For example, broad variations among units have been documented across eight European countries in parental visiting policies,[25] in breastfeeding support[26] and in the use of mechanical lance and non-pharmacological analgesia,[27] Consequently, it is possible that NICUs integrate only some practices of DC into their conventional care, resulting in different levels of DC quality provided. In very preterm (VPT) infants, differences in the actual level of quality of care incorporated in a NICU's standard care have been evaluated in relation to neurobehavioral profile during the neonatal period[28] and behavioral problems at 18 months.[29] However, it is unknown whether the level of care routinely used in NICUs (as opposed to *ad hoc* interventions) contributes to lasting effects on language skills during preschool age.

In the current study, we evaluated the relationships between the quality of care with respect to inclusion of DC practices in 19 Italian NICUs and language skills at 36 months of age for children born very preterm, including an age-matched sample of full-term children as a control group. To evaluate the level of DC in NICUs we used a specifically developed questionnaire, the Neonatal Adequate Care for Quality of Life (NEO-ACQUA) Quality of Care Questionnaire (QCQ). We compared language skills of children by splitting the NICUs into units characterized by high and low quality of DC, then examining whether language performance was associated with these two quality of care categories. We

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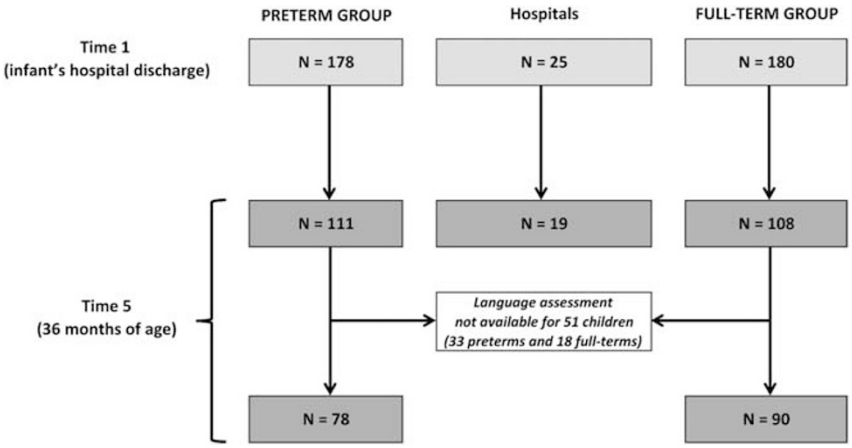

Figure 1. Flow chart of the initial study enrolment, and infants tested for language skills at 36 months of age.

hypothesized that children from NICUs with a high-quality DC had better language skills than children from NICUs with low-quality of DC. Furthermore, we expected that children from NICUs characterized by high-quality DC would exhibit language skills similar to the those displayed by a control group of full-term children. Importantly, one could expect that language performance at 36 months of age might be related to some perinatal variables including neonatal illness severity, rather than quality of care. Furthermore, previous research has documented that negative parental emotional states are associated with language development[30,31] and behavioral problems have been found to be related with lower language performance.[32,33] Thus, in order to control for these variables, we have preliminarily compared perinatal variables, children's behavioral problems and maternal depressive symptomatology among three groups (low-care group, high-care group and control group).

