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## **Developmental care and very preterm infants : neonatal, neurological, growth and developmental outcomes**

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## CHAPTER 3

# Effects of Basic Developmental Care on Neonatal Morbidity, Neuromotor Development and Growth at Term Age of Infants Who Were Born at < 32 Weeks

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## Abstract

**Objective:** The goal of this study was to investigate the effect of basic elements of developmental care (DC, incubator covers and positioning aids) on days of respiratory support and intensive care, growth and neuromotor development at term age in infants born < 32 weeks gestation.

**Methods:** Infants were randomly assigned within 48 hours of birth to the developmental care group or the standard care control group (no covers or nests). The intervention continued until the infant either was transferred to a regional hospital or was discharged from the hospital. Respiratory support was defined as days of mechanical ventilation and/or CPAP. Intensive care was defined as requiring mechanical ventilation and/or CPAP and/or weight <1000 grams. Length, weight and head circumference were measured (bi)weekly and at term age. Neuromotor development was defined as definitely abnormal (presence of a neonatal neurological syndrome, such as apathy or hyperexcitability, hypotonia or hypertonia, hyporeflexia or hyperreflexia, hypokinesia or hyperkinesia, or a hemi-syndrome), mildly abnormal (presence of only part of such a syndrome), or normal.

**Results:** A total of 192 infants were included (developmental care: 98; control: 94). Thirteen infants (developmental care: 7; control: 6) were excluded according to protocol (admitted for less than or died within the first 5 days:  $n=12$ ; taken out at parents' request:  $n=1$ ), which left a total of 179 infants who met inclusion criteria. In-hospital mortality was 12 (13.2%) of 91 in the developmental care group and 8 (9.1%) of 88 in the control group. There was no significant difference in the number of days of respiratory support, number of intensive care days, short-term growth, or neuromotor developmental outcome at term age between the developmental care and control groups. Duration of the intervention, whether only during the intensive care period or until hospital discharge, had no significant effect on outcome.

**Conclusions:** Providing basic developmental care in the NICU had no effect on short-term physical and neurological outcomes in infants who were born < 32 weeks gestation.

## Introduction

Advanced technology in the treatment of premature infants has resulted in decreasing mortality rates<sup>1,2,3</sup>. Follow-up studies, however, have shown either an unchanging or increased incidence of physical disabilities, developmental delays and learning or behavioral and/or attention deficit/hyperactivity disorders<sup>1,2,4,5</sup>. Because premature infants cannot regulate incoming stimuli, they become easily overstimulated and stressed, which can lead to hypoxemia, apnea and variations in blood pressure. Als et al propose a sensory mismatch of the premature infant's developing nervous system's expectations for environmental inputs and the actual sensory overload that is experienced in the NICU. This in turn can lead to a greater chance for later developmental problems<sup>6-8</sup>. To prevent these secondary consequences, several investigators have begun to focus on ways to improve the NICU environment for infants and parents through the use of developmental care (DC) programs.

Most research has been based on the NIDCAP (Newborn Individualized Developmental Care Program), which is a comprehensive approach in which caregiving is based on the individual behavior of the infant<sup>8</sup>. A meta-analysis by Jacobs et al concluded that the evidence showing a positive effect from the NIDCAP program is inconclusive, and they recommended additional studies with a larger sample size, long-term follow-up and the inclusion of cost-effectiveness evaluations<sup>9</sup>. A Cochrane review evaluated the effects of various elements of DC (positioning, clustering of nursery care activities and modification of external stimuli) as well as the NIDCAP individualized developmental care approach. Although there was evidence of limited benefits of developmental care interventions and no major harmful effects reported, there were a large number of outcomes with no or conflicting results. The single developmental care trials that did show a significant effect of an intervention on a major clinical outcome were based on small sample sizes, and the findings were often not supported in other small trials<sup>10</sup>. More randomized trials were recommended in which the effectiveness of developmental care programs can be evaluated. No studies have been carried out to examine a less intensive, more basic developmental care program.

The aim of this randomized controlled trial (RCT) was to explore the effectiveness of the implementation of elements of basic developmental care to reduce stress and improve physiological stability in preterm infants on neonatal morbidity, neuromotor development and growth at term age.

