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

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

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The work described in this thesis was performed at the departments of Clinical Epidemiology and Pediatrics of the Leiden University Medical Center in Leiden, the Netherlands, and at the department of Cancer Research and Molecular Medicine of the Faculty of Medicine, Norwegian University of Science and Technology in Trondheim, Norway.

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

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**Anne Margriet Euser**

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in 1981

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# 1

## General introduction





## Background

Morbidity and mortality caused by aberrant metabolic profiles and subsequent disease form a considerable health problem world-wide.<sup>1</sup> 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.<sup>2-5</sup> 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.<sup>6-8</sup> 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.<sup>9</sup> Infants born very preterm almost invariably experience postnatal growth failure during this trimester *ex utero*, often followed by later catch-up growth.<sup>10-15</sup> 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.<sup>16,17</sup> 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.<sup>18</sup>

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,<sup>19</sup> a higher prevalence of hypertension,<sup>20</sup> and a reduced kidney size<sup>21</sup> compared with the general population. Less growth in the early postnatal period leads to a high risk for short stature in adulthood<sup>22</sup>, while more growth in childhood aggravates insulin resistance after low birth weight<sup>19</sup>. No associations were found with the lipid profile and intima-media thickness at this age<sup>23</sup>. The combination of preterm birth and intrauterine growth retardation seems to contribute to abnormal renal function at young adult age.<sup>24</sup> Antenatal treatment with the corticosteroid betamethasone was associated with reduced kidney function in preterm females only.<sup>25</sup>

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 inaccuracy 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.<sup>26</sup>

### 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.<sup>27</sup>

## 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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# 2

## Growth of preterm born children

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*Hormone Research 2008; 70: 319-328*



## **Abstract**

### **Background**

In this review, we describe the growth of (very) preterm infants or (very) low-birth-weight infants from birth until adulthood.

### **Methods**

A systematic analysis of growth of these infants is thwarted by different definitions (classification by gestational age or birth weight) used in the literature.

### **Results**

The early postnatal period of these individuals is almost invariably characterized by substantial growth failure. In the majority of preterm infants this is followed by a period of catch-up growth, which starts in early infancy and usually stops at 2–3 years of age, although in some cases it may continue into adolescence. Catch-up growth is usually incomplete, so that infants born preterm remain shorter and lighter than term-born peers during childhood, adolescence, and adulthood. Disproportionate catch-up growth in height and weight may lead to an altered body composition in adulthood, especially in females.

### **Conclusion**

Though early catch-up growth has shown to be beneficial for neurodevelopmental outcome, it is also associated with adverse metabolic consequences in adulthood. As the first generation of (very) preterm infants is now reaching young adulthood, future follow-up studies on these effects are warranted.

## Introduction

Based on a systematic review of the literature the definitions and determinants of prematurity, prenatal growth, reference charts for preterm born infants, early postnatal growth of the preterm infant, catch-up growth, and growth in childhood, adolescence and adulthood size are discussed, followed by a brief review of late metabolic consequences.

## Methods

We conducted a systematic literature search in PubMed of articles published between 1998 and October 2007. Our search strategy is shown in table 1. Relevant articles were selected on title and abstract. We primarily focused on original research conducted in the past 10 years in humans and written in English. Additional articles were sought by checking the reference lists of the included articles. Recent review articles that provided comprehensive overviews were also included. For the present paper, we selected approximately 50% of the encountered articles; a full list can be obtained from the authors.

**Table 1.** Search strategy for PubMed

Search No.	
1	'infant, premature' (MeSH terms) or 'premature infant' (TiAb) or preterm (TiAb) or 'infant, low birth weight' (MeSH terms) or low birth weight (TiAb)
2	'growth' (MeSH terms) or growth (TiAb)
3	growth (Ti) or 'cohort studies' (MeSH terms) or cohort studies (TiAb) or cohort study (TiAb) or 'body height' (MeSH terms) or body height (TiAb) or 'body weight' (MeSH terms) or body weight (TiAb)
4	1 and 2 and 3
5	4 limits: publication date from 1998, humans

