Summary
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Preterm birth interrupts the normal fetal growth and developmental processes of many organs and regulating systems. The combination of preterm birth itself, postnatal morbidity and stress and impaired postnatal growth could have consequences for later health.

Preterm born children have impaired growth in early postnatal life. This period corresponds with the last trimester of pregnancy and the impaired postnatal growth might therefore result in comparable adaptations as in third trimester intra-uterine growth restriction. These changes in structure and metabolism (programming) are functional for survival in the adverse intra-uterine or extra-uterine environment, but may be permanent and lead to diseases in later life, including coronary heart disease, type 2 diabetes and hypertension. This so called Barker hypothesis, is nowadays called Developmental Origins of Health and Disease (DOHaD) hypothesis (https://dohadsoc.org/).

It is unknown whether the long-term endocrine and metabolic consequences of preterm birth and programming in the postnatal period are already detectable in early childhood. The studies in this thesis were aimed to evaluate endocrine and metabolic consequences of preterm birth in early life. The hypothalamic-pituitary-gonadal (HPG) axis, hypothalamic-pituitary-adrenal (HPA) axis, the growth hormone/insulin-like growth factor I (GH/IGF-I) axis and the components of the metabolic syndrome were studied in infancy and early childhood in children born with very-low-birth-weight (VLBW) (birth weight < 1500 g). As the VLBW infants were part of the Neonatal Insulin Replacement Therapy in Europe (NIRTURE) trial, the effects of early insulin therapy on the neuroendocrine axes and on the components of the metabolic syndrome were also investigated. The background and aims of this thesis are further addressed in chapter 1.

Chapter 2 and 3 describe the postnatal activation of the HPG axis in male and female VLBW infants. Serial measurements of gonadotropins and testosterone/estradiol levels, by making use of urine samples, provided an accurate description of the postnatal activation of the HPG axis without the burden of frequent blood sampling. In VLBW boys, levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) showed a peak at a mean postnatal age of 1 to 4 weeks (mean postmenstrual age of 30 to 32 weeks). Testosterone levels did not show a significant peak, but decreased with increasing age; this decrease was faster in infants receiving early insulin therapy compared to those receiving standard care. In VLBW girls, levels of FSH and LH showed a peak at a mean postmenstrual age of 32 weeks (postnatal age of 4 weeks) and estradiol levels were highest shortly after birth.
Chapter 4 describes the prevalence of the components of the metabolic syndrome in VLBW infants at the corrected age of 2 years, using reference values published earlier. The majority of the VLBW infants already had one or more components of the metabolic syndrome at that age. Especially the prevalence of raised blood pressure was high: 63% had systolic and/or diastolic blood pressure ≥ 90th percentile for age, sex and height. Approximately one third of the VLBW children had high triglycerides (≥ 0.98 mmol/l) and one third had low HDL cholesterol (≤ 1.03 mmol/l). At 2 years corrected age, VLBW children treated with insulin in the first week of life had lower triglycerides than children who received standard care and, for the subgroup with BMI SDS < 0 at 2 years corrected age, they also had higher HDL cholesterol levels. These findings suggest that early insulin treatment may have long-term benefits for some of the components of the metabolic syndrome.

Chapter 5 compares the components of the metabolic syndrome in VLBW infants at the corrected age of 2 years to those in 2-year-old term appropriate-for-gestational-age (AGA) born children from our own population. At 2 years corrected age, VLBW children had higher glucose levels than term AGA children. This suggests that VLBW children already have reduced insulin sensitivity at 2 years corrected age.

In chapter 6, the relation between cortisol levels and blood pressure is investigated. At 2 years corrected age, cortisol levels were positively correlated to blood pressure in VLBW boys. This suggests that programming of the HPA axis may contribute to the high prevalence of raised blood pressure in early childhood in VLBW infants. This chapter also confirms the reliability of salivary cortisol measurements, which are preferable to serum measurements because of the non-invasive sample collection.

Chapter 7 compares serum cortisol and cortisone levels and cortisol/cortisone ratio in VLBW infants to term AGA born infants. During the first 2 years of life, cortisol/cortisone ratio was higher in VLBW children compared to term children, suggesting lower activity of 11ß-hydroxysteroid dehydrogenase type 2 (11ß-HSD2). Considering the relationship between cortisol/cortisone ratio and metabolic syndrome components, lower 11ß-HSD2 activity probably contributes to the long-term metabolic and cardiovascular risks of VLBW infants. Over the first 2 years of life, both cortisol and cortisone were higher in VLBW children treated with insulin in the first postnatal week compared to children in the standard care group. This suggests that early insulin treatment may affect the programming of the HPA axis.

Chapter 8 compares IGF-I and its relation to growth in VLBW infants to term AGA born infants. During the first 2 years of life, IGF-I levels were higher in VLBW children com-
pared to term children. In both VLBW and term born infants, IGF-I levels were related to (change in) length and weight over the first 2 years of life. The difference in length between VLBW and term born infants decreased over the first 2 years of life, suggesting that higher IGF-I levels in VLBW infants may have an important role in catch-up growth in length in early childhood.

Chapter 9 discusses the results of the studies in this thesis and the implications of the endocrine and metabolic changes in early childhood in VLBW infants. The higher prevalence of metabolic syndrome components and the risk of cardiovascular disease have implications for life style and follow-up; this should be taken into account by healthcare professionals, parents and the VLBW children during their entire lives. Several suggestions for future research are described. Finally, the development of interventions that may reduce the metabolic risks in later life of VLBW infants is discussed.