Early-life endocrine regulation and neurodevelopmental outcomes

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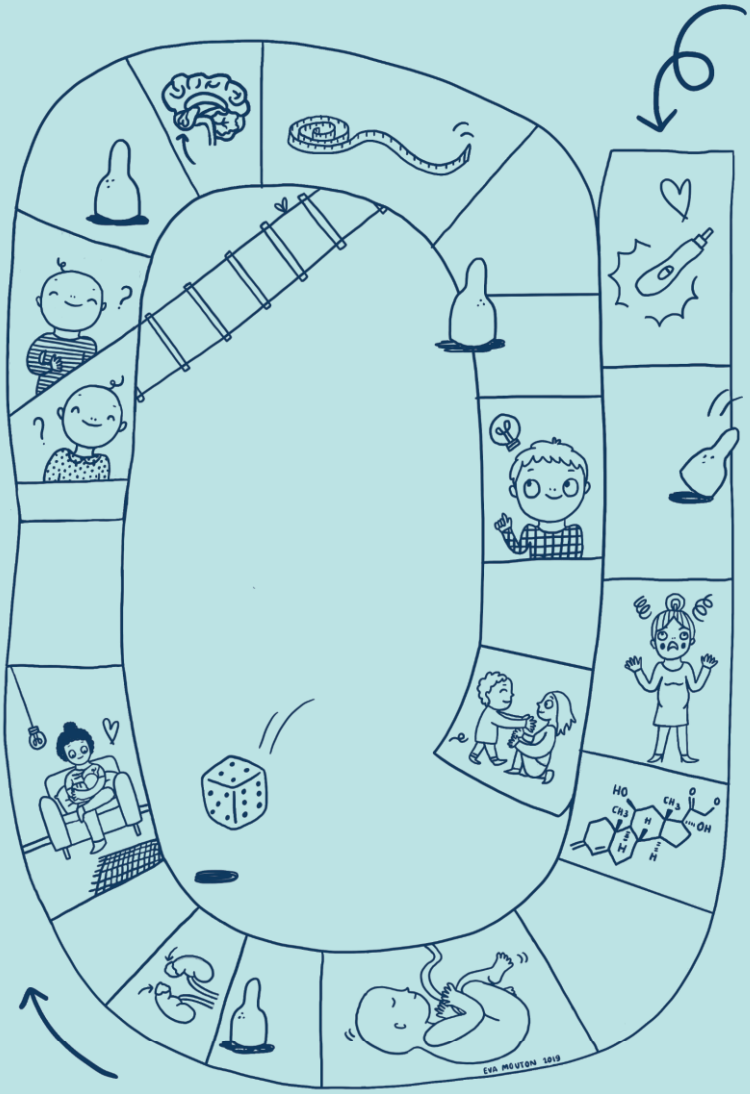
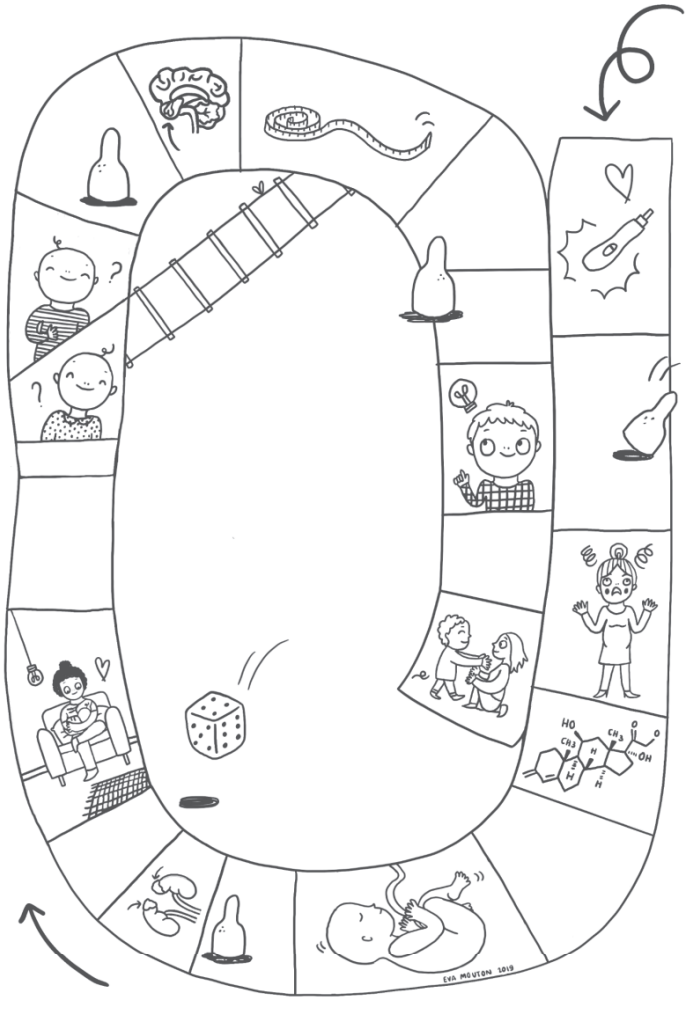
Introduction

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General introduction and outline of thesis

This thesis is centered around the premise that occurrences early in life, or even antenatally, can have effects in the long-term. This hypothesis is called the Developmental Origins of Health and Disease (DOHaD). An extensive body of evidence has already shown that adverse events in early life can lead to an increased risk of, among others, cardiovascular disease [1] and psychopathology.[2]

Prematurely born infants form a special risk group. Their safe place in the womb is traded for an incubator in the Neonatal Intensive Care Unit (NICU), where they can be subjected to interventions such as ventilation assistance, routine controls, a myriad of medications, surgeries, and other (painful) procedures. Their bodies are also still immature, which hampers their ability to digest milk, to breathe unassisted and to fight off infections, all while being constantly exposed to external risks.