METHODS

Participants

The research is part of the Neonatal Adequate Care of Quality of Life (NEO-ACQUA) project, a multicenter, longitudinal study of the relationship between the quality of care received by infants in the NICU and their subsequent outcomes and quality of life.[28,34,35] The study design included behavioral, cognitive and language follow-up assessments until 7 year of age with very preterm children compared with a control group of full-term children (see below). Both groups (preterm and full-term) were assessed at seven time points: just prior to the infant's hospital discharge (Time 1), at 6 months (Time 2), 18 months (Time 3), 30 months (Time 4), 36 months (Time 5), 60 months (Time 6), and 84 months (Time 7). The current study is focused on data from the Time 5 (36 months) follow-up language assessment. At Time 1, a group of 178 very preterm infants were recruited consecutively from 25 Italian tertiary care NICUs between January 2006 and December 2007. Inclusion criteria for preterm infants were: gestational age between 22 and 29^{+6} weeks and/or birth weight between 401 and 1500 g. Exclusion criteria included: major brain lesions as documented by cerebral ultra-sound (grade III - IV intraventricular hemorrhage according to Papile classification, periventricular leukomalacia > stage 1 - periventricolar iperechogenicity lasting more than 2 weeks); neuro-sensorial deficits (rethinopathy of prematurity > stage 2; neonatal hearing deficit as detected by auditory brainstem response (ABR) or otoemission at 34 weeks' post-conceptional age (PCA) and confirmed by audiological examination at 40 weeks PCA; genetic syndromes and/or major malformations. At Time 1, a group of 180 full-term infants (gestational age $\geqslant$ 37 week and birth weight $\geqslant$ 2500 g) were selected from the sequential register of births held in the delivery ward of the participating hospitals. For each preterm infant, the first suitable full-term newborn born after each preterm infant, who was not admitted to the NICU, was enrolled. Full-term infants were healthy, with no pathologies and risk factors in pregnancy and during the perinatal period. Furthermore, full-term infants were matched for gender, mothers' age, mothers' education, and family socio-economic status with preterm infants.

At Time 5, six NICUs did not participate in the study for organizational reasons. No differences between participating and not participating were found in general characteristics of the units, such as admission for year, days of recovery for year, number of beds. From the original sample 111 preterm infants and 108 full-term infants participated in the study, resulting in a 37.6 and a 40.0% attrition rate, respectively. Language assessments, coordinated by the remaining 19 NICUs, were not available for 51 children (33 preterms and 18 full-terms), leaving 78 preterm children and 90 full-term children (see flow chart in Figure 1). Causes for lack of participation at the follow-up included children's illness and family related reasons (i.e., impending relocation, lack of time for participation). No significant differences in gender, gestational age, birth weight, days of hospitalization, mothers' age, mothers' education and family socio-economic index were found between children participating and not-participating in the follow-up session. All families spoke Italian as the primary language and no parent reported a family history of language delay.

Procedure

The study was approved by the Ethics Committee in each participating hospital, with all parents signing a written informed consent form. Data regarding the 19 NICUs and infant's perinatal data were obtained from the NEO-ACQUA database and medical records. At 36 months, during a scheduled visit, a standardized language test (see below) was administered both to preterm children and the control group. All children were tested individually in a quiet room of each hospital by trained professionals (e.g., psychologist). Finally, mothers were asked to fill out questionnaires on maternal depressive symptomatology and child behavior (see below).

Measures

Measurement of developmental care. To evaluate the level of DC in NICUs, we used the NEO-ACQUA Quality of Care questionnaire[28,35] (QCQ which is available from the corresponding author). The QCQ is a 29-item questionnaire designed to measure a variety of DC practices used in NICUs, covering several areas: 1. general information about the unit, such as number of cots, admissions per year, staffing; 2. application of specific developmental care practices and policies toward parents and kangaroo care; 3. control of the environment; 4. procedures for infant pain management. For each NICU, a neonatologist with at least 5 years of clinical experience, who was not involved in the direct care of the infants filled out the QCQ and rated the level of DC quality on items ranging from 0 (low quality of care) to 1 or 2 (high quality of care). In order to aggregate the items into a reduced number of DC descriptors, we applied factor analysis to QCQ responses, revealing a three-factor structure. The first factor, labeled *Nursing Staffing*, accounted for 12% of the variance, included items such as number of physicians per bed, number of graduate students, fellows, or consultants per bed, nurse chiefs per bed, nurses per

