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## Outcomes 8 years after preterm birth

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# Chapter 10

General discussion

Over the past decades, the incidence of preterm birth in developed countries has increased and survival has improved, making insight in long-term outcomes as well as possibilities to influence these outcomes more important. We hypothesized that feeding a protein-enriched formula after initial hospital discharge, as compared with a standard term formula, might improve early-life growth and body composition and that this effect would persist into childhood. Furthermore, we hypothesized this might lead to favorable neurodevelopmental as well as cardiometabolic outcomes in childhood. In addition, we explored various outcomes at age 8 years after very preterm birth regardless of type of nutrition after discharge.

## **EFFECT OF NUTRITION AFTER DISCHARGE ON GROWTH, BODY COMPOSITION AND NEURODEVELOPMENT**

### **Growth and body composition**

In **Chapter 3**, we showed that at 8 years there were no differences between the feeding groups in anthropometric variables or body composition, and the benefits of the protein-enriched formula with regard to lean mass accretion that were present at 6 months CA did not persist in childhood. Although tracking of body composition has been suggested,<sup>1</sup> we could not confirm this in our study, possibly because of loss to follow-up. Unfortunately, no reference data of body composition in term-born children of the same age were available.

An interesting finding from the post hoc analyses was that infants with poor weight gain during the first 6 months after term age may benefit from protein-enriched formula (**Chapter 3**): those fed PDF had a weight and BMI at 8 years close to 0 SDS compared to -1.5 SDS for those fed TF. In addition, head circumference and lean mass index (i.e., adjusted for height<sup>2</sup>) were higher in the PDF-group. Longer follow-up is necessary to evaluate whether these differences persist and might have positive consequences.

### **Metabolic health outcomes**

One of the main goals of interventions in preterm infants is to decrease the risks of later cardiometabolic diseases and diabetes mellitus type 2. We included a set of outcomes that has previously been associated with the metabolic syndrome. No differences in metabolic health variables were found between the feeding groups, including the human milk (HM) group (**Chapter 3**), even though HM has been previously associated with favorable metabolic outcomes on the longer term.<sup>2</sup> Possibly, the duration of our follow-up was insufficient to observe differences in metabolic risk factors. In preterm-born subjects,

these parameters were mostly investigated in adolescents or adults,<sup>3</sup> although increased glucose and triglyceride levels have been described as early as age 2 years.<sup>4</sup>

### Neurodevelopment

In **Chapter 4** we found that feeding a protein-enriched formula during the first 6 months after discharge, as compared with a standard formula, did not result in better neurodevelopmental scores at 24 months CA or 8 years. This was unexpected, because protein in particular has been suggested to contribute to improving neurodevelopmental outcomes, in part through enhancing early-postnatal growth<sup>5,6</sup> and increasing lean mass accretion.<sup>7</sup> The small sample size, in particular at 8 years, may have limited the chances of finding a difference between the feeding groups. Children fed HM, however, did perform better on the mental developmental index at 24 months CA, even after adjustment for parental educational level, a well-known confounder for this association. At age 8 years, parental education was the most significant influence on the association, though a trend towards a benefit of HM was observed. Based on these results the conclusion is that feeding HM to preterm infants is preferred for later neurodevelopmental outcomes. Unfortunately, a conclusion with respect to formula feeding cannot be drawn based on our results.

Furthermore, as visually represented in **Figure 4.2**, individual results at 24 months CA cannot be extrapolated to school age. Dutch guidelines regarding follow-up care after NICU admission suggest that children born < 30 weeks gestation and/or with a birth weight < 1000 g or < 1500 g (if < 10<sup>th</sup> percentile on national growth curves) should be monitored carefully. According to this guideline, follow-up should take place at 6, 12 and 24 months CA, and at 5 and 8 years.<sup>8</sup> With respect to neurodevelopment, the poor correlation between results obtained at 24 months CA and 8 years underlines the importance of follow-up of preterm infants.

## CHANGES IN THE QUALITY OF CARE, CHANGES IN OUTCOMES?

Considering the extensive changes in perinatal care for preterm infants we speculated that this might be reflected in improved outcomes for more recently born preterm infants. In **Chapter 5** we describe the comparison of two cohorts of very preterm-born children (from 1983 and 2003–2006, respectively). Indeed we found that early-life growth and growth parameters at follow-up had improved in the more recent cohort, although we could not directly attribute this to improvement in care.

The adverse impact of early-life growth restriction on neurodevelopmental outcomes, however, remained unchanged between the cohorts: infants born SGA or showing postnatal growth restriction were still at increased risk for unfavorable neurodevelopmental outcomes (Chapter 5). We recommend that interventions to stimulate both motor and cognitive development should already start during the NICU stay. Close monitoring of children that experienced adverse early-life growth seems warranted, not just during infancy, but extending into childhood.