Globally, approximately 10.6% of births occurred prematurely, and 15.4% of those were with a gestational age of <32 weeks.[3] With advancing medical developments in the NICU, such as aggressive feeding strategies, antenatal glucocorticoids and improved ventilation techniques, mortality has decreased significantly in preterm populations.[4-6] Therefore, focus is shifting towards improving long-term outcomes in these children. Preterm infants have previously been shown to be at an increased risk for neurodevelopmental problems, cardiovascular diseases and deviating growth.[7-9] It is important to know which factors contribute to these adverse outcomes, and it is equally important to study which interventions can improve or prevent the adverse consequences of preterm birth. Treatment of preterm infants is likely to be most successful when normal physiology is pursued, and a comprehensive understanding of these processes is therefore crucial.

The work presented in this thesis aimed to elucidate both normal physiology, as well as some of the factors contributing to or preventing adverse outcomes in preterm infants, with a focus on early-life endocrine regulation.

PART 1 "EARLY-LIFE GLUCOCORTICOID REGULATION"

A mal-adapted hypothalamus pituitary adrenal (HPA) axis has been implicated as one of the underlying mechanisms behind the DOHaD hypothesis.[10,11] However, not much is known yet about normal fetal and neonatal HPA-axis development, and recognizing aberrant developmental patterns is therefore difficult. In this part, we aimed to shed more light on normal HPA-axis development and its influencing factors.

Glucocorticoids (GCs) can be measured in hair, which offers a retrospective view of HPA-axis activity.[12] We aimed to explore whether this medium provides a reliable insight into fetal HPA-axis activity, and which factors are associated with neonatal hair GC levels

in **Chapter 2**. In **Chapter 3**, we analyzed the association between experienced maternal distress pre- and perinatally and hair GC levels in the neonate and mother.

Exposure to aberrant maternal cortisol levels in utero has been associated with adverse outcomes in the offspring.[13] After birth, infants are still exposed to small amounts of maternal GCs through breastmilk. Several studies have found associations between breastmilk GCs and outcomes in both animal and human studies.[14-21] However, our research group recently reported that GCs in breastmilk follow the diurnal rhythm of maternal HPA-axis activity,[22] and this was not taken into consideration by previous studies. We have reviewed existing evidence concerning breastmilk GCs in **Chapter 4**. Next, we have explored associations between breastmilk GC rhythmicity and (neurodevelopmental) outcomes in the offspring. We assessed the correlation between breastmilk GCs and macronutrients in **chapter 5**, to determine whether associations between breastmilk GCs and outcomes in offspring could actually be attributed to macronutrient variations instead. Subsequently, we described GC rhythmicity in infants at age 1 month and explored associations between this rhythm and breastmilk GC rhythmicity as well as other possible rhythm-influencing factors (**Chapter 6**). Lastly, we researched the associations between breastmilk GC rhythmicity and infant body composition (**Chapter 7**) and behavior and sleep (**Chapter 8**).

PART 2 "GLUCOCORTICOID REGULATION AND SEX"

Sex differences in the production and metabolism of cortisol are present in adults, which have been suggested to arise during puberty under the influence of sex steroids.[23,24] However, sex differences in mortality and short- and long-term morbidity are already present in preterm populations. To explore whether these differences might be partly caused by sex differences in cortisol levels, we performed a systematic review and meta-analysis with regard to basal cortisol levels (**Chapter 9**) as well as a systematic review concerning sex differences in HPA-axis reactivity (**Chapter 10**).

PART 3 "EARLY-LIFE THYROID REGULATION IN PRETERM INFANTS"

Maternal hypothyroxinaemia and congenital hypothyroidism have been associated with adverse neurodevelopmental outcomes (in offspring).[25-27] Transient hypothyroxinaemia of prematurity (THoP), a condition in which circulating T4 concentrations are low due to immature endocrine systems as well as acute illnesses, has also been associated with adverse neurodevelopmental outcomes in infancy and childhood.[28-30] However, it is unclear whether these adverse outcomes persist into adolescence and adulthood. We

therefore used the data of the Project On Preterm and Small-for-gestational-age (POPS) cohort to assess whether THoP was associated with IQ and neuromotor outcomes (**Chapter 11**) as well as behavioral outcomes (**Chapter 12**) at age 19.

PART 4 "EARLY-LIFE GROWTH AND NEURODEVELOPMENT"

Both infants who are born very preterm (VP, i.e., gestational age <32 weeks) and/or who are born with a very low birth weight (VLBW, i.e., birth weight <1,500 grams) require admission to a NICU. Many of these infants are both VP and VLBW, and results of studies in one research population are therefore often applied to the other research population. Nonetheless, previous studies have shown that short-term outcomes differ between infants who are born VP versus those with VLBW.[31] We explored whether long-term outcomes were also different between these two entities. First, using the data of the POPS cohort, we assessed differences in growth and final height between children who were born VP and/or with a VLBW (**Chapter 13**). Next, we also analyzed differences in IQ, neuromotor outcomes, behavior, and functional outcomes at age 19 years between these populations (**Chapter 14**).

Lastly, we explored whether improved care has led to different growth patterns and long-term growth and neurodevelopmental outcomes in two preterm cohorts, established 20 years apart. We analyzed the occurrence of prenatal and postnatal growth restriction, whether these growth patterns are associated with long-term growth and neurodevelopmental outcomes, and whether these associations changed between cohorts (**Chapter 15**).

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