Outcomes 8 years after preterm birth

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Summary

In **Chapter 1** we discuss the importance of prenatal and postnatal growth in relation to nutrition and long-term health and developmental outcomes of preterm infants.

In **Chapter 2** we define the aim, design and outline of this thesis. The main aim was to report the follow-up of preterm-born children at age 8 years who originally participated in the nutritional RCT called 'Study Towards the Effects of Postdischarge nutrition' (STEP). In the original RCT, infants born at a gestational age of ≤ 32 weeks and/or with a birth weight ≤ 1500 g were included. At term age formula fed infants were randomly assigned to receive either a protein- and mineral-enriched formula (PDF) or a standard term formula (TF) until 6 months corrected age (CA). Human milk (HM) fed children were included as a control group.

The first part of this thesis describes the outcomes at follow-up at 8 years of the original RCT. In **Chapter 3** we compare the feeding groups (i.e., PDF, TF and HM) on growth, body composition, bone mineralization, and metabolic variables. We found no differences in any of these outcomes, possibly in part because of substantial attrition at follow-up.

In **Chapter 4** we compare neurodevelopmental outcomes at 24 months CA and 8 years between the feeding groups. PDF did not improve neurodevelopmental outcomes as compared with TF. At both ages the HM group scored better on cognitive measures. The correlation between outcomes at different ages was weak, which emphasizes the need for long-term follow-up of preterm-born children.

In **Chapter 5** we investigate whether early-life growth of preterm infants has improved over time and whether the association between early-life growth and neurodevelopment has changed. We compare two cohorts of preterm-born children born in 1983 and 2003–2006, respectively. The incidence of adverse growth decreased between the cohorts. The adverse impact of early-life growth restriction on neurodevelopmental outcomes, however, remained unchanged. We concluded that achieving adequate early-life growth may be crucial for later neurodevelopment, in particular for preterm infants born SGA.

The next part of this thesis is focused on endocrine regulation of and hormonal influence on different outcome parameters, including growth, body composition and risk factors for later cardiometabolic disease.

In **Chapter 6** we explore the associations between early-life growth and HPA-axis development. Our results suggested that poor intrauterine as well as postnatal growth were associated with HPA-axis suppression during infancy. Although this association was no longer found at age 8 years, we do not know what the implication might be of this altered development of HPA-axis setting in relation to later cardiometabolic disease risk.

Chapter 7 describes part of the complicated, multifactorial regulation of body composition and bone health, in particular the involvement of leptin and IGF-1. Both hormones were associated with body composition in infancy and childhood. In addition, leptin was associated with bone parameters in early infancy, but not at 8 years, which may suggest a change in regulatory pathways over time.

The relatively unexplored phenomenon of salt sensitivity of blood pressure in preterm-born children is assessed in **Chapter 8**. We found that 16% (n = 10) of our cohort could be classified as salt sensitive at 8 years already, and we speculated that this feature may explain part of the increased cardiovascular risk at later age.

In **Chapter 9** we review the evidence on the impact of suboptimal early-life growth and nutrition after very preterm birth. Furthermore, short-term and long-term outcomes of nutritional intervention studies are briefly summarized and translated into a recommendation for the nutritional management of very preterm infants in the first months of life.

In **Chapter 10** we put all our results into perspective and consider the implications of what we found. We conclude that optimal early nutrition, in part through improving early-life growth, may contribute to improving neurodevelopmental as well as to minimizing risks of cardiometabolic diseases in later life. Long-term follow-up of nutritional intervention studies in preterm infants is important to assess the effects beyond infancy and childhood, and to unravel the complicated associations between preterm birth and its long-term sequelae.