## **ENDOCRINE REGULATION OF GROWTH, BODY COMPOSITION AND METABOLIC HEALTH OF PRETERM-BORN CHILDREN**

### **Cortisol**

After birth, a preterm infant is exposed to an excessive amount of stress during a critical window in terms of growth, brain development and setting of endocrine systems such as the HPA-axis. HPA-axis activity and reactivity are important for regulation of homeostasis, for example in adaptation to stressors. We assessed cortisol levels in preterm-born children and studied the association with early-life growth (Chapter 6). Growth restriction, either prenatal or postnatal was associated with lower cortisol levels over time (Chapter 6), which is consistent with studies in term SGA infants that found a blunted cortisol response to painful procedures.<sup>9,10</sup> We found no evidence for a subsequent shift towards a hyperactive cortisol response: it is possible that this response develops after 8 years.

### **Leptin and IGF-1**

In Chapter 7 we investigated the role of leptin and IGF-1 in (bone) growth and body composition in our cohort of preterm-born children. These two hormones are involved in many more processes, which are beyond the scope of this thesis. Therefore, only a brief summary of the relevant actions as discussed in chapter 7 will be described here.

The adipocytokine leptin is a key regulator of food intake and energy expenditure, is strongly associated with fat mass,<sup>11</sup> and possibly related to neonatal nutrition. At 8 years we found no differences in leptin concentrations or in fat mass or fat mass percentage between the feeding groups (Chapters 3&7). With respect to the role of leptin in bone metabolism, we found a positive association between leptin and bone variables in infancy but not at 8 years.

IGF-1 is a key regulator of growth and has been specifically associated with longitudinal growth and lean mass accretion.<sup>12</sup> Furthermore, an in-vitro association of IGF-1 with

adipocyte differentiation and lipid accumulation has been shown,<sup>13</sup> which may explain the association between IGF-1 and leptin both in infancy and childhood (**Chapter 7**). Alternatively, leptin can activate the hypothalamic-pituitary-growth hormone axis with subsequent secretion of IGF-1,<sup>14</sup> and through this pathway leptin might also indirectly influence bone metabolism. With respect to the feeding groups, IGF-1 concentrations were higher in the PDF group at 3 and 6 months CA (**Chapter 7**), which is consistent with studies that describe a positive relation between protein intake and IGF-1 in both term and preterm infants.<sup>15,16</sup> Although the increased IGF-1 concentration did not result in increased growth, it may have contributed to the increased lean mass found in the PDF group at 6 months CA.<sup>17</sup>

### **Salt sensitivity of blood pressure**

Finding an explanation for the association between low birth weight and preterm birth with an increased risk of cardiovascular disease is an ongoing quest. One of the possible pathways to hypertension might be through the relation between salt intake and blood pressure (BP), i.e. salt sensitivity of BP.<sup>18</sup> We found that 16% of our cohort could be classified as salt-sensitive (**Chapter 8**). Comparison to literature is hampered though, because no gold standard definition exists. While salt sensitivity has been suggested to be part of a cluster of metabolic risk factors, including insulin resistance, for later cardiovascular disease, the associations we found were rather counter-intuitive: salt-sensitive children were more likely to have a lower fat mass and BMI (**Chapter 8**). However, no firm conclusions about this can be drawn from our exploratory results in a small sample.

## **STRENGTHS AND LIMITATIONS**

The main strength of this thesis is the extensive description of the follow-up of a nutritional intervention in a preterm-born cohort from birth to 8 years. Considering the lack of long-term follow-up data of nutritional intervention studies, our results add to the current evidence.

The main limitation of this study is the attrition at age 8 years, a common issue for follow-up studies in general, but nutritional intervention studies/RCT's in particular. Part of the explanation why we could not find an effect of different types of nutrition after discharge may be attrition, but likely also confounding variables in the 7.5 years after the intervention. Nevertheless, it has been emphasized that, with proper consideration of the consequent (statistical) limitations, reporting long-term outcomes is of great importance.<sup>19</sup> Another

limitation is that the majority of the analyses were post hoc analyses. Whenever groups other than the original feeding groups were compared, only associations can be described, and these results have to be interpreted with caution.

