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

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CHAPTER 7

# General Discussion

In this thesis we evaluated the effect of basic developmental care and the comprehensive NIDCAP developmental care program in preterm infants < 32 weeks gestational age born between April 2000 and August 2004 on short-term morbidity, growth and neurodevelopment at term age, as well as growth and neurodevelopment at 1 and 2 years corrected age.

## Pilot study

We started with a pilot study in 1999 of a short-term, hospital based intervention with parents of preterm infants < 32 weeks in the NICU with the goal of positively influencing parental knowledge and responsiveness to premature infant signals and behavioral cues. This was a phase-lag study in which the control group parents were first included. They completed a questionnaire concerning confidence in caregiving when their child was 1 week old and again 2 weeks later. Once the inclusion of the control group parents was completed we began to include parents in the intervention group. Starting after the first week of their infant's birth, parents were given 4 lessons over a period of 2 weeks concerning preterm infant behavior with the emphasis on understanding their own infant's behavior. They were asked to complete questionnaires on knowledge of preterm infant behavior and also confidence in caregiving before and at the end of the intervention. The study showed that the instructions significantly increased their knowledge of preterm infant behavior, and while their level of confidence in caregiving improved, the difference was not significant. There was no improvement in confidence in caregiving found in the control group parents. Very few fathers in the intervention group completed the lessons and questionnaires, and even though mothers claimed to share what they had learned with their spouse, this "transferring" of knowledge was not measurable because most fathers did not complete the questionnaires after week 3. Interviews of parents after the intervention indicated that they appreciated having the lessons and being able to better understand their infant's behavior, as well as the support provided by a developmental specialist. Parents in the control group expressed the need for more knowledge of preterm infant behavior.

While this was a small study with only 10 sets of parents and 22 infants, it did indicate that it is feasible to start an intervention program with parents early on in the NICU period. The pilot study also raised the level of interest in developmental care in the neonatal team. We concluded that a longer, more intensive program with a larger sample size and finding ways of incorporating more participation from fathers was necessary.

## Randomized Controlled Trial: Phase 1

In Phase 1, we examined the effect of basic developmental care, which we defined as the use of standardized incubator covers and nests and positioning aids, on short and long-term outcomes up to 2 years of age corrected for prematurity. We hypothesized that by providing protection from the environment with incubator covers and boundaries through the use of nesting, we would decrease the infants' stress and physiological instability, which would result in positive short-term outcomes. There was a wide range of the number of days infants spent in the participating NICU, which reflected days of intervention given. We hypothesized that infants receiving basic developmental care for a longer period would show better results in term age outcomes. However, we found no effect on short-term morbidity, growth or neurological outcomes up to term age, even when we corrected for length of stay.

We were able to report that there were no detrimental effects of basic developmental care, which was a concern of the neonatal staff when we first proposed this trial, as the use of incubator covers and nests for infants was a new concept. At that time, it was felt that perhaps it would be more difficult to observe the infants and that having an infant lie in a softly flexed position might alter the effect of ventilation. In fact, the intervention infants required less days of ventilation and oxygen although this difference was not significant. In addition two secondary outcomes (postnatal steroids and requiring oxygen after 28 days of life) while not reaching the level of significance, suggested that there may be an advantage of developmental care on pulmonary morbidity.

We did find a positive effect on psychomotor development (PDI) at 1 year CA, but this improvement did not continue at 2 years and we found no significant effect on mental development (MDI) at 1 and 2 years CA. We also found more infants in the control group with definitely abnormal neurological outcome, but since it was not statistically significant we could only conclude that developmental care may have a positive influence on neurological outcome at 1 and 2 years.

We could find no other study examining basic developmental care on neurodevelopment, so were unable to compare our results with other studies. Our findings did provide an answer to the question of whether a basic developmental care program, which does not entail major funding to implement, has an effect on development. We concluded that while it did have a positive effect on psychomotor development at 1 year of age, these effects did not continue up to 2 years of age.

## Randomized Controlled Trial: Phase 2

In Phase 2, we examined the effect of the comprehensive NIDCAP program on short and long-term outcomes up to 2 years of age corrected for prematurity. This consisted of formal behavioral observations of the infant, individual care plans based on these observations and support to the parents in understanding and responding to their child's behavior. After inclusion in phase 1 was completed and before starting inclusion of infants into phase 2, we spent 2 months providing extra lessons to a team of nurses that would be primarily caring for the NIDCAP infants. This was done to try to prevent as much contamination of the control group as possible. There were 5 nurses in the group who were completing NIDCAP training and who became certified and were able to assist under guidance from the developmental psychologist in carrying out NIDCAP observations and supporting the care team, infants and parents.

