1 General introduction
Background

Small-for-gestational-age (SGA) is mostly the result of intrauterine growth retardation (IUGR), a process of slow fetal growth velocity according to intrauterine growth diagrams used in obstetrics (1). Different cut-off levels for SGA can be found in the literature, including birth size below the 10th or 5th percentile. By international consensus in 2001, SGA is defined as a birth weight and/or length of >2 SDs below the sex-specific population reference mean for gestational age (2). This was confirmed by a recent consensus meeting (3).

Being born SGA is associated with a short final stature (<-2 SD score, SDS), especially among persons who failed to catch up in height before the age of 2 years. However, at least 85% of SGA children have a height >-2 SDS at age 2 years (4;5). Those who fail to catch up within 2 years after birth have a 7- to 10-fold increased risk of becoming short as adult (4;5). Growth hormone (GH) treatment has in recent years become available for short children born SGA.

Poor intrauterine growth is not only associated with a short stature. A number of studies, initiated by Prof. David Barker, have demonstrated associations between lower birth weight and cardiovascular mortality, non-fatal cardiovascular diseases, and narrowing of the carotid artery (6-8). Lower birth weight has also been associated with several risk factors for cardiovascular disease, such as insulin resistance, dyslipidaemia, and hypertension (reviewed in (9-12)). Furthermore, it has been shown that persons with accelerated weight gain in infancy after a lower birth weight for gestational age were the most insulin-resistant (13;14).

Several hypotheses have been proposed as explanations for these associations. The “thrifty phenotype” hypothesis, proposed by Barker’s group, postulates that the undernourished fetus responds with (permanent) β-cell hypoplasia and peripheral insulin resistance in order to increase central nutrient availability at the expense of somatic growth (15). The “fetal salvage” hypothesis offers a similar explanation but is dissimilar regarding the β-cell hypoplasia, which is, according to this hypothesis, not a part of the adaptive response of the fetus to intrauterine malnutrition (16). The “catch-up growth” hypothesis postulates that the insulin resistance after IUGR develops in neonatal life to protect the small newborn against hypoglycaemia, when abundant food supply leads to markedly elevated concentrations of insulin and insulin-like growth factor-I (17). Because fetal growth is in part insulin-mediated, the “fetal insulin” hypothesis postulates that lower birth weight is an epiphenomenon of type 2 diabetes susceptibility genes (18-20). Increased glucocorticoid bioactivity has also been proposed as an explanation for the associations, since there is a clustering of Cushingoid features after lower birth weight (21).
Rationale for this thesis

In The Netherlands, like in most industrialized countries, there is a rising incidence in the number of preterm births. This is attributed to an older maternal age at first birth, more widespread application of assisted reproduction technologies, and, hence, more twin gestations. Nowadays, 1% of children is born at a gestational age <32 weeks (22). Furthermore, local data indicate that, in comparing the years 1983 and 1996-1997, neonatal survival has increased from 70% to 89% for infants born <32 gestational weeks (23). The implication of these changes is that the number of preterm infants reaching adulthood will rise in the following years.

There is some evidence for analogies in the endocrine-metabolic state of preterm infants and children born SGA. At 7 years of age, prematurely born children were, regardless of their intrauterine growth, found to be as equally insulin-resistant as term children born SGA (24). However, another study in prematurely born children aged 6 years found that those with birth weights below the 10th percentile were the most insulin-resistant (25). Nonetheless, follow-up of preterm populations into adulthood has not been performed yet. Therefore, it remains uncertain whether the observed associations persist into adult life.

The work presented in this thesis explores in individuals born very preterm (i.e., <32 gestational weeks) the effect of early growth on subsequent height development and the adult metabolic profile, as well as it investigates a few candidate pathophysiological mechanisms for the observed associations.

Population

The studies described in this thesis were conducted in the Project On Preterm and Small-for-gestational-age infants (POPS) cohort, which was recruited in 1983 and comprised of 94% of the very preterm (<32 gestational weeks) and/or very-low-birth-weight (<1,500 g) infants born in The Netherlands in that year (26). The main objective of the POPS study was to assess general and disease-specific mortality of such infants. From birth onwards, follow-up was continued which enabled to study handicaps, cognitive performance, linear growth, and various other characteristics (27). In 1999, an initiative was launched to study the POPS cohort at young adult age. Assessments took place between April 2002 and May 2003, at 19 years of age. Among others, venous blood was obtained after an overnight fast, anthropometry was performed, and blood pressure and carotid intima-media thickness (CIMT) were measured. The response rate was 62% (28).
Outline of this thesis

Chapter 2 discusses the rationale for GH treatment in short children with a history of neonatal growth retardation after preterm birth. Chapter 3 compares the growth pattern up into adulthood between preterm infants born SGA and those with an appropriate birth size for gestational age followed by neonatal growth retardation. Chapters 4 to 7 address the effects of early growth on adult body composition (chapter 4), CIMT (chapter 5), the serum lipid profile (chapter 5), insulin resistance (chapter 6), and blood pressure (chapter 7). Chapter 8 reports on the effect of maternal glucocorticoid treatment, given for impending preterm delivery, on the adult metabolic profile of her offspring. Chapter 9 addresses the effects of 2 glucocorticoid receptor polymorphisms on the growth pattern and the adult metabolic profile. Chapter 10 presents a meta-analysis of published reports on the association between birth weight and basal cortisol level. Chapter 11 gives a brief overview of the major findings and limitations of the work presented in this thesis, and discusses the implications of these findings for patient care.

References