bed, and nursery nurse, assistants per bed. Given the goal of this study, we used two indexes of DC: the *infant centered care* (ICC) index and the *infant pain management* (IPM) index. The ICC accounted for 20% of the variance and included four items (Cronbach's alpha = .84): 1. parent's involvement in care, such as parents to spend the night in the unit; 2. use of parental kangaroo care as a routine procedure; 3. duration per day of kangaroo care ($<$ or $\geqslant$ 45 min); 4. presence of nursing interventions to support infant development by decreasing infant energy expenditure and promoting stability (i.e., infant containment, postural maneuvers and reduction of disturbing tactile stimulation). The IPM accounted for 9% of the variance and included five items (Cronbach's alpha = .75): 1. number of invasive medical procedures (e.g., intravenous lines, drainage tubes, endotracheal tubes, etc.) in which non-pharmacologic procedures (i.e., pacifier, glucose, containment with towels or blankets) are used for reducing pain; 2. number of invasive medical procedures in which pharmacologic procedures are used for reducing pain; 3. use of pharmacologic analgesia or sedation during continuous mechanical ventilation; 4. use of a blood collection procedure (i.e., heel stick by manual lance or mechanical one); 5. use of a clinical evaluation scale of infant pain and/or a protocol designed for pain management of newborn infants, including guidelines and well-established recommendations. Factor loadings were utilized to compute composite scores for ICC and IPM indexes for each NICU. The ICC index ranged from 0 to 8, with higher scores indicating higher level of ICC. The IPM index ranged from 0 to 10, with higher scores indicating higher levels of IPM. Examples of QCQ items for ICC and IPM indexes are reported in Supplementary Appendix 1.

Infant's perinatal data. Infants' perinatal variables including gestational age, birth weight, length of stay in the NICU, were obtained from medical records. As neonatal illness severity has an effect on language outcomes,[36] we assessed the infant clinical status computing the Vermont Oxford Network Risk Adjustment index (VON-RA;[37]). The VON-RA index considers clinical and demographical variables, such as gestational age, presence of congenital anomaly, multiple gestation, Apgar score at 1 minute, gender, mode of delivery (vaginal vs caesarean section), and out-born status. Low VON-RA scores indicate less serious clinical outcomes.

Socio-demographic variables. Socio-demographic data such as maternal age, years of education and occupational status were obtained for both parents through a questionnaire. According to Hollingshead's classification,[38] the more prestigious occupational level between mother and father (i.e., the highest of the two ratings) was considered to indicate the family socioeconomic status (SES). Score ranges from 0 (occupations that do not require high school graduation) to 90 (occupations that require highly specialized education and training). Lower scores reflected lower socio-economic status.

Language assessment. Language skills were investigated through a standardized Italian test for preschool children 'Test di Valutazione del Linguaggio' (TVL;[39]). The TVL evaluates receptive and expressive language abilities and it's structured into following four sections: 1. word comprehension, assessed using images representing body parts, common objects, adjectives and colors; 2. sentences comprehension, assessed using pictures representing actions, objects and spatio-temporal concepts; 3. sentence repetition, assessed by a repetition task of 15 sentences of increasing complexity; 4. naming ability, assessed by asking the child to name pictures representing body parts and objects of common use. Raw scores for each scale were converted in standardized scores, following the TVL test manual procedures. Score ranges from 0 to 10, with lower scores reflected lower language skills.

Children's behavioral and emotional problems. Mother were asked to fill out the Italian version of the Child Behavior Checklist for children ages 1½ to 5 years (CBCL-1.5/5;[40,41]), found to have satisfactory reliability and validity. The CBCL-1.5/5 was developed to obtain standardized parental report on children's behavioral and emotional problems. It includes 99 items describing a broad range of children's problems. Parents indicated if a problem was 0 (not), 1 (sometimes), or 2 (often) true for their child. The CBCL provides seven syndrome scales: 1. emotionally reactive (e.g., moody), 2. anxious/depressed (e.g., nervous), 3. somatic complaints (e.g., does not eat well), 4. withdrawn (e.g., avoids eye contact), 5. sleep problems (e.g., nightmares), 6. attention problems (e.g., cannot concentrate), and 7. aggressive behavior (e.g., hits others). Two broad-band scales are also derived by summing syndrome scales: Internalizing scale (which encompasses the first four syndrome scales) and Externalizing scale (which includes attention problems and aggressive behaviors), and will be utilized for the purposes of this study.