Because we only found a transient significant positive effect of basic developmental care on psychomotor development at 1 year of age, we hypothesized that a more intensive, individualized developmental care program such as the NIDCAP program would show more improvement. This however was not the case and in fact the developmental outcomes and growth at 1 and 2 years CA did not much differ from the outcomes obtained in the first RCT, with the exception of the drop in PDI between 1 and 2 years of age in the phase 2 children.

There were significantly more infants in the NIDCAP group with PDA requiring medication or medication and surgical ligation. This was unexpected as the infants were randomized precisely in the same manner as in phase 1. As PDA usually develops in the first days of life we did not feel that the intervention played a significant role in the incidence of PDA, but realized that it could affect some of our short-term primary outcomes. There was no difference in days of phototherapy between the 2 groups, so that could not have affected the incidence of PDA. When we carried out a Kaplan Meier analysis we did indeed find that PDA had negatively affected the respiratory outcomes of the NIDCAP infants as after the analysis they required significantly less days (expressed in median) of CPAP and total ventilatory support as compared to the control infants.

We found no positive effects at 1 and 2 years of age on mental or psychomotor development or neurological outcomes in the NIDCAP group as compared to the control group. While the difference in developmental scores between the two groups was not significant, both groups' mean PDI scores were lower at 2 years

when compared to the 1 year PDI and the NIDCAP group was more than a half standard deviation lower. It should be noted that even with this drop all the mean PDI and MDI scores of both groups were classified in the normal range of development. The neurological outcomes were comparable at 1 year of age, but at 2 years of age, the NIDCAP group had a higher percentage of children with scores defined as definitely abnormal, however this difference was not significant.

Because of these outcomes, we concluded that NIDCAP had no effect on neurological outcome or development at 1 and 2 years of age. In addition, we found no effect on growth at 1 and 2 years of age.

## Behavior at 1 year of age

In questionnaires completed by parents when children were 1 year of corrected age, children in the basic developmental care group had significantly higher behavior scores on the total competence domain and the competence subscale mastery motivation of the Infant–Toddler Social and Emotional Assessment (ITSEA) questionnaire, meaning that the children showed more curiosity, persistence, obedience and enjoyment with small accomplishments. No significant effects were found on problem behavior or parenting stress. We concluded that introducing a basic form of developmental care in the neonatal intensive care unit has a positive influence on the child's competence behavior at 1 year of age[1].

When parents completed questionnaires concerning their child's behavior and temperament at 1 year corrected age, the children in the NIDCAP group tended to show more social relatedness behavior than the children in the control group, especially when their length of admission was more than 1.5 months, which would reflect how long the NIDCAP intervention was given. In addition parents in the NIDCAP group reported more positive experiences and effects on the well-being of their infant during admission[2]. Further research when the children are school age will show if these effects remain.

## Comparison to previous NIDCAP studies

We were not able to duplicate the findings of previous NIDCAP studies even with our large sample size. When we compared our Phase 2 RCT to other NIDCAP development care studies, our total days of intensive care for both groups was much less, which could be due to a difference in the population and care provided, or simply a difference in their definition of intensive care[3-6]. Days of intensive care were also less when we compared our outcome with a study from another NICU in

the Netherlands, however they did not provide a clear definition or criteria for days of intensive care[7] (Table 1).

Contrary to the inclusion criteria of many NIDCAP studies, we chose the inclusion criteria of infants < 32 weeks gestational age because we know from previous studies that infants < 32 weeks GA are vulnerable and have an increased risk of developmental problems[8,9]. This was different than other NIDCAP studies previously published in which the inclusion age was between < 28 and < 30 weeks and infants required some form of ventilation in the first 48 hours. Westrup's study also included infants < 32 weeks GA but had some restrictions on respiratory support in their inclusion criteria[10]. We did not make any restrictions concerning ventilation because we hypothesized that all infants < 32 weeks GA could benefit from this intervention.

We did not find significant differences in follow-up neurodevelopmental outcomes as reported in other NIDCAP studies[11-13]. In our study we chose 2 points of follow-up at 1 and 2 years corrected age as we wanted to be able to compare our results with previous NIDCAP studies. There have been questions raised, however, concerning the poor predictive value of the Bayley Scales of Infant Development as one large study reported that a subnormal MDI score at 20 months in ELBW infants is not predictive of a subnormal cognitive functioning at school age[14]. This could mean that decisions of whether to continue with an intervention in the NICU based on 1 and 2 year outcomes may not be appropriate, as effects may not be seen until the child is older.