Although infants were included at birth, the actual data collection commenced for the most part at term age. In an attempt to relate prenatal and early-postnatal events to later outcomes, additional data collection at birth could have been of added value. In particular for the assessment of hormonal systems, the period between birth and term age may provide useful information.<sup>20</sup>

Another important limitation of the STEP-RCT is the lack of a term-born control group, which hampered direct comparison of outcomes between preterm-born children and matched term-born peers. Instead, results had to be compared with results of other studies and reference data. When interpreting results of (partly) observational follow-up studies a number of biases should be considered. In this study, selection bias is probably the most important to take into account. A few moments during the study almost inevitably caused selection: 1) at inclusion, because specific inclusion/exclusion criteria applied for participation in the RCT, 2) at initial follow-up until 6 months CA by choice/motivation of parents and 3) at follow-up at 8 years whereas children with for instance severe cerebral palsy that could not perform all motor assessments were excluded, as well as children with incomplete follow-up until 24 months CA. In addition, parents of children with medical problems were less likely to consent to participation in the follow-up because of the additional burden for their child. This means a relatively healthy group of preterm infants/children was included in the RCT and follow-up which may limit generalizability to the general preterm population. When possible, we used all available data to avoid further selection. Another inevitable bias in a nutritional RCT is of course the fact that infants cannot be randomly assigned to receive HM or formula. In addition, as with any historical cohort, generalizability to current NICU populations may be hampered because of ongoing changes in perinatal care.

## **GENERAL CONCLUSIONS**

The results of this thesis show that the positive effects of feeding a protein-enriched formula in the first 6 months after term age did not persist into childhood or could not be confirmed due to attrition at follow-up. No differences were found at 8 years between the formula groups with respect to growth, body composition, bone mineralization or neurodevelopment. With the exception of favorable cognitive outcomes, the HM group was comparable to both formula groups. In addition, this thesis confirms the importance

of adequate early-life growth for later growth and neurodevelopment, and may give reason to reconsider nutritional practice. With respect to long-term outcomes, this thesis shows that multiple factors, including HPA-axis activity and salt sensitivity of BP may contribute.

The ultimate goal of optimal early nutrition, both during hospital admission and after discharge, and adequate early postnatal growth is to improve neonatal outcomes and to achieve neurodevelopment comparable with term-born children as well as to minimize risks of metabolic syndrome and cardiovascular disease in later life. Nevertheless, it is important to realize that early nutrition is only one aspect of a composite of many factors that contribute to these associations. Early nutrition, disease severity and early-life growth – among others – are strongly related and of influence on each other, and, therefore, cannot be seen as separate entities. This may complicate drawing conclusions with regard to the effects of early nutrition on later health outcomes. Long-term follow-up of nutritional intervention studies in preterm infants is, however, of importance to assess the effects beyond infancy and childhood and to further unravel the complicated associations between preterm birth and its long-term sequelae. Ideally, follow-up would extend into (late) adulthood, the time that cardiovascular diseases may become apparent.

## **FUTURE PERSPECTIVES AND SUGGESTIONS FOR DAILY PRACTICE**

### **Suggestions for the optimal timing of protein-energy adaptations in nutrition for preterm infants**

Adequate nutrient supply shortly after preterm birth reduces the risk of EUGR. Human milk is the most important source of early-life nutrition, especially with the increasing possibilities to provide preterm infants with donor HM. In case of formula feeding, a nutritional switch from a high energy/high protein diet to a high protein only diet should be considered already during hospital admission from postconceptional age 32–34 weeks. From 3 months CA onward, continuation of a protein-enriched formula should be reconsidered based on the infant's growth pattern. More individualized nutritional care, based on the assumption that the long-term cardiometabolic risks can be mitigated by ensuring appropriate linear growth without excess fat mass accretion, seems important. These recommendations may contribute to acknowledging the in-hospital and postdischarge periods as a continuum instead of separate entities, resulting in healthier early growth and a reduction in the associated risks of neurodevelopmental problems and cardiometabolic diseases. The recommendation was described in more detail in **Chapter 9**. In the future, other variables such as insulin-like growth factor type 1 (IGF-1), which is

related to both nutritional intake<sup>21</sup> and growth regulation, may also contribute to nutritional decision making.

### **Suggestions for follow-up of preterm-born children**

- Follow-up until (at least) the age of 8 years, as suggested by our national guidelines, including assessment of growth, BP and neurodevelopment is supported by our findings;
- Appropriate scores on neurodevelopmental assessments at 24 months CA should not exclude children from follow-up of cognitive and motor development at later ages;
- Children that experienced postnatal growth restriction should be included in the scheduled follow-up after preterm birth/NICU admission.

### **Suggestions for future nutritional intervention studies**

- To be able to directly compare results of preterm-born children with term-born peers, the concurrent inclusion of a term-born control group would have a large added value;
- Nutritional interventions should not be primarily based on arbitrarily defined periods such as pre-discharge and post-discharge, but rather on growth pattern;
- To facilitate comparison between nutritional intervention studies we would strongly recommend following the advice with respect to collecting and reporting a standard data set by Cormack et al. and Koletzko et al.<sup>22,23</sup>;
- Increasing the cooperation between (neonatal nutrition) research groups would facilitate recruiting adequate numbers of participants to obtain reliable and valuable results within a limited time frame.

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