Maternal depressive symptoms. The Beck Depression Inventory (BDI;[42]) is a 21-item scale questionnaire widely used to assess depressive symptomatology. Each item is rated on a 4-point intensity scale. This scale is commonly used in research on non-clinically depressed samples.[43]

Statistical analysis

To examine differences within the preterm group, taking into consideration the level of DC quality, each NICU was assigned to a low- or high-quality of DC group, based on median splits for the ICC and IPM. For the ICC, 8 NICUs had low-quality DC (38 infants) and 11 NICUs had high-quality DC (40 infants). For the IPM, 10 NICUs had low-quality DC (49 infants) and 9 NICUs had high-quality DC (29 infants). Such dichotomization resulted in a categorical measure of high/low exposure to level of DC quality, avoiding bias from extreme scores. Descriptive statistics and percentiles of ICC and IPM scores are reported in Supplementary Appendix 2. The minimum sample size of 29 infants obtained following the dichotomization was adequate to detect a significant difference in the primary outcome measure in this study (i.e., language ability) with a power of 80% and α of 5%. The calculation was based on differences in language performance between preterm and full-term children at 3.6 years of age reported in a recent Italian study.[43] Normality of the distribution was evaluated for the variables included in this study using the Kolmogorov-Smirnov test, which provided evidence of some deviation of the normal distribution, an assumption for carrying our parametric procedures.[44] However, ANOVA tests have been shown as robust with respect to violations of normality.[45]

Preliminarily statistical analyses evaluated perinatal data, socio-demographic variables as well as children behavior problems and maternal depression (BDI score). General characteristics of the units, length of hospitalization and VON-RA score was also considered for preterm children. Categorical variables were analyzed by chi-square tests, while continuous variables were analyzed through a series of univariate analyses of variance (ANOVAs), separately for ICC and IPM indexes as factor (low-care group vs high-care group vs control group).

One-way multivariate analyses of variance (MANOVA) with Bonferroni-corrected post-hoc tests were conducted, separately for IPM and ICC, to determine the effects of quality of care (low-care group vs high-care group vs control group) on the four TVL scores. To test the MANOVA assumption that the within-group covariance matrices were equal, Box's M test was employed.

Where appropriate, for the determination of effect size, partial η^2 for significant effects were estimated. All analyses were conducted with two-tailed tests, and $P \leqslant .05$ was considered statistically significant. Data were analyzed using SPSS Statistics (SPSS version 17.0 for Windows, SPSS Inc., Chicago, IL, USA).

RESULTS

Units, infants and mothers characteristics

Descriptive statistics are presented in Tables 1 and 2. No differences were found for general characteristics of the NICUs, as well as for infant perinatal data (i.e., birth weight, gestational age, gender, length of hospitalization and VON-RA score). There were no significant differences in age, education, family SES and BDI scores amongst the mothers of children from the low-care, high-quality care and control groups. Finally, no significant differences were found in Internalization and Externalization scales among the three groups, both for ICC and IPM indexes.

Language assessment

Descriptive statistics are presented in Supplementary Information file. Significant differences among the three groups (low-care group vs high-care group vs control group) on Word comprehension scores, $F(2,168) = 8.28$, $P = .000$, $\eta^2_p = .91$ and for Sentences comprehension scores, $F(2,168) = 10.50$, $P = .000$, $\eta^2_p = .11$, were observed for the IPM index. Bonferroni-adjusted *post hoc* comparisons showed that for both scales, the effect was related

Table 1. Summary of NICUs characteristics and perinatal variables subdivided for high and low quality of care, separately for *Infant Centered Care* (ICC) index and *Infant Pain Management* (IPM) index and for full-term children