To date only the Swedish studies have published developmental outcomes beyond 2 years, reporting positive effects on behavior and mother-child interaction at 3 years of age from their phase-lag study[12] and results at preschool age from their RCT which showed no difference in cognition and a possible positive effect on behavior in the NIDCAP group. Because the power was low and recruitment was half of what they had expected, caution was suggested when interpreting their results[12,15] (Table 1). It is therefore important that our cohort is followed to at least school age to see if there are any effects only evident as the children mature.

**Meta-analysis**

A Cochrane meta-analysis of NIDCAP trials found 3 studies with significantly fewer days of ventilation[4,10,16], 3 studies with no differences in days of oxygen[3,4,13] and one study with fewer days CPAP and a lower age for oxygen withdrawal[10], but concluded that results on respiratory support should be viewed with caution due to significant heterogeneity among the sites[17]. It should be noted that they did not

**Table 1.** NIDCAP studies published from 2000

| Author and year | Design | Participant's | N | Intervention | Main outcomes |
|---|---|---|---|---|---|
| Westrup 2000 | RCT | GA < 32 weeks<br>Requiring ventilatory assistance at 24 hours of life | E=12<br>C=13 | Caregiving by NIDCAP trained personnel and weekly observations until 36 weeks post-conception | Days CPAP<br>PCA at O2 withdrawal<br>BPD |
| Kleberg 2000 | Phase lag | Birthweight ≤ 1500 g<br>GA < 30 weeks<br>Ventilated within first 3 hours and > 24 hours of first 48 hours | E=21<br>C=21 | Caregiving by NIDCAP trained personnel starting within 3 days after birth and continuing until discharge. Control group was born prior to NIDCAP implementation. | No difference in DQ at 3 years<br>Subscale hearing-speech<br>Behavior scale<br>Communication in "mother- infant" scale (ns) |
| Kleberg 2002 | RCT | GA < 32 weeks<br>Requiring ventilatory assistance by 24 hours of life | E=11<br>C=9 | Follow-up of surviving participants of RCT by Westrup, 2000 | MDI at 12 months |
| Als 2003 | RCT | Birthweight < 1250 g<br>GA < 28 weeks<br>Ventilated within first 3 hours and > 24 hours of first 48 hours | E=45<br>C=47 | 3-center trial<br>Caregiving by NIDCAP trained personnel until discharge | Ventilation days, days ICU and LOS<br>Weight at 2 wk PCA<br>Days parenteral feeding<br>PCA at discharge, hospital costs<br>Weight at 42 wk PCA, HC at 42 wks PCA |
| Als 2004 | RCT | GA 28+ 4 – 33+3 weeks<br>< 72 hours ventilation including CPAP | E=16<br>C=14 | Caregiving by NIDCAP trained personnel until discharge | 2 APIB system scores at term age<br>6 Prechtl summary scores and total Prechtl score at term age<br>MDI and PDI at 9 months<br>BRS scores at 9 months |
| Westrup 2004 | RCT | GA < 32 weeks<br>Requiring ventilatory assistance by 24 hours of life | E=11<br>C=15 | Follow-up at 69.9 months of surviving participants of RCT including 4 C infants who originally declined to participate in study by Westrup, 2000 | OR for surviving with normal behavior after correcting for group differences |

All outcomes are significant in favor of the intervention group unless otherwise indicated.
E = experimental group, C =control group, GA= gestational age, PCA=postconceptional age, BPD=bronchopulmonary dysplasia, ICU-Intensive Care Unit, HC= head circumference, DQ= developmental quotient according to Griffiths' Developmental Scale II, MDI= Mental Development Index, PDI =Psychomotor Development Index, BRS= Behavioral Rating Score, LOS= length of stay of total hospitalization, OR = odds ratio

include the 3-center trial by Als[6] in this meta-analysis because they felt that there was too much heterogeneity between the 3 sites. They also reported that NIDCAP had a significant effect on moderate-severe chronic lung disease and incidence of necrotizing enterocolitis, no effect on length of hospitalization and no effect on feeding and growth in infants surviving to 9 months. The effects on neurodevelopment were conflicting with a significant difference in Bayley MDI at 12 months in a meta-analysis of 2 trials[11,18], but no difference in PDI. They found some positive evidence of the long-term effect of NIDCAP at 5 years on behavior and movement but no effect on cognition. The authors' final conclusion was that while there was limited benefit of developmental care and no major harmful effects, that the outcomes were conflicting and further studies were recommended[17].

