Long-term consequences of differences in early growth : epidemiological aspects

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General introduction

Background

Morbidity and mortality caused by aberrant metabolic profiles and subsequent disease form a considerable health problem world-wide.[1] At present, a wealth of studies have shown an association between low birth weight as an indicator of poor intra uterine growth, and adult metabolic diseases like obesity, type 2 diabetes, hypertension, and cardiovascular incidents.[2-5] More recently, it has been found that especially the combination of small size at birth followed by increased catch-up growth in later life is detrimental for adult cardiovascular health.[6-8] However, despite this abundance of studies on the early origins of adult disease, unresolved questions still remain.

In the majority of the original publications, the focus has been on the population born at term. The number of subjects born preterm included is very low, and often no clear distinction has been made between low birth weight due to term birth small for gestational age, or due to preterm birth. Nevertheless, studies in subjects born preterm could provide unique and important information about the timing of the early origin of adult metabolic disease. The third trimester of gestation is a critical developmental period, and malnutrition during this time span has been related to reduced adult glucose tolerance in the Dutch famine studies.[9] Infants born very preterm almost invariably experience postnatal growth failure during this trimester *ex utero*, often followed by later catch-up growth.[10-15] Recently, it has been speculated that individuals born preterm might experience similar metabolic consequences in adult life as term born individuals with low birth weight.[16,17] This has important implications for population health, because the frequency of preterm birth as well as the survival rates of infants born very preterm are increasing, which leads to a higher proportion born prematurely in the population.[18]

As the first generation of infants surviving very preterm birth has now reached adulthood, we assessed the effects of both prematurity and early growth on young adult metabolic outcomes in the Dutch national Project On Preterm and Small-for-gestational age infants (POPS) cohort. In this cohort, described in more detail below, 19 year old individuals born with a gestational age <32 weeks in general have a lower insulin sensitivity,[19] a higher prevalence of hypertension,[20] and a reduced kidney size[21] compared with the general population. Less growth in the early postnatal period leads to a high risk for short stature in adulthood[22], while more growth in childhood aggravates insulin resistance after low birth weight[19]. No associations were found with the lipid profile and intima-media thickness at this age[23]. The combination of preterm birth and intrauterine growth retardation seems to contribute to abnormal renal function at young adult age.[24] Antenatal treatment with the corticosteroid betamethasone was associated with reduced kidney function in preterm females only.[25]

However, before remaining research questions in this field will be addressed, some specific methodological issues indissolubly attached to these studies deserve special attention. Although part of the findings described above have been confirmed in animal studies, one should realize that in the human all "evidence" results from epidemiological studies. Preferably these data arise from prospective cohort studies to avoid recall bias and inaccurateness in perinatal data e.g. birth weight. Yet, the effects searched for are often small and come into existence only a long time period after birth, while during this period life style effects are considerable intervening variables. This raises the need for a large study population resulting often in a multi-centre design. For a correct interpretation of the results, it is important to know the reliability of measurements between the participating centres, which can be estimated in different ways. Preferably this reliability should be assessed within the study population itself.

While in this way most research questions concerning the early origins of adult disease can be analyzed with a straightforward approach in a classical epidemiological design with a linear regression model, special attention is required when the effect of both birth weight and subsequent postnatal growth on adult outcome are taken into account. These two effects can be estimated by using two separate models for the two separate research questions, but often these are combined in one model. In the latter situation, the regression coefficient of early growth will change when later-life variables are added to the model, which should be interpreted correctly.

Rationale for this thesis

In this thesis first three specific methodological issues related to early origins of adult disease studies will be addressed. Subsequently, three questions about the effects of prenatal and early postnatal growth on adult health outcomes will be studied.

1. In the methodological part of the thesis, we will focus on three points:
    a. the optimal regression model for analyzing and interpreting the effect of both prenatal and postnatal growth on adult health outcomes,
    b. the efficiency of reliability studies in a multi-centre study,
    c. the correct and clear assessment of reliability for log transformed outcomes.
2. In the clinical part of the thesis about the effect of early growth on adult health, we will focus on three main outcomes:
    a. adult renal function in non-premature subjects with low birth weight,
    b. the adult metabolic syndrome and its separate components,
    c. adult body composition in subjects born very preterm.

Study populations

HUNT-2

The follow-up studies of subjects born at term described in this thesis were conducted as part of the Norwegian Second Nord-Trøndelag Health (HUNT-2) Study. By performing unique linkage with the national Norwegian birth registry a cohort could be formed of all subjects aged 20 to 30 years living in this Norwegian county, which has a stable and homogeneous Caucasian population. Subjects were born between 1976 and 1977, with birth weights ranging from 1000 to 5600g, mean 3500 grams. About 4.5% of them was born preterm, of whom 0.4% very preterm. Perinatal data were registered at birth. Assessments in the HUNT-2 study took place between 1995 and 1997. Among others, venous blood was obtained, anthropometry was performed, and blood pressure was measured. The response rate in this age group was 49%, with living outside the county and lack of time as the main reasons of not attending.[26]

POPS-19

The study in subjects born preterm originates from the Project On Preterm and Small-for-gestational-age infants (POPS) 19 study. The POPS cohort comprises 94% of all live born infants born very preterm (< 32 gestation weeks) or with a very low birth weight (< 1500g) in the Netherlands in 1983 (85% of Caucasian origin). The POPS-cohort has been intensely studied over the years with regard to physical and psychosocial outcomes. In 2002-2003 a new follow-up assessment took place and among others anthropometry at age 19 was measured. The response rate was 62%, with male sex, non-Dutch origin, and low maternal education overrepresented in the non-response group.[27]

Outline of this thesis

In chapter 2 we provide a systematic overview of the literature about the somatic growth of infants born (very) preterm or with a (very) low birth weight from birth until adulthood. The metabolic consequences in adulthood of the preterm birth are briefly discussed. We compare and interpret various linear regression models in the context of optimally studying the early origins of adult disease in chapter 3. In these models, the effects of both prenatal and subsequent postnatal growth are assessed and disentangled, which is important for a correct interpretation of the results obtained. As reliability of measurements is important especially in multi-center studies, we assessed the reliability of relevant anthropometric outcomes in the POPS cohort. In order to design such a reliability study in the most efficient way, we developed a method to estimate correct and more precise intra-class correlation coefficients (ICCs) by integrating variance components from different sources, i.e. from both the reliability study

and the clinical (POPS) study itself (chapter 4). While the estimation and interpretation of these ICCs are not changed by log transformation of the outcome variable, this is not the case for other important reliability measures as Bland and Altman plots with Limits of Agreement, and Coefficients of Variation. Therefore, in chapter 5 we provide a practical approach in which existing statistical methods are applied in the field of reliability in order to present easy interpretable indicators of reliability on the original scale. Next, in chapter 6 we report on the effect of low birth weight on the metabolic syndrome at young adult age in a large Norwegian population study. In chapter 7 the effects of low birth weight on kidney function are assessed in the same population, which was predominantly born at term. In chapter 8 we present the effect of both prenatal and early postnatal weight gain on young adult body composition in a Dutch population born very preterm. Finally, in chapter 9 we give a brief overview of the main findings and limitations of the work presented in this thesis, and the implications for further research.

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