## Definitions

Preterm birth is defined by the estimated gestational age as a proxy of maturity. Three subgroups are distinguished by the World Health Organisation (WHO): preterm (< 37 weeks gestation), very preterm (< 32 weeks), and extremely preterm (< 28 weeks).<sup>1</sup> In the United States of America and several other countries a classification according to birth weight is

generally used. Low birth weight infants are defined as those with a birth weight of 2,500 g or less, which may be due to prematurity, being born small for gestational age (SGA), or both. Similarly, lower cut-off limits for weight have been used to describe more severe cases, i.e. very low birth weight (VLBW < 1,500 g)<sup>2,3</sup> and extremely low birth weight (ELWB < 1,000 g).<sup>4</sup> In very preterm and/or VLBW infants, gestational age is a better predictor of short-term survival than birth weight.<sup>5</sup> The decision about which parameter is applied to define a cohort of small infants has considerable consequences for the characteristics of the population studied.

## **Determinants of prematurity and low birth weight**

### **Determinants of prematurity**

Various risk factors have been consistently associated with premature birth, such as multiple pregnancy, low socioeconomic status, African-American origin, second teenage pregnancy, parity and past reproductive history, substance misuse, infection and hypertensive disease during pregnancy.<sup>6</sup> Approximately 14% of the variation in gestational age is explained by maternal genetic factors, and 11% by fetal genetic factors.<sup>7</sup> The effect of specific polymorphisms in the foetus, e.g. in genes encoding immunologic or haemostatic proteins, seems to be modest compared to maternal risk factors.<sup>8</sup>

### **Determinants of a low birth weight for gestational age**

The risk factors for SGA are usually divided into foetal, placental, and maternal factors, the latter including maternal age, height, and parity,<sup>9</sup> for details see.<sup>10</sup> Foetal genetic factors explained 31% of the normal variation in birth weight and birth length and 27% of the variation in head circumference; maternal genetic factors explained 22% of the variation in birth weight, and 19% of the variation in birth length and head circumference.<sup>7</sup> One of the foetal genes involved may be insulin, as polymorphisms in its promoter are associated with size at birth.<sup>10</sup> Paternally and maternally imprinted genes oppose each other in the regulation of foetal growth and development, illustrated by observations that genomic imprinting of the IGF-II gene has a considerable effect on foetoplacental development and thus delivery of nutrients to the foetus.<sup>10</sup> Although the variation in birth weight may be mainly caused by differences in growth in the third trimester, there is recent evidence that both the growth trajectory of the fetus and its adaptive responses to the prenatal and postnatal environment may be determined as early as the period around the time of conception.<sup>11,12</sup>

## Prenatal growth

### SGA

At birth, the newborn can have an appropriate weight and/or length for gestational age (AGA), be small for gestational age in weight and/or length (SGA), or large for gestational age (LGA).<sup>13</sup> Ideally, the cut-off limit for SGA should best discriminate between infants who are at high risk of short-term and long-term growth impairment, disease, and death, and those who are at a low risk.<sup>14</sup> However, in practice there are various cut-off limits based on arbitrary statistical criteria. Among paediatric endocrinologists there is consensus that a birth weight and/or length of  $< -2$  SDS should be the cut-off value.<sup>9,15</sup> Neonatologists tend to use the 5th or 10th percentile for gestational age,<sup>16</sup> since these cut-offs are related to later developmental problems.

Within the SGA population, three subgroups can be distinguished; infants with a low weight but normal length for gestational age (SGA W or SWGA), infants with a low length but normal weight for gestational age (SGA L or SLGA), and infants with the combination of both (SGA LW or SLWGA).<sup>17,18</sup> The growth patterns of the three subgroups are somewhat different<sup>17,19</sup> and SLWGA males have on average a poorer neurologic outcome than those born SWGA but not SLGA.<sup>20</sup>

We have previously argued that the third auxological parameter that should be measured at birth is head circumference. SGA H or SHGA could be added to the nomenclature to indicate a small head circumference for gestational age,<sup>21</sup> which is indicative for early intrauterine growth retardation or, in extreme cases, for a decreased biological effect of IGF-1 due to primary IGF-I deficiency or resistance.<sup>22</sup>

