Chapter 8

This thesis describes the etiology of individual differences in growth and the influence of early (i.e. intrauterine and postnatal) growth on physical and mental outcome in later life. To this end a sample of 18-year-old twins and their siblings were invited to participate in medical and psychological testing. Anthropometry and IQ tests were performed and blood samples were collected.

The *first chapter* of this thesis served as an introduction into the variation in growth in fetal and postnatal life and its possible effects on developmental outcome in later life. This chapter also described the study protocol and different designs used in this thesis and the longitudinal sample that was initially recruited at the age of 5 years.

C*hapter 2* examined the causes of individual differences in height, weight and BMI in 5-year-old twins using data from a large questionnaire sample. In addition, the data from twins were compared with Dutch reference growth data and the twins' target height, derived from parental height, was investigated. As expected, genetic influences were an important source of variation in height, weight and BMI and the main source of covariation between height and weight. At the age of 5 years, female twins were as tall as singleton children, while male twins were shorter than singletons. All twins had a lower BMI than singletons. Twins grow fairly well compared with singletons, but they grow below their target height, which may be due to the above-average height of their parents.

In *chapter 3* growth data of twins were compared with data from their non-twin siblings and secondly, twin and sibling data were compared with population standards. Data from the longitudinal sample were analyzed. Twins attained normal adult height compared with siblings and children from the general population. Birth weight was shown to have a considerable effect on height in adolescent twins. As for BMI, no differences were shown between 18-year-old twins and children from the general population, whereas the siblings of twins had increased BMI values.

Chapter 4 describes the study of the heritability of testis size of the 18-year-old male twins and their non-twin brothers from the longitudinal sample. There was significant familial resemblance, with an estimated heritability of 59%, but a model that excluded genetic influences and attributed all familial resemblance to shared environment, fitted the data only marginally worse. Dizygotic twins and their brothers had a larger mean testis volume than monozygotic twins and their brothers which may be of interest for future research into the mechanisms underlying dizygotic twinning, as testicular size may the phenotypic expression of 'twinning' genes in men.

In *chapter 5* the influence of genes and early growth on hormone levels in late adolescence were studied using the longitudinal sample of twins and their siblings. Low birth weight has been associated with higher childhood levels of dehydroepiandrosterone-sulfate (DHEAS) and insulin-like growth factor-I (IGF-I). It has been hypothesized that these hormones may contribute to links between reduced fetal growth and adult disease risks, possibly by enhancing insulin resistance. Genetic influences on the variation in DHEAS, IGF-I and fasting insulin levels were high in late adolescence. However, there was no significant influence of birth weight on hormone levels in the study population, but in subjects with catch-up growth birth weight was significantly inversely related to DHEAS and IGF-I levels. There was no association between insulin and DHEAS or IGF-I levels, leaving the mechanism whereby early growth is linked to disease in later life unclear.

In *chapter 6* we explored whether postnatal catch-up growth was associated with long-term negative consequences for cognitive function as was suggested by Fisher et al. in 2006 with a study in zebra finches. Indeed, a greater gain in weight during the first 2 years of life was associated with lower IQ scores at ages 12 and 18 years. However, catch-up growth was correlated with birth weight and this correlation may have explained part of the association. In conclusion, the findings in the present thesis show that genes were the most important source of variation in growth and hormonal parameters. Concerning the reduced size of twins at birth, twins showed almost complete catch-up growth compared with non-twin siblings and children from the general population. Twins attained normal adult height, but twins were still somewhat leaner at the age of 18 years than their non-twin siblings. There was no association between birth weight and the hormonal parameters that were tested in late adolescence. Regarding mental development, we found that catch-up growth might be associated with a slightly impaired cognitive function.

Based on these results we conclude that findings from twin studies into growth and hormonal parameters that we studied in this thesis can be generalized to the general population, particularly when analyzing covariance structures (familial resemblance).

Samenvatting

Groei is een zeer complex proces van veranderingen in vorm, lichaamssamenstelling en verdeling van verschillende soorten weefsels. Dit proces wordt beïnvloed door biologische, psychologische en sociale factoren.
Er zijn grote individuele verschillen in lichamelijke en geestelijke ontwikkeling, zowel vroeg in het leven (tijdens de zwangerschap en op de zuigelingenleeftijd) als later in het leven (kinderleeftijd en adolescentie).
In dit proefschrift wordt ingegaan op de oorzaken van individuele verschillen in fysieke groei en cognitieve ontwikkeling tijdens verschillende fases van groei (zwangerschap, zuigelingenleeftijd, kinderleeftijd en adolescentie). Daarbij richt dit proefschrift zich op de vraag in hoeverre variatie in groei verklaard kan worden door genetische en niet-genetische ('omgevings') factoren.
Dit soort onderzoeksvragen kan met behulp van tweeling- en familieonderzoek bestudeerd worden. Eeneiige tweelingen zijn genetisch (vrijwel) identiek, terwijl twee-eiige tweelingen gemiddeld de helft van hun genetisch materiaal delen, net als gewone broers en zussen. Als eeneiige tweelingen van elkaar verschillen kan dit worden veroorzaakt door omgevingsinvloeden (naast bijv. epigenetische invloeden). Verschillen tussen twee-eiige tweelingen kunnen zowel door omgevingsinvloeden als door verschillen in genetische aanleg worden veroorzaakt. Dit geldt ook voor gewone broers en zussen, maar zij zijn daarnaast ook nog op een ander moment geboren en opgegroeid. Door het vergelijken van de gelijkenis van eeneiige tweelingen en twee-eiige tweelingen en hun niet-meerling broers en zussen kan worden onderzocht in hoeverre genetische en omgevingsinvloeden van belang zijn bij het verklaren van verschillen tussen mensen in bijvoorbeeld lengte of gewicht. De omgevingsfactoren kunnen worden onderscheiden in twee soorten invloeden. De gedeelde factoren zijn de invloeden die voor een ieder binnen het gezin hetzelfde zijn en doen gezinsleden meer op elkaar lijken. Daarnaast zijn er omgevingsinvloeden die voor ieder gezinslid uniek zijn, en ervoor zorgen dat gezinsleden van elkaar verschillen.
Een andere belangrijke onderzoeksvraag wanneer men groei bestudeert in tweelingen, is of resultaten van tweelingenstudies gegeneraliseerd kunnen worden naar de algemene bevolking. Tweelingen worden vaker