## Comparison of Phase 1 and 2

We then looked at the outcomes from both phases 1 and 2 of our study. Even though they were 2 separate RCT's, the level of developmental care given was progressive in each phase, as we started in phase 1 with a control group with no DC and then in phase 2 a control group of basic DC (nests and incubator covers), which was comparable to the DC intervention group in phase 1. We hypothesized that if the infant characteristics in both phases were comparable, then there would be an increasing improvement in outcomes with a more pronounced improvement seen between the control group of phase 1 who received no elements of developmental care and the intervention group of phase 2 who received the complete NIDCAP intervention. Comparing these 2 groups would be the equivalent of a phase-lag design.

However we decided not to perform such an comparison based on the following methodological reasons. The first reason was that these were 2 separate RCT's carried out over a period of 4 years in which clinical changes occurred between the implementation of the 2 phases. That could mean that the C group in phase 1 possibly had different medical care approaches than the NIDCAP intervention group in phase 2. The second reason was that although various infant characteristics such as birthweight, gestational age, Apgar scores at 5 minutes, CRIB scores and inborn at birth were comparable between the C group in phase 1 and the NIDCAP group in phase 2, there were some differences in infant characteristics between these 2 groups. There were more twins and SGA infants born in the NIDCAP group phase 2, and both characteristics can have a negative influence on developmental outcome. On the other hand, there were more males born and a higher percentage of RDS in the C group of phase 1 than in the NIDCAP group in phase 2 which could lead to poorer outcomes in the C group and an advantage for the outcomes

in the NIDCAP intervention group. We decided not to correct for these differences between the groups with statistical methods and to hold on to the original design of the study as 2 separate RCT's.

## Strengths and limitations of the study

This was a large randomized controlled trial with a low percentage of lost to follow-up. In the phase 1 RCT there could be no blinding of the intervention as the developmental care infants had incubator covers and nesting, however it did make it possible to ensure a strict control group. The amount of respiratory support given to an infant was decided upon by several neonatologists so was not influenced by the study group the infant participated in. Discharge from the intensive care was based on two criteria: the infant required no mechanical ventilation and/or CPAP for 24 hours and weighed at least 1000 grams, so days of IC could also not be influenced by group participation. The assessors for both the neurological and developmental outcomes were blinded to the treatment group in which the children participated. The neurological outcomes were obtained using a standardized neurological examination and the Bayley Developmental Index scores were scored using the Dutch norms[19].

**Length of the Intervention**

The trial was carried out in a tertiary NICU in two locations. Both locations were able to provide intensive care as well as intermediate care, however the length of stay in one location was longer as most infants were not transferred to regional hospitals but discharged from the NICU nursery to home and only a small percentage of the infants in the other location stayed until discharge to home. This meant that there was a wide range in length of stay in the participating NICU's, which mainly reflected the period of hospitalization in the intermediate care unit. We had hypothesized that an increase in days that infants spent in the two participating locations and thereby more days of developmental care would positively affect growth and neuromotor outcomes. This however was not the case as was shown via an interaction analysis of the intervention duration and the term age outcomes.

It may be that there were not enough infants who received developmental care until discharge to home to show an effect, however we also did not find site differences in the IC days or days of ventilatory support, which would not be influenced by total length of stay. These results were disappointing and we can only conclude

that in a subsequent trial the intervention should continue when the infants are transferred to regional hospitals. This was beyond the scope of this study as our main goal was to look at the effect of developmental care in the Dutch neonatal system with centralization of perinatal care.

It could also be that an early intervention program provided only in the period of hospitalization of the preterm infant is not enough. Perhaps a subsequent study should be carried out in which the NIDCAP program is implemented along with another program such as the Infant Behavioral and Assessment Intervention Program (IBAIP)[20]. This is an early intervention program based on the NIDCAP approach which provides support to parents and their infant up to 6 months corrected age. This would be the logical continuation of an approach that would help parents in the difficult first months at home with their still fragile infant. It would also help to build on the support and knowledge parents received in the NICU and guide them in responding to their infant's quickly changing developmental needs.