### SGA versus IUGR

Formerly, the terms SGA and intrauterine growth restriction (IUGR) were used for the same condition, but nowadays there is consensus that the term IUGR should be limited to the process of decreased intrauterine growth rate detected by – preferably several – ultrasound measurements.<sup>9,15</sup> If prolonged and/or severe enough, this may lead to the delivery of an SGA infant. SGA refers only to the condition at birth.<sup>15,18,21</sup> When the prenatal growth pattern is unknown, SGA may be regarded as a proxy for IUGR.<sup>14</sup>

### References and standards for birth size for gestational age

For the classification of prematurity, a reliable estimate of gestational age is necessary. This is usually performed by combining information on the last menstrual period, and early ultrasound assessment,<sup>2</sup> but neither is perfectly reliable.<sup>23</sup> It is noteworthy that according to international recommendations gestational age is expressed in complete weeks,<sup>24,25</sup> while in the frequently used reference of Usher and McLean gestational age was calculated to the nearest week from the last normal menstrual period.<sup>26</sup> In the former approach, the reference curves are shifted to the left by half a week, which appears irrational.

For the classification of SGA (or LGA) versus AGA, anthropometric data are compared with reference charts for gestational age. Ideally, up-to-date reference data from the same or a similar population are required.<sup>14</sup> The choice of the reference population has a considerable impact on the classification, especially for preterm infants.<sup>27</sup>

Currently used neonatal charts differ substantially, and there are essentially four types of diagrams:

(1) Most reference charts are based on the birth size of all newborns in a certain area or country and are presented separately for boys and girls. The American charts (by Lubchenco<sup>28,29</sup> and later by Usher and McLean<sup>26</sup>) are based on small samples (so that combined charts for males and females were prepared) and it was shown recently that both are inaccurate for use in current populations in the US.<sup>30</sup> For Northern European countries the Swedish reference is most appropriate.<sup>24,31</sup>

(2) In some countries separate reference charts are used for primipara and multipara mothers, and for different ethnic groups.<sup>32</sup>

(3) Conditional, customized charts are based on various conditions with a known impact on birth weight weighted in a computer model in order to calculate the degree of normality.<sup>33</sup> On top of adjustments for foetal sex, gestational age and parity, additional adjustments are made for a number of characteristics such as maternal height, weight at first antenatal clinic visit, ethnic group,<sup>34</sup> maternal birth weight and birth weight of previous siblings.<sup>35</sup> These charts are primarily used by obstetricians.

(4) 'Standard' charts are based on intrauterine growth measurements in babies subsequently born at term, from which birth weight is calculated.<sup>36</sup> While these charts have a high sensitivity in detecting a neonate with a growth anomaly, calculating body weight from ultrasound measurements leads to an inevitable loss of precision, so that many centres continue to use regular reference charts based on birth weight data.<sup>37</sup>

### **Early postnatal growth**

In the first weeks of extra-uterine life, (very) preterm infants often develop cumulative energy and protein deficits, despite caloric and protein supplements at recommended intakes.<sup>38</sup> Even with active regimens of parenteral and/or early enteral feeding,<sup>39</sup> this causes on average a substantial postnatal growth failure, with growth curves that are sharply deviating from the reference data.<sup>40-44</sup>

The typical growth pattern is an initial postnatal weight loss (the lowest weight is reached at the fourth to seventh day), followed by an early neonatal peak in growth velocity mimicking in utero growth rates beginning in the second week of life. Birth weight is usually regained in the period between the 8th to the 24th day of life, but earlier in infants with higher birth weights.<sup>39,40,45</sup> Typically, VLBW infants have weights less than the 10<sup>th</sup> percentile at 36 weeks

postmenstrual age,<sup>42</sup> and have an average weight at 40 weeks postmenstrual age of -2.6 SDS.<sup>46</sup> In cohorts based on a low birth weight, the relatively high proportion of SGA infants has a negative effect on growth outcome. While weight is the most documented auxological parameter during these first weeks, also extra-uterine growth restriction with regard to length and head circumference is common.<sup>43</sup>

Although preterm infants are usually lighter and shorter at 40 weeks after the last menstrual period than term born infants, no difference in total adiposity was found. Moreover, preterm infants had an altered fat distribution, with a decrease in subcutaneous fat and an increase in intra-abdominal adipose tissue.<sup>47</sup> At 1 year of age, still a slightly greater fat mass normalized for weight was found in infants born < 34 weeks of gestation.<sup>48</sup>