## Methods

The study was carried out from April 2000 to May 2002 at a tertiary NICU at 2 locations in the Netherlands: Leiden University Medical Center in Leiden and Juliana Children's Hospital in The Hague. The inclusion criteria was birth at a gestational age of < 32 (31+6) weeks. Exclusion criteria were major congenital anomalies, need for major surgery and having a drug-addicted mother. After parental informed consent was obtained by the resident or staff member on call, infants were randomly assigned within 48 hours of birth to the DC group or the control group using sealed envelopes made in groups of 6 using a computer-generated randomization allocation. According to protocol, infants in both groups who were admitted for less than 5 days were excluded from follow-up, because the duration of the basic DC intervention was hypothesized not to be long enough to obtain an effect. A power analysis performed before the study showed that a total sample size of 140 infants was needed to show a significant difference ( $p < .05$ ) with a power of 80%; based on a difference of half a standard deviation on the developmental test scores at 1 and 2 years of age, corrected for prematurity, and was deemed sufficient power for the short-term primary neonatal outcomes.

The intervention included the reduction of light and sound through the use of standardized incubator covers and supporting motor development and physiological stability by positioning the infant in ways that encourage flexion and containment through the use of standardized nests and positioning aids. Infants in the control group received standard care, which at that time consisted of no covers or nesting. The Ethical Committees of both locations approved the study.

## Definitions

Severity of illness was analyzed using the CRIB (Clinical Risk Index for Babies) score which assesses initial neonatal risk. Scores are given for birth weight, gestational age, maximum and minimum fraction of inspired oxygen and maximum base excess during the first 12 hours, and the presence of congenital malformation<sup>11</sup>. Inborn infants were infants who were born in the participating tertiary neonatal center.

The primary medical outcome variables included duration of respiratory support, number of days in intensive care and short-term growth. Mechanical ventilation and/or continuous positive airway pressure (CPAP) were measured in days. When an infant received both mechanical ventilation and CPAP in 1 day, the method of respiratory support given for the most hours was chosen. In addition, the total number of days of respiratory support was defined as total combined days of mechanical ventilation and CPAP. Discharge from the intensive care was based on

2 criteria: the infant required no mechanical ventilation and/or CPAP for 24 hours and weighed at least 1000 grams.

Infants were weighed at least biweekly; head circumference and length were measured within the first 2 days of life and thereafter weekly by trained medical students until the infant was either transferred or discharged. Short-term growth (weight, head circumference, length) was defined as measurement at birth and at term age as well as mean daily weight gain in grams and mean weekly length and head circumference growth in centimeters. Weight was measured on neonatal pediatric digital scales, length was measured from crown to heel and head circumference was measured around the largest area of the head, occipital-frontal circumference (OFC), using a non-stretch tape measure.

In addition, secondary outcomes were analyzed. Mortality was defined as early neonatal death when the infant died within the first 7 days of life and late neonatal death when the infant died after 7 days but before 28 days of life. Days of oxygen were calculated as total days of supplementary oxygen as well as the need for oxygen after 28 days of life.

Bronchopulmonary dysplasia (BPD) was defined as oxygen dependency at 36 weeks postconceptional age (PCA) according to the criteria of Shennan<sup>12</sup>. Postnatal steroids were divided into 3 classifications; 7 to 10, 15 to 20, and > 20 days. Intra-ventricular hemorrhage (IVH) was recorded according to Volpe<sup>13</sup>. Periventricular leukomalacia (PVL) was classified according to grades 1-4<sup>14</sup>. Sepsis was based on a positive blood culture (congenital infections excluded). Meningitis was defined as a positive cerebrospinal fluid (CSF) culture and/or pleocytosis. In addition, the incidence of necrotizing enterocolitis (NEC), persistent ductus arteriosus (PDA), retinopathy of prematurity (ROP), need for treatment of hypotension and hyperbilirubinemia was analyzed.

### **Follow-up**

At term age, infants were seen in the follow-up clinics to assess growth, morbidity and neuromotor development by neonatologists who were experienced in developmental assessments and blinded to the group assignment of the infant. A standardized neurological examination according to Prechtl<sup>15</sup> was administered and was defined as definitely abnormal (DA), mildly abnormal (MA) or normal. Definitely abnormal means the presence of a full-blown neonatal neurological syndrome, such as apathy or hyperexcitability, hypotonia or hypertonia, hyporeflexia or hyperreflexia, hypokinesia or hyperkinesia, or a hemi-syndrome. Mildly abnormal denotes the presence of only part of such a syndrome. Examples of minor neurological signs are abnormal posture, abnormal head control and absent or abnormal responses or reflexes.