**Central Nervous System**

We found no significant differences in IVH or PVL between the intervention and control groups in both RCT's. It is of course possible that some infants had already experienced an IVH prenatally or before entering the study as inclusion was allowed up to 48 hours after birth. It was not feasible to include all infants on day one as parents needed time to decide whether to participate in the study. It is possible that by decreasing the stress and physiological instability the infant experienced through providing developmental care may have helped to prevent more cerebral damage, but this was not something we were able to measure. A study by Wielenga showed a possible decrease in severe cerebral damage in favor of the NIDCAP group but stated that the results should be interpreted with caution as it was a phase-lag study and there were some differences between the 2 groups[21]. Als et al have published outcomes on MRI studies showing positive effects of NIDCAP on the developing brain, however it was a relatively small number of infants and not all infants underwent an MRI at term age[13]. It was unfortunately not feasible at the time of our study to perform MRI's at term age, however it is something that perhaps could be studied in future trials.

## Practical considerations

At the onset of our study, little was known about developmental care and implementation had not yet begun to occur in our NICU's. This made it easier to have a pure control group in Phase 1 with no covers or nesting as that was the standard care at that time. As the use of these materials was very visible, it made it easy to prevent contamination of the control group. In Phase 2 both groups appeared much the same, as both were given basic developmental care which consisted of incubator covers and nesting, however the NIDCAP group infants were formally observed every 7-10 days and were given individualized developmental care plans based on these observations. It is possible to conceive that there was more of a chance for contamination as the parents and nurses of the control group infants would be able to see some of the interventions being carried out and apply them to the infants in the control group. We did feel that since it is an individual approach, the argument could be made that what works for one infant may not apply for another, however general methods of support during caregiving could conceivably be copied.

Both intervention and control infants were cared for in the same NICU nursery, which can create a greater chance for contamination. However Westrup's study had to be ended before inclusion was completed precisely because the infants were cared for in different rooms and it became harder to motivate parents and nurses to continue including infants in the control group as the difference in care was so obvious[10]. At the time we did not have the capacity to use two separate rooms and it ended up being to our advantage as we were able to include the number of infants required by the power analysis. Having all the participating infants in the same nursery appeared to actually make it easier for the parents as there was a wide variety of infants in the room, including older infants who did not participate in the study.

One way we tried to diminish the effect of contamination was to give extra training to the group of nurses who primarily cared for the infants in the NIDCAP group. This also permitted more continuation of the care and allowed the nurses to become more familiar with the infants' and parents' needs. There were only 5 nurses that underwent the formal NIDCAP training, the rest of the caregiving team were given extra instructions in caregiving based on the NIDCAP approach. As recommendations have been made to train at least 10% of the staff in order to generate a change it is possible that more formally trained nurses are necessary to have an effect.

## Methods of studying developmental care

Perhaps a randomized controlled trial is not necessarily the best method to measure the effects of a complicated psychological intervention such as the NIDCAP program. It is much more difficult to measure than a study of the effect of a new medication. In these studies, often double blind, the infant either receives the medication or not with less chance of contamination and outcomes are quantifiable and therefore easier to measure. There have been recommendations made for future research of developmental care such as randomization by site instead of patients, evaluating neurobiological mechanisms or using other approaches to developmental care research such as qualitative research and continuous quality benchmarking as an alternative to RCT's[22]. It has been proposed that these approaches may be a more effective way of examining the effects developmental care has on infants in the NICU nursery[23]. However each approach has some methodological restrictions. For example, a trial in which sites are randomized instead of patients would be difficult to implement as there would be too many differences in medical and nursing practices at each site. It may be that a combination of outcomes based on various research methods will be needed to produce a body of evidence of the effects of developmental care.

## Developmental care research in the Netherlands

Since we began our study there have been 2 other neonatal centers in the Netherlands carrying out research on NIDCAP developmental care. A phase-lag study of 51 infants < 30 weeks was carried out in the AMC/Emma Children's Hospital in Amsterdam in which first a group of 26 infants received conventional care, followed by a group of infants who received NIDCAP care. They found a decreased risk for more severe cerebral damage in the NIDCAP group after correcting for neonatal differences in the groups (birthweight, head circumference, incidence of twins, incidence of pneumonia) but did comment that these findings should be interpreted with caution[21]. In addition, parents of the NIDCAP group infants reported significantly more satisfaction in caregiving than the parents of the conventional care infants[24]. The neonatal department of the Erasmus-MC Sophia Children's Hospital in Rotterdam is currently carrying out an implementation research trial in which the effect of the implementation of the NIDCAP program on staff as well as parental stress is being studied. A pilot study carried out to evaluate parental stress in the NICU showed the following factors caused stress in parents: health status of the infant, parental role alteration, staff behaviors and communication and equipment and sound [25]. They are now in the process of completing their study

of providing NIDCAP for infants born ≤ 30 weeks. Once all results are published, we will be able to have a clearer view of the effect of implementing NIDCAP in the Dutch neonatal system.