### **Factors influencing early growth**

Preterm infants are often admitted to a Neonatal Intensive Care Unit (NICU), and face the consequences of unintended postnatal life such as respiratory distress syndrome, bronchopulmonary dysplasia, necrotizing enterocolitis, and infections, with concomitant treatment regimens of, e.g., mechanical ventilation, parenteral nutrition, and administration of steroids.<sup>43,49</sup> Both illness severity and clinical practice in treatment and nutrition vary widely between infants and between NICUs as well.<sup>50,51</sup>

A low birth weight and gestational age,<sup>43,44</sup> postnatal dexamethasone,<sup>43,49</sup> a long duration of respiratory support,<sup>49</sup> pulmonary and circulatory problems,<sup>44</sup> severity of illness,<sup>45</sup> infections,<sup>43,44</sup> NEC,<sup>43,44</sup> and male sex<sup>43</sup> have been negatively associated with early postnatal growth. On a biological level, an important mediator of the early postnatal growth in preterm infants may be IGF-1.<sup>52,53</sup> Not surprisingly, a very important factor that has been positively related to growth in early life is caloric intake.<sup>38,49,54</sup>

### **Postnatal growth references**

The non-physiological situation of preterm birth makes it difficult to provide appropriate postnatal growth references in order to distinguish postnatal growth failure from growth that is normal for this specific group. Separate growth references for infants with parenteral and/or early nutrition have been suggested,<sup>39,55</sup> but generally the charts of birth weight, length and head circumference for gestational age are used. Postnatal growth failure has been defined as weight below the 10th centile at 36 weeks corrected gestational age,<sup>41</sup> or as a decrease in z-score of 1 > 2 between birth and 36 weeks corrected gestational age.<sup>56</sup> We have coined the term 'preterm growth restraint' (PGR) to indicate poor growth in the third trimester, either spent in utero (the term born SGA infant) or ex utero (the preterm born infant with a normal weight for gestational age, but a low length and/or weight at term age, i.e. < -2 SDS).<sup>57</sup>

## Catch-up growth

### Catch-up growth

Catch-up growth is usually defined as reaching an SD score of  $1 > -2$  SDS of the reference population,<sup>9</sup> but in other studies a change  $1 > 0.67$  SD has been used as cut-off.<sup>58</sup> Similar to term infants born SGA, most preterm born infants (approximately 80%) show catch-up growth in weight, length and head circumference after initial postnatal growth failure,<sup>59-62</sup> generally starting early in the first months of life and often achieved within the first 2 years of life.<sup>59-61,63,64</sup> However, late catch-up growth of preterm subjects has been described throughout childhood<sup>61,62</sup> and even in adolescence.<sup>65-67</sup>

It is generally considered that catch-up growth in weight, length, and particularly in head circumference is important for neurodevelopmental outcome.<sup>68-70</sup> Motor impairment was less common if preterm infants were fed an enriched preterm formula in comparison to a regular term formula in the first month after birth,<sup>71</sup> especially in males.<sup>72</sup> However, on average adolescents born very preterm have decreased brain volumes compared to term controls.<sup>73</sup>

### Determinants of catch-up growth

Little is known about the factors that determine if catch-up growth occurs in preterm infants and whether it is complete. Also for term born SGA infants these questions have not been fully elucidated, but birth length and target height,<sup>74</sup> a lower serum leptin, lower birth weight, early weaning from the ventilator and plasma IGF-I are associated with catch-up growth in weight.<sup>75,76</sup>

In preterm infants early growth and genetic potential as reflected by parental height seem important for catchup growth in height as well, though this effect might be different for different durations of gestation.<sup>61,62,66,77,78</sup> Examples of specific genetic polymorphisms that have both been related to increased postnatal catch-up growth in preterm infants are the d3-isoform polymorphism of the growth hormone receptor gene,<sup>79</sup> and the R23K polymorphism in the glucocorticoid receptor gene.<sup>80</sup>