	Preterm group								*Full-term group*	
	ICC index				*IPM index*					
	Low (NICU = 8) (N = 38, 21 F)		*High (NICU = 11) (N = 40, 22 F)*		*Low (NICU = 10) (N = 49, 27 F)*		*High (NICU = 9) (N = 29, 16 F)*		*(N = 90, 50 F)*	
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*
NICUs variables										
Total admission for year	452.13	218.11	593.18	416.31	496.6	213.19	575.11	463.69	—	—
Days of recovery for year	5923.38	3557.14	7410.20	3553.04	5656.56	3235.43	7842.22	3653.31	—	—
Number of beds	21.38	10.2	20.82	12.46	20.2	8.47	22.00	14.24	—	—
Perinatal variables										
Birth weight (g)	1173.74	205.69	1093.83	264.84	1157.98	233.32	1090.14	248.45	3251.5	511.81
Gestational age at birth (wks)	28.92	1.78	28.65	2.41	29.12	1.98	28.21	2.26	39.12	1.92
Length of hospitalization (days)	59.53	17.83	58.05	25.25	56.98	20.82	61.79	23.5	—	—
VON-RA score (range: 0,01 ÷ 0,99)	0.08	0.08	0.14	0.2	0.1	0.12	0.15	0.21	—	—

Abbreviations: F, female; VON-RA, Vermont Oxford Network-Risk Adjustment index (Zupancic *et al.*[37]).

Table 2. Summary of maternal variables, children's behavioral and emotional problems and language assessment at 36 months subdivided for high and low quality of care, separately for *Infant Centered Care* (ICC) index and *Infant Pain Management* (IPM) index and for full-term children

	Preterm group								*Full-term group*	
	ICC index				*IPM index*					
	Low (NICU = 8) (N = 38, 21 F)		*High (NICU = 11) (N = 40, 22 F)*		*Low (NICU = 10) (N = 49, 27 F)*		*High (NICU = 9) (N = 29, 16 F)*		*(N = 90, 50 F)*	
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*
Maternal variables										
Mother's age (yrs)	32.19	4.53	33.52	5.81	32.86	4.91	32.88	5.84	33.66	4.16
Education mother (yrs)	11.74	3.5	13.21	3.74	12.27	3.85	12.83	3.4	12.56	3.56
SES score	46.32	15.67	56.75	18.45	49.39	18.19	55.52	16.82	55.8	20.10
Depressive symptoms (BDI score)	6.49	7.59	5.66	5.35	7.02	7.24	4.55	4.93	4.60	5.57
CBCL1,5-5 (score)										
Internalization scale	7.68	10.77	6.68	5.71	7.93	9.91	5.97	5.7	7.51	6.47
Externalization scale	10.51	8.93	9.45	6.05	10.78	8.82	8.69	4.89	10.53	7.35
Language assessment (weighted score)										
Word comprehension	5.17	3.62	6.60	3.45	6.21	3.76	5.38	3.27	7.86	2.87
Sentence comprehension	3.89	3.10	5.85	3.05	4.85	3.40	4.98	2.90	7.04	2.84
Sentence repetition	4.55	3.11	5.77	3.04	5.49	3.25	4.65	2.86	5.91	2.98
Naming ability	6.76	3.29	6.95	3.33	6.98	3.39	6.65	3.16	7.70	2.58

Abbreviations: BDI, Beck Depression Inventory (Beck *et al.*[42]); CBCL 1,5-5, Child Behavior Checklist (Achenbach & Rescorla, 2000); F, female.

to preterm status rather than the level of DC. That is, compared to the control group, children from both low- and high-IPM care NICUs showed lower performance in Word comprehension (respectively, $P = .014$ and $P = .001$) and Sentence comprehension (respectively, $P = .001$ and $P = .005$). No significant difference among the three groups were found in Sentences repetition and Naming ability.

For the ICC index (see: Figure 2), significant differences were found among the three groups (low-care group vs high-care group vs control group) on Word comprehension scores, $F(2,168) = 9.74$, $P = .000$, $\eta_p^2 = .11$ and Sentence comprehension scores, $F(2,168) = 15.31$, $P = .000$, $\eta_p^2 = .16$. Bonferroni-adjusted *post hoc* comparisons suggested that preterm infants from units with low-quality in ICC obtained lower Word comprehension scores compared to full-term infants ($P = .000$). Children from ICC low-care units received significantly lower scores than either children from ICC high-care units ($P = .012$) or control group children ($P = .000$) on Sentence comprehension. Significant differences between children from ICC high-care units and full-terms were not noted for Word or Sentence comprehension subscales.