## Parents

One of the effects of the NIDCAP intervention was that fathers were encouraged to participate in the caregiving of their infant. This was a recommendation we made after our pilot study findings because fathers stated that they wanted to become more involved in their child's care and acquire more knowledge of preterm infant behavior[26]. We found that fathers of infants in the NIDCAP group exhibited more stress than fathers of infants in the control group and concluded that this was perhaps because they were more involved in their child's care, so would not be able to maintain the emotional distance that they would have if not so involved in the caregiving[27]. It is therefore important to not only find ways of including fathers in the caregiving in future programs but find ways of providing them with support.

Both parents and the nursing team were positive about NIDCAP and the nurses expressed an interest in receiving more developmental care in-services and bedside support[28]. This finding has been reported in previous trials as well as our study[24,29]. As NIDCAP is a humane way of caring for infants and does no harm[30], it is important that the wishes of parents and nurses should also be taken into consideration when deciding whether to implement this approach to caregiving. In a study of mothers of infants in the NIDCAP group, the mothers perceived more closeness to their infants at 36 weeks post menstrual age (PMA) than did the control mothers and rated the staff's ability to support them in their role as a mother somewhat higher. They also expressed more anxiety than did the control group mothers which was similar to our findings of fathers of the NIDCAP infants. Kleberg suggests that the reason may be that the mothers in the NIDCAP group had already bonded to their infants during the hospital stay[31]. We felt also that perhaps fathers were more involved in their infant's care and this raised their level of stress.

## Developmental care in NICU's in the Netherlands

There has been an increasing centralization of perinatal care in the Netherlands, with a twofold increase in the number of very preterm infants being born in tertiary centers[9,32,33]. Infants are often transferred from the neonatal centers to regional hospitals with intermediate care once stable enough to be discharged from the

intensive care. This policy is used in order to ensure sufficient intensive care beds are available for new admissions but may also impact any programs implemented in the NICU, as infants may be transferred out within weeks after birth. Because this may directly affect outcomes of these early intervention programs in the NICU, the importance of a continuation of such programs once the infant is transferred to a regional hospital should be emphasized.

## Conclusions

Based on our findings the following conclusions can be made concerning the implementation of developmental care and with emphasis on the NIDCAP developmental care program.

Basic developmental care has a positive effect on psychomotor development at 1 year of age in children born < 32 weeks. Since it is fairly inexpensive and not time consuming to implement, NICU nurseries should at least implement basic developmental care.

It is possible that the NIDCAP intervention was not provided long enough to be able to make any final conclusions concerning outcome effects. A subsequent study is needed involving not only the neonatal centers but also the regional hospitals with intermediate care since infants may be transferred to them within weeks after birth.

In addition, early intervention programs provided only in the period of hospitalization of the preterm infant are possibly not enough to produce results and that a subsequent study should be carried out in which the NIDCAP program is implemented along with a home-based intervention for parents and infants when they are discharged from the hospital.

We have examined the effects of developmental care in the NICU in the Dutch neonatal system of centralized perinatal care and hope that we have been able to answer some of the questions posed back when developmental care was first introduced in the Netherlands. However we feel that more research is warranted before a definite conclusion can be made concerning the effect of developmental care on preterm infants and families.

## Recommendations for future research

Based on our conclusions, recommendations for further studies are:

1. A follow-up study at school age of the infants from our 2 RCT's to see if there are any later effects of the intervention and ideally continuing to follow these children as they mature; as this is a large cohort, they may reveal answers to long term effects of prematurity.
2. Examine the effect of developmental care provided not only in the neonatal centers but also in the regional hospitals in order to see if a longer intervention has an effect on outcomes.
3. Initiate a phase 3 study in which the NIDCAP intervention in the neonatal nursery is combined with an intervention program once infants are discharged to home to see if this continuing support of infants and families will show improved outcomes.
4. Measure the effect of developmental care on younger, sicker preterm infants such as ventilated infants born < 30 weeks GA to compare results with previous NIDCAP studies and to see if the effect is greater.
5. A developmental care study in which the biological effect on the brain such as in MRI studies or other quantifiable biological stress measurements are used to measure outcomes.

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