Recently, a prediction model was presented on growth of a cohort of very low birth weight survivors. The following factors explained height SDS at 5 years: height SDS at 1 year, mid-parental height SDS, 1st year weight SDS, and birth weight SDS.<sup>61</sup> We have shown that infants born very preterm who reach the normal range for length ( $1 > -2$  SDS) at 3 months post-term display a virtually normal growth pattern in childhood, adolescence and adulthood, but infants who do not catch up (labelled pre-term growth restraint, PGR) show a similar growth pattern as term born SGA babies. In approximately 10% of them length remains below the  $-2$  SDS line.<sup>64</sup> Most studies have shown that postnatal corticosteroid treatment has a negative effect on postnatal catch-up,<sup>63,81,82</sup> but others did not find such effect.<sup>60,83-85</sup> Other factors that have been negatively related to later (catch-up) growth in preterm infants include male gender,<sup>3</sup> medical complications,<sup>86</sup> and being born SGA.<sup>59-62,87</sup>

## Growth and body composition

### Growth in childhood

With respect to growth in early and mid-childhood, the general pattern reported is that despite catch-up growth (if defined by reaching a height within the normal range) and a steady increase in SDS or z-score for all anthropometric measurements,<sup>60,61,88</sup> both male and female infants born preterm remain smaller and lighter with a smaller head circumference than their term-born or normal birth weight peers,<sup>61,65,77,88</sup> particularly if they were born SGA<sup>59-62,87,89</sup> (table 2, page xx). The data in table 2, collected from recent studies, however, indicate that there is likely to be a trend towards normal height and weight after a decrease in z-scores in the first years of life. Only one study reported that preterm infants born < 29 weeks of gestation as a group reached normal weight, height, and weight for height before puberty.<sup>90</sup> With regard to body composition in infancy, a reduced fat mass when normalized for height at age 8-12 years was observed in children born < 37 weeks of gestation.<sup>91</sup>

### Growth in adolescence and adulthood

In studies describing growth of preterm infants reaching adolescence ( table 3 ), puberty has not always been accurately reported. This complicates a comparison between studies, as puberty has an important effect on growth velocity.<sup>77</sup> Studies reporting puberty have shown no difference in the timing of puberty between preterm born adolescents and term controls.<sup>3,65,67</sup> In adolescence, upwards percentile crossing has been reported,<sup>65-67,92,93</sup> but adolescents born preterm generally continue to be shorter in puberty than term born controls.<sup>65,78</sup>

**Table 3.** Growth of preterm and LBW infants in puberty and adulthood

	N	Inclusion criteria birth weight or gestational age	Age (years)	Height z-score	Weight z-score
Hack 2003 ♂ <sup>3</sup>	103	<1500 g	20	-0.44	-0.35
Hack 2003 ♀ <sup>3</sup>	92	<1500 g	20	-0.26	0.26
Doyle 2004 <sup>67</sup>	42	500-999 g	20	-0.52	+0.14
Brandt 2005 <sup>66</sup>	21	<1000 g, SGA* and preterm**	22.8	-1.02	
Euser 2005 ♀ <sup>95</sup>	216	<32 weeks	19	-0.60	-0.48
Euser 2005 ♂ <sup>95</sup>	187	<32 weeks	19	-0.55	-0.41
Farooqi 2006 <sup>78</sup>	83	<26 weeks	11	-0.53	-0.15
Saigal 2006 ♀ <sup>65</sup>	82	<1000 g	11-16	-0.59	-0.24
Saigal 2006 ♂ <sup>65</sup>	65	<1000 g	11-16	-0.46	-0.53