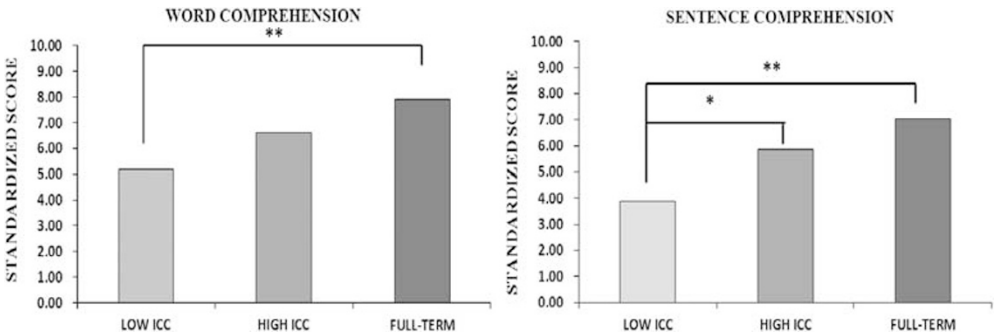

Figure 2. Means of the standardized scores for Word comprehension and Sentence comprehension in the preterm children from high- and low-care units for *Infant Centered Care* (ICC) index and in full-term children. *$P < .05$; **$P < .001$.

DISCUSSION

This pattern of findings suggests that on the whole VPT children showed lower performance in word and sentence comprehension, compared to full-term children. This result further supports the existing evidence indicating that preterm birth is followed by poor language outcomes during the preschool period, characterized by difficulties and delays which are not explained by major cerebral damage or medical complications.[2,46,47] Interestingly, compared with preterm children who received a high level of DC, those who were exposed to low level of DC showed worse receptive language skills. Thus, the presents study makes a unique contribution, indicating that language impairments may be better understood taking into account the levels of DC quality provided in the neonatal period. Importantly, general characteristics of the units, perinatal variables (including the VON-RA clinical status score), socio-demographic factors, maternal depression symptomatology and children's behavioral profile did not differ between NICUs with high- and low- quality of DC, so that these factors did not appear sufficient in-end-of themselves to account for the difference in language skills observed in children from NICUs with low-quality care.

Our findings also demonstrate that children from NICUs with high-quality of ICC scored higher in sentence comprehension compared to children from NICUs with low-quality of ICC. The ICC index includes DC practices that promote parental involvement and nursing interventions to reduce infant energy expenditure and promote stability. The ICC is a global index so that it is not possible to identify which specific practices are related to language performance of children from high-care units. However, it is possible to suggest some speculative interpretations. First, while we did not measure the amount of adult speech (i.e., adult word count) that infants heard from parents during the NICU stay, one might speculate that more parental visiting, kangaroo care and parental holding provide more opportunities for parents to talk to the infants. In other words, preterm infants from high-care units would have been exposed to adult language input for a higher percentage of the time than their counterparts from low-care units. This, increased amount of parent talk exposure could explain the observed superior language performance at 36 months. This finding is reminiscent of previous studies suggesting that early adult speech during the NICU stay is associated with improved language outcomes after discharge.[48] Second, more physiological and behavioral stability associated with high-quality of ICC[28] may have an impact on language ability. It is worth noting that vocal maternal stimulation has beneficial effects on physiological and behavioral parameters of preterm infants in the NICU, such as oxygen saturation levels and prevalence of a calm alert state.[49] Third, nursing interventions aimed to reduce infant energy expenditure and promote stability have positive effects in reducing physiological distress and increasing self-regulatory ability.[50,51] To the best of our knowledge, no study has assessed associations between regulation and language skills in preterm infants. However, one study examining typically developing children of 13 months of age has shown that attention control and emotional stability (which are thought to be measures of infant self-regulation) predicted language productivity seven months later.[52] Furthermore, preschoolers' language skills have been positively correlated with their self-regulation ability in a frustrating situation.[53] Clearly, it is unlikely that above- mentioned explanatory mechanisms function in a mutually exclusive manner, and future research is needed for more specific conclusions about the links between DC procedures and language skills.