### Statistical Analysis

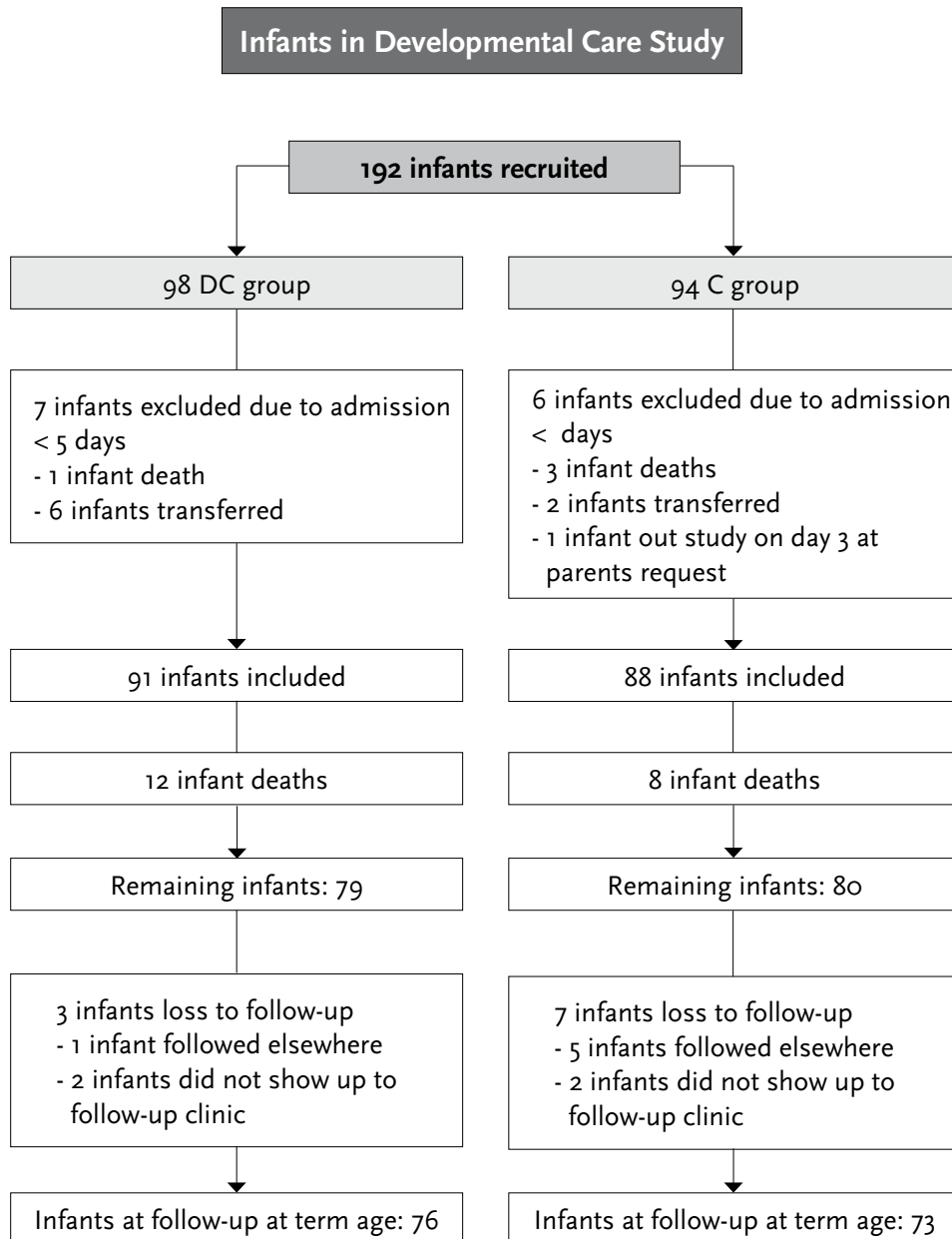
Data was analyzed using SPSS 12.0 for Windows (SPSS Inc, Chicago, IL). The infant and parent characteristics were compared with the Chi-square test, the Chi-square test for trend or the two-sample t-test, where appropriate. Outcome parameters were compared between the two treatment groups with the t-test, Mann-Whitney test or Chi-square test where appropriate. A  $p$ -value of  $< 0.05$  was considered significant. Linear regression was used to evaluate the influence of the duration of the intervention on term age outcomes by testing whether there was an interaction effect between the intervention duration and the 2 treatment groups.

### Results

In total, 192 infants were originally included for the study: 98 in the DC group and 94 in the control group. Thirteen infants (DC: 7; control: 6) were excluded according to protocol because they were admitted less than 5 days or died within the first 5 days. One of the 6 infants in the control group was taken out of the study on day 3 at the parents' request. This left a total of 179 infants who met inclusion criteria. Of the 179 included infants, 12 (13.2%) of 91 in the DC group and 8 (9.1%) of 88 in the control group died during hospitalization, with the main cause of death being cerebral or pulmonary complications. The difference between the 2 groups was not significant ( $p=0.40$ ). Two infants in each group died of NEC. One infant was lost to follow-up in the DC group and 5 infants in the control group because either they were transferred to hospitals out of the health region or parents did not want to come back for follow-up. Two infants from the DC group and 2 from the control group did not show up for the term age follow-up assessment, resulting in 76 infants in the DC group and 73 infants in the control group who were assessed at the outpatient clinic. All infants who were lost to follow-up survived. The mortality rate and loss to follow-up are shown in Figure 1. The data from the infants who were lost to follow-up were comparable to the infants who were assessed at follow-up (data not shown).

Parent characteristics for the study population were similar, with no significant differences found, and are shown in Table 1. There was no difference in infant characteristics between the DC and the control group, with the exception of more infants in the control group with grade 4 RDS, however the difference was not significant (Table 2).

Some of the infants were transferred to regional hospitals once stabilized. Seven infants (DC: 5; control: 2) were hospitalized temporarily elsewhere for surgical or other necessary treatment. These infants were included in the outcome under the intention-to-treat protocol.





**Table 1.** Maternal medical and parental demographic background variables

	<b>DC n=91</b>	<b>Control n=88</b>
<b>Obstetrical history</b>		
Pre-existing disease (diabetes, renal, hypertension, other)	8/82 (9.8)	11/82 (13.4)
Pregnancy induction	13/86 (15.1)	12/84 (14.3)
Diseases during pregnancy		
Diabetes mellitus gravidarum	4/87 (4.6)	5/84 (6.0)
(Pre)eclampsia or HELLP syndrome	19/87 (21.8)	13/84 (15.5)
Medication during pregnancy		
Antihypertensives	12/91 (13.2)	14/84 (16.7)
Antibiotics	35/91 (38.5)	34/84 (40.5)
Tocolytics	46/91 (50.5)	48/84 (57.1)
Other	8/91 (8.8)	7/84 (8.3)
Antenatal glucocorticoids		
1 dose	17/90 (18.9)	28/88 (31.8)
1 course (2 doses)	47/90 (52.2)	41/88 (46.6)
Mode of delivery		
Vaginal	51/91 (56.0)	47/88 (53.4)
Caesarean section	40/91 (44.0)	41/88 (46.6)
PROM > 24 hours	16/91 (17.6)	22/88 (25.0)
Primipara	76/91 (83.5)	73/86 (84.9)
<b>Parental demographic background</b>		
Maternal age		
(mean in years, sd)	n=89 30.1 (5.6)	n=85 30.4 (5.1)
Paternal age		
(mean in years, sd)	n=70 34.3 (5.3)	n=69 35.0 (5.7)
Mother Caucasian	59/90 (65.6)	62/87 (71.3)
Father Caucasian	63/90 (70.0)	65/87 (74.7)
Mother's education level*		
Low	36/78 (46.2)	24/73 (32.9)
Intermediate	26/78 (33.3)	33/73 (45.2)
High	16/78 (20.5)	16/73 (21.9)
Father's education level*		
Low	30/78 (38.5)	21/73 (28.8)
Intermediate	30/78 (38.5)	29/73 (39.7)
High	18/78 (23.0)	23/73 (31.5)

Data shown is n (%), unless otherwise indicated

HELLP indicates hemolysis, elevated liver enzymes, and low platelet count; PROM: premature rupture of membrane

\* Low indicates vocational training, intermediate = high school, high = college/university

**Table 2.** Infant medical background variables

<b>Birth Characteristics</b>	<b>DC n=91</b>	<b>Control n=88</b>
Gestational age, wk	n=91	n=88
Mean (SD)	29.3 (1.8)	28.9 (1.9)
Range	25.0-31.9	25.0-31.9
Birthweight,g	n=91	n=88
Mean (SD)	1216 (358)	1196 (354)
Range	538-2155	640-2080
Length,cm	n=79	n=79
Mean (SD)	37 (4.0)	37 (3.8)
Range	25.0-46.0	28.5-45.0
Head circumference	n=86	n=86
Mean in cm, sd	26.7 (2.4)	26.5 (2.3)
Range	22.0-33.6	22.0-31.6
Male gender	49/91 (54.0)	58/88 (65.9)
SGA p < 10 and p ≥ 3	8/91 (8.8)	8/88 (9.1)
SGA p < 3	8/91 (8.8)	6/88 (6.8)
Twin	26/91 (28.6)	18/88 (20.5)
Inborn	56/91 (61.5)	53/87 (60.9)
Apgar scores at 5 minutes		
Mean (SD)	8.1 (1.8)	8.1 (1.4)
Median (range)	9 (2-10)	8 (3-10)
CRIB Score	n = 91	n = 87
Median (range)	2 (0-20)	3 (0-12)
RDS		
Grade 1	15/91 (16.5)	15/87 (17.2)
Grade 2	16/91 (17.6)	17/87 (19.5)
Grade 3	19/91 (20.9)	14/87 (16.1)
Grade 4	9/91 (9.9)	17/87 (19.5)
Surfactant	41/91 (45.1)	50/88 (57.5)
Hyperbilirubinemia	82/91 (90.1)	81/88 (92.0)

Data shown is n (%), unless otherwise indicated

SGA indicates small for gestational age; p: percentile; CRIB: Clinical Risk Index for Babies; RDS: respiratory distress syndrome

**Primary outcomes**

No significant difference was found in the number of intensive care days, days of respiratory support or growth between the DC and control groups (Table 3). Eighty-six (94.5%) infants in the DC group and 79 (89.8%) infants in the control group required some form of respiratory support. A total of 149 infants (DC: 76; control: 73) of the surviving 159 (93.7%) infants were seen at the follow-up clinic at term age. One infant was too ill to undergo a Prechtl examination. No significant difference was found in the neurological outcomes between the DC and control groups. Of the 149 infants, 4 in the DC group and 3 in the control group were not measured or weighed at term age. Four surviving infants (DC: 3; control: 1) who had a diagnosis of post-hemorrhagic ventricular dilatation were excluded from the weekly and term age head circumference analysis. No significant difference was found between the DC and control groups in the growth parameters at term age or in daily weight gain (g), and weekly length and head circumference (cm) growth.

We also conducted a linear regression analysis to determine whether the number of days when infants received the DC intervention influenced the neuromotor outcome according to Prechtl and growth at term age by testing whether there was an interaction effect between the intervention duration and the 2 treatment groups. No significant effect on the neuromotor outcome ( $p=0.45$ ), term age head circumference ( $p=0.56$ ): term age weight ( $p=0.61$ ) or term age length ( $p=0.92$ ) was found.

**Secondary outcomes**

A total of 15 (19.2%) of 78 infants in the DC group required oxygen after 28 days of life as opposed to 22 (29.3%) of 75 infants in the control group; however, the difference was not significant ( $p=0.15$ ). No difference was found in the incidence of BPD between the 2 groups. In total 4 (4.4%) of 91 infants in the DC group required postnatal corticosteroids as opposed to 10 (11.4%) of 88 infants in the control group ( $p=0.08$ ). A total of 19 (20.9%) of 91 infants in the DC group had grade 1 or 2 IVH as opposed to 28 (31.8%) of 88 in the control group, and twice as many infants (11 of 91 [12.1%]) in the DC group had grade 3 IVH or grade 3 IVH and periventricular echodensity than in the control group (5 of 88 [5.7%];  $p=0.12$ ). At term age, there was no difference in the incidence of PVL or the number of infants who required physical therapy. Also, no significant differences were found in the remaining secondary outcomes (Table 4).

**Table 3.** Comparison of data of primary outcome measures

	<b>DC n=91</b>	<b>Control n=88</b>	<b>p-value</b>
Days of hospitalization			
Mean (SD)	37.2 (29.1)	36.4 (28.1)	0.86
Median (range)	31 (6-142)	30 (5-165)	
Days intensive care			
Mean (SD)	15.9 (13.7)	16.7 (15.3)	0.74
Median (range)	12 (0-53)	11 (0-60)	
No. of infants requiring respiratory support	86/91 (94.5)	79/88 (89.8)	0.28
Days of mechanical ventilation			
Mean (SD)	6.1 (7.3)	6.9 (7.1)	0.45
Median (range)	3.5 (0-39)	4.0 (0-29)	
Days of CPAP			
Mean (SD)	8.6 (9.6)	10.1 (10.5)	0.34
Median (range)	4.5 (0-35)	6.0 (0-39)	
Total days ventilatory support			
Mean (SD)	14.6 (13.6)	17.0 (15.1)	0.30
Median (range)	10.0 (1-52)	12.0 (1-59)	
Growth parameters at term age	n = 72	n = 70	
Age, mean (SD), wk	40.8 (1.2)	40.7 (1.5)	0.72
Weight, mean (SD), kg	3.12 (0.64)	3.15 (0.50)	0.76
Head circumference*, mean (SD), cm	35.6 (1.8)	35.5 (1.6)	0.81
Length, mean (SD), cm	48.6 (3.3)	48.6 (2.3)	0.95
Daily weight gain, mean(SD), g	23.7 (4.9)	23.6 (4.8)	0.95
Weekly head circumference growth*, mean (SD), cm	0.78 (0.13)	0.75 (0.14)	0.38
Weekly growth in length, mean (SD), cm	1.00 (0.23)	0.97 (0.20)	0.34
Neurological outcome at term (Prechtl)			
Normal	42/76 (55.3)	43/72 (59.7)	0.46
Mildly abnormal	30/76 (39.5)	27/72 (37.5)	
Definitely abnormal	4/76 (5.2)	2/72 (2.8)	

Data shown is n (%), unless otherwise indicated

Comparisons were performed by using chi-square test (for linear trend), t-test or Mann-Whitney test where appropriate

\* Infants with posthemorrhagic ventricular dilatation (DC: n=3, control: n=1) were excluded from head circumference analysis

**Table 4.** Comparison of data of secondary outcome measures

	<b>DC n=91</b>	<b>Control n=88</b>	<b>p-value</b>
In-hospital mortality	12/91 (13.2)	8/88 (9.1)	0.40
Early neonatal death	3/91 (3.3)	2/88 (2.3)	
Late neonatal death	9/91 (9.9)	6/88 (6.8)	
Total days supplemental oxygen			
Mean (SD)	12.0 (17.7)	14.9 (20.5)	0.31
Median (range)	5 (0-93)	4.5 (0-90)	
Oxygen requirement > 28 days of life	15/78* (19.2)	22/75* (29.3)	0.15
BPD (oxygen dependent > 36 wk GA)	6/78 (7.7)	10/75 (13.3)	0.30
Postnatal corticosteroids			
7-10 days	2/91 (2.2)	1/88 (1.1)	0.08
15-20 days	1/91 (1.1)	8/88 (9.1)	
> 20 days	1/91 (1.1)	1/88 (1.1)	
IVH			
Grade 1-2	19/91 (20.9)	28/88 (31.8)	0.12
Grade 3 and periventricular echodensity	11/91 (12.1)	5/88 (5.7)	
Posthemorrhagic ventricular dilation	4/91 (4.4)	2/88 (2.3)	0.68
NEC	6/91 (6.6)	4/87 (4.6)	0.75
Sepsis	40/91 (44.0)	32/87 (36.8)	0.36
Meningitis	5/91 (5.5)	5/88 (5.7)	0.99
PDA (indomethacin and/or surgery)	19/91 (20.9)	23/88 (26.1)	0.48
Dopamine/Dobutamine	32/91 (35.2)	25/87 (28.7)	0.42
ROP	3/70 (4.3)	5/70 (7.1)	0.19
PVL at term age follow-up			
Grade 1	3/71 (4.2)	6/67 (9.0)	0.53
Grade 2	3/71 (4.2)	3/67 (4.5)	
Grade 3	0/71 (0.0)	0/67 (0.0)	
Grade 4	0/71 (0.0)	0/67 (0.0)	
Physical therapy required at term	14/76 (18.4)	9/74 (12.2)	0.49

Data shown is n (%), unless otherwise indicated

Comparisons were performed by using the chi-square test (for linear trend) or t-test where appropriate

\* n is lower as a result of in-hospital deaths and loss to follow-up infants

BPD indicates bronchopulmonary dysplasia; GA: gestational age; IVH: intraventricular haemorrhage; NEC: necrotising enterocolitis; PDA: patent ductus arteriosus; ROP: retinopathy of prematurity; PVL: periventricular leukomalacia

## Discussion

In this RCT to examine the short-term effects of basic DC (incubator covers, nests and positioning aids) on neonatal morbidity, neuromotor development and growth at term age of infants who were born at < 32 weeks gestation, we found no significant positive effects of the intervention on intensive care days or need for respiratory support. Although the control infants had more pulmonary problems than the infants in the DC group, the difference was not significant. There were also no differences between the DC and control groups in growth and neurological outcomes at term age, even when correcting for days of intervention. This study is to our knowledge the largest RCT to examine the effects of basic developmental care on preterm infants. Of the surviving 159 infants, 93.7% were seen at follow-up at term age.

The Cochrane Review<sup>10</sup> looked at 4 separate developmental care interventions (positioning, clustering of care, modification of external stimuli and individualized developmental care), but no studies that combined nesting, positioning aids and incubator covers have been published to our knowledge. Because NICU's may start with these basic elements when embarking on the implementation of a developmental care program, we believed that it was important to study the effects of these basic interventions. Most previous RCT's examined the effects of the more intensive, individually-focused NIDCAP program and although a few of them showed positive results<sup>16-21</sup>, we were not able to duplicate this with the less intensive basic developmental care.

One limitation of our study was the variation in total days of hospital admission of studied infants. In the Netherlands' neonatal care system, infants may be transferred to regional hospitals once they no longer require intensive care. This was also the case with a number of infants in our study. This would not affect the short-term outcomes such as days of intensive care or respiratory support, because all infants remained in the participating hospitals during this period, but could have an effect on growth and secondary outcomes at term age. If this were true, then infants who received more days of developmental care would show less morbidity and better short-term growth and neurodevelopmental outcome; however, our analysis showed that this was not the case. It seems that at least concerning short-term outcomes, the duration of providing basic developmental care, whether only during the intensive care period or continuing developmental care until hospital discharge, has no significant effect.

The infants were randomly assigned in an appropriate manner; however, there could be no blinding of the intervention because the infants in the DC group had incubator covers and nesting. This did make it easier to ensure a strict control

group whereby control infants were not provided with any nesting or incubator covers, because this was the standard method of care when this trial began and so was easy to maintain during the study period. The amount of respiratory support given to an infant was decided on by several neonatologists and so was not influenced by the study group in which the infant was placed. Because the discharge from the intensive care was based on two criteria: the infant's requiring no mechanical ventilation and/or CPAP for 24 hours and weight at least 1000 grams, IC days also could not be influenced by group participation. In addition, the neonatologists who performed the term age assessments were blinded to group participation.

## Conclusions

This was a RCT with a large sample size in comparison with previous developmental care studies; however, no significant results were found. Our findings showed that a less intensive, cost-saving form of developmental care (incubator covers, nests and positional aids) does not have a significant effect on short-term medical outcomes (respiratory support, intensive care days), growth or neurodevelopment at term age. Although some of the secondary analyses were suggestive of an advantage to developmental care, they did not reach a level of significance and would therefore need to be replicated in a larger sample to confirm a trend. Additional research of the developmental outcomes at 1 and 2 years of age of the children in this study will be addressed in future publications.

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