\* SGA as defined <10<sup>th</sup> percentile for height and/or weight

\*\* preterm birth undefined



**Table 2.** Early postnatal and childhood growth of preterm, LWB, VLBW and ELBW infants

	N	Inclusion criteria birth weight/ gestational age	Mean gestational age (wks)	Mean birth weight (g)	Mean birth weight SDS	Percentage SGA at birth	Measure point	Percentage growth failure at measure point	Height z-score at measure point	Weight z-score at measure point
Fevitrel 2000 <sup>77</sup>	765	'preterm' & < 1850 g	31.0	1364			18 months 7.5-8 years 9 to 12 years		0.91 -0.47 -0.44	
Lemons 2001	4438	501-1500 g				22 <sup>a</sup>	36 weeks <sup>b</sup>	97 <sup>a</sup>		
Niklasson 2003 <sup>90</sup>	52	<29 wks		28 wk 1180 27 wk 1015 ≤26 wk 720			40 weeks <sup>b</sup> 6 months 3 years 7 years	19.2 5.8 <sup>c</sup>	-1.08 -1.70 -0.60 +0.09	-0.19 -1.73 -0.88 -0.02
Bertino 2006 <sup>45</sup>	262	500-1500 g	30.4	1140	-0.98	38.5 <sup>a</sup>	40 weeks <sup>b</sup>	100 <sup>d</sup>		
Saigal 2006 <sup>65</sup>	82	<1000 g	27.2	838		28 <sup>a</sup>	2 years	100 <sup>e</sup>	-1.04	-1.96
Saigal 2006 <sup>65</sup>	65	<1000 g	27.0	844		20 <sup>a</sup>	1 year 2 years 8 years		-0.77 -0.94	-1.68 -1.05
Trebar, 2007 <sup>61</sup>	1320	<1500 g	29.17	1097	-1.16	55.3 <sup>a</sup>	1 year 2 years 8 years		-1.59 -0.92 -0.84	-2.49 -1.90 -1.05
Hovi 2007 <sup>46</sup>	166	600-1500 g	29.17 ± 2.22			33.1 <sup>c</sup>	1.8 years 4.0 years 6.1 years	13.3 <sup>c</sup> 18.2 <sup>c</sup> 11.1 <sup>c</sup>	-0.69 -0.93 -0.62	-1.28 -1.32 -0.85
Bracewell 2007 <sup>88</sup>	241	<25 <sup>6</sup>				≤23 wks + 0.70 24 wks + 0.37 25 wks + 0.07	40 weeks <sup>b</sup> 6 years			-2.6 ± 1.15 -1.18

a as defined <10<sup>th</sup> percentile for weight at birth b postmenstrual age c as defined <-2.0 SDS for weight and/or height d as defined < 3<sup>rd</sup> percentile for weight e as defined < 25<sup>th</sup> percentile for weight

An increasing number of studies have reported data on adult height in preterm born individuals (table 3), but one should note that these studies only concern the very preterm and very or extremely low birth weight population, from which severely handicapped subjects are usually excluded. Growth data of individuals born preterm at a more advanced gestational age are scarce. Mean height of young adults born (very) preterm is shorter than that of term-born controls<sup>65,67,94</sup> and than target height.<sup>65</sup> Again, preterm infants born SGA are at higher risk of short stature, as only 46% of SGA-VLBW born young adults showed complete catch-up.<sup>66</sup>

#### **Adult weight and body composition**

Young adults born (very) preterm weigh less than the average population<sup>65</sup> (6.5 and 7.1 kg for males and females).<sup>65</sup> However, catch-up for weight of individuals born preterm is generally more pronounced than catchup in height (table 3). The mean BMI that has been reported in young adulthood is close to that of the reference population in most studies,<sup>65,95</sup> but lower<sup>94</sup> and higher<sup>3,67</sup> percentages of overweight have been reported, particularly in females.

One of the cohorts that has been followed up to young adulthood is the POPS cohort, consisting of infants born very preterm and/or with a very low birth weight.<sup>95,96</sup> In young adulthood, the average height SDS was -0.55 and -0.60 for males and females respectively, but BMI SDS was -0.10 and -0.17, and waist circumference SDS +0.24 for males and even +0.73 for females.<sup>95</sup> This indicates that the altered fat distribution at term age noted in preterm born infants might persist into adulthood, which might in turn contribute to a less favourable cardiovascular disease risk profile.<sup>47,95</sup>

#### **Late metabolic consequences of preterm birth**

Since the original observations of Barker and collaborators,<sup>97-100</sup> a wealth of studies have shown an association between low birth weight and adult metabolic diseases like obesity, type 2 diabetes, hypertension and cardiovascular incidents. More recently, it has been shown that especially the combination of small size at birth followed by increased catch-up growth in later life is detrimental for adult cardiovascular health.<sup>101-103</sup> Although these findings have been confirmed in animal studies, one should realize that in the human all 'evidence' results from epidemiological studies. The mechanism behind these associations has remained obscure thus far.<sup>104,105</sup> In the majority of the original publications, no clear distinction has been made between low birth weight due to term SGA or due to preterm birth, and the number of preterm subjects included is very low.