Unexpectedly, for the IPM index there were no differences in language skills between children from high and low quality-of-care NICUs. The result is not readily explained, given that previous research has provided evidence supporting an association between early exposure to painful experiences and later behavioral problems beyond infancy.[54] For example, one study has documented that higher exposure to neonatal pain during the NICU stay was related to internalizing problems in children born preterm at 18 months.[55] In addition, VPT children from NICUs with high-quality in DC procedures related to pain management scored lower in internalizing behaviors at 18 months compared to children from NICUs with low-quality.[29] A possible interpretation of the current finding is that neonatal protection from pain-related stress may have long lasting effects for the child at the behavioral level, rather than in terms of cognitive functioning (i.e. language skills). Alternatively, it is possible that potential positive effects of high-quality neonatal pain management are transient, becoming less notable over the first years of life. It is thus imperative to pursue further research examining effects of neonatal pain management on later language delay/problems in preterm children to discern among these possible explanations.

This study has limitations. First, the 19 included NICUs self-selected themselves into the NEO-ACQUA study. Thus, although the use of data from a wide number of NICUs represents a substantial strength of the current study, the available units cannot be considered representative of DC quality in the overall 130 Italian NICUs. Furthermore, despite study power was adequate and no differences emerged between participating and non-participating units/children/mothers, the detected high attrition rates may affect the findings generalizability.[56] Thus, caution is needed in translating results to the whole preterm population and future research is warranted to replicate findings. Second, not all the aspects of DC were examined, and those that were not captured by two indexes (e.g., disruption of sleep) may have an impact on child outcomes. Third, the use of care-provider

self-report to assess DC practices could attenuate the associations between the QCQ responses, actual clinical practice, and language outcomes. However, it is also important to take in consideration that: 1. the care level at each NICU was established based on a statistical procedure (i.e., a median split), so the informant completing the QCQ and professionals responding at follow-up were unaware of the care level assigned to units; 2. the QCQ data were collected separately from the language assessment, which was completed by professionals blind to all other information gathered via the QCQ. Overall, this methodological approach had the advantage of: 1. limiting bias in the NICUs sampling in term of high- and low-quality DC; 2. reducing the risk of bias due to possible relationships between language assessment at 36 months of age and any clinical procedures in the participating NICUs.

In spite of these limitations, to our knowledge, this is the first study showing that DC procedures in the NICU are positively associated with language outcomes beyond infancy. A recent systematic review and meta-analysis has shown the effect of early DC programs on cognition lasting up to 36 months,[11] consistent with the current study indicating that protective effects of DC practices related to language skills persist in VPT preterm children up to three years. Importantly, evidence that VPT children from NICUs with higher ICC obtained word and sentence comprehension scores similar to those reported for full-term children has implications for DC practices in NICUs. Specifically, it seems critical to encourage DC practices promoting parents' closeness (i.e., free visiting, kangaroo care) and nursing procedures aimed to increase stability and containment of infants, which might mitigate later linguistic difficulties in VPT children. On the other hand, our results suggest that DC interventions routinely used in NICUs (as opposed to *ad hoc* programs) likely make differential contributions in preventing the development of later problematic child outcomes. Thus, it is important to highlight that likely not all of these practices have an equivalent impact or efficacy. The evidence from the current study suggests that a generic assumption that some DC procedures embedded in clinical practice are intrinsically helpful for child development would be, at the best, limited. More research is needed in this area to guide our understanding of which specific kinds of DC routinely carried out in NICUs might effectively prevent negative outcomes in VPT children, including promoting language skills.

Language ability is developed through an interplay of perceptual, sensorial and communicative experiences in the physical and social environment.[57,58] These early experiences in the case of preterm infants are largely disrupted during the NICU stay. Previous longitudinal studies showed that even without documented brain damage, there is an association between preterm birth and language impairments in VPT children,[59] and the current findings extends this existing evidence, adding that an array of DC practices may play a protective role with respect to delay and later difficulties in language development, specifically in receptive/comprehension skills. Further research is warranted to examine the protective role of these and other DC factors in relation to later language outcomes in VPT children.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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