The aim of this thesis was to explore the influences of a genetic predisposition to altered glucocorticoid sensitivity, antenatal glucocorticoid treatment, maternal perinatal stress and mother’s milk glucocorticoids on HPA axis functioning in very preterm newborns as well as their effect on adverse long-term outcomes.

In Chapter 2 and 3, we explored factors that influence neonatal hair glucocorticoid levels and their relation with maternal HPA axis activity, and showed that neonatal hair cortisol and cortisone levels could offer insights into intra-uterine glucocorticoid regulation.

In Chapter 4, 5 and 6, we described the development of a reliable LC–MS/MS assay to determine cortisol and cortisone in human breast milk, and explored variations in human milk glucocorticoid concentrations. Subsequently, by showing the existence of a diurnal rhythm in milk glucocorticoid levels that correlated highly with maternal HPA axis activity, we identified a plausible pathway through which biochemical signals from the mother could reach the neonate.

In Chapter 7, we found that genetic variation in glucocorticoid sensitivity could affect an individual’s predisposition of long-term sequelae of early life stress. In young adults who were born very preterm, independent of antenatal glucocorticoid treatment, carriage of the R23K SNP (associated with decreased glucocorticoid receptor [GR] sensitivity) was associated with a higher IQ score and a more favorable parent-reported total problem behavior score; the -2G/C CC genotype (associated with increased mineralocorticoid receptor [MR] sensitivity) with a poorer IQ score; and the I180V SNP (associated with decreased MR sensitivity) with a more favorable internalizing behavior score. Interaction with antenatal glucocorticoid treatment resulted in more favorable total problem behavior scores for exposed R23K carriers, and poorer IQ scores for both exposed N363S (associated with increased GR sensitivity) and I180V carriers.

In Chapter 8, we explored the association between impaired early life growth and HPA axis development. Our data suggested that intra-uterine and early life conditions associated with poor growth resulted in a long-lasting suppression of neonatal HPA axis activity. Although, these effects had disappeared by age 8 years, they might still be a signal for adaptation of developmental pathways.

In Chapter 9 and 10, we showed that gender-specific differences in HPA axis activity and reactivity were already present during childhood, and changed during puberty. These findings highlight the importance of studying sexual dimorphism in the field of the DOHaD hypothesis.

To conclude, in this thesis we explored the effects of genetic predisposition, gender, early life conditions, and later life challenges that may lead to long term disease risk in
very preterm survivors. Moreover, more insights will be gained with future research, due to the efforts that we made on developing and validating new techniques to assess different indices of HPA axis functioning.