It has been speculated that individuals born preterm experience similar metabolic consequences in adult life as term born individuals with low birth weight.<sup>106,107</sup> The third trimester is a critical developmental period, and malnutrition during this time span has been related to reduced adult glucose tolerance in the Dutch famine studies.<sup>108</sup> Infants born preterm almost invariably

experience postnatal growth failure during this time window, often followed by later catch-up growth. Evidence for this similarity in adverse metabolic sequelae in adulthood between term SGA infants and infants born preterm mostly results from studies on glucose tolerance and blood pressure during childhood and young adulthood in preterm or VLBW survivors (recently reviewed by Hofman et al.<sup>106</sup>). Both in the neonatal period<sup>109</sup> and in childhood,<sup>110,111</sup> individuals born (very) preterm have a decreased insulin tolerance.

Survivors of preterm birth are still too young to allow for studying the effect on full-blown cardiovascular disease, and studies are limited to early markers of cardiovascular disease in young adulthood. In a recent study, glucose tolerance was reduced in a cohort of VLBW young adults,<sup>46</sup> and in the POPS study we found that insulin sensitivity at 19 years of age in individuals born very preterm was particularly decreased if BMI in young adulthood was relatively high.<sup>112</sup> No associations were observed between early growth and intima-media thickness.<sup>113</sup> With respect to blood pressure, we found an increased incidence of hypertension and borderline hypertension,<sup>114</sup> in accordance with other studies,<sup>115,116</sup> irrespective of nephrocalcinosis.<sup>117</sup>

## Conclusion

Individuals born preterm usually show a substantial growth failure in the early postnatal period, which is usually followed by catch-up growth over 2–3 years, but a slightly lower mean adult height than term born peers. Although catch-up growth is beneficial for neurodevelopmental outcome, it might lead to adverse metabolic consequences in adulthood. Future follow-up studies on these effects are warranted.

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# 3

**A regression model with unexplained residuals was preferred in the analysis of the fetal origins of adult diseases hypothesis**

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## **Abstract**

### **Background and objective**

A continued controversy exists whether the assessment of the influence of low birth weight on adult blood pressure necessitates adjustment for adult weight in the analysis on the fetal origins of adult diseases hypothesis. Here we first explain the difficulty in understanding an adjusted multivariate regression model, and then propose another way of writing the regression model to make the interpretation of the separate influence of birth weight and changes in weight later in life more straightforward.

### **Study design and setting**

We used a multivariate regression model containing birth weight (standard deviation score; SDS), and residual adult weight (SDS) to explore the effect on blood pressure (or any other outcome) separately. Residual adult weight was calculated as the difference between actual adult weight and the expected adult weight (SDS) given on a certain birth weight (SDS).

### **Results**

The coefficients of birth weight and residual adult weight show directly the effect on the analyzed outcome variable.

### **Conclusions**

We prefer to use this regression model with unexplained residuals when the adjusted variable is in the causal pathway in the analyses of data referring to the fetal origins of adult diseases hypothesis.

## **Introduction**

In the literature on the fetal origins hypothesis, a continued controversy exists whether the assessment of the influence of low birth weight on adult blood pressure necessitates adjustment for adult weight.<sup>1,2</sup> The controversy was fueled by the meta-analysis of Huxley et al.,<sup>3</sup> who described little or no relation between birth weight and adult blood pressure if unadjusted for adult weight, and implied that such adjustment might even be misleading. The effect of adding adult weight as a variable in the regression of blood pressure on weight at birth is intricate: a review by Lucas et al.<sup>4</sup> suggested that such a regression model should in fact be interpreted as the influence of a change in weight between birth and adulthood -and no longer as the influence of birth weight. Nonetheless, the interpretation of data by this concept remains confusing.

Our objective here is first to explain the difficulty in understanding the adjusted regression for the general reader, and then to propose another way of writing the regression model to make the interpretation of the separate influence of birth weight and changes in weight later in life more straightforward. We will explain the model not only conceptually and algebraically, but also by an example on data from an ongoing study on the effect of birth weight on blood pressure. Validation of the model in future analysis is warranted.

## **The adjusted regression analysis**

Originally the association between birth weight and adult blood pressure was analyzed mainly without adjustments for additional variables.<sup>5</sup> Later, it was shown that subjects born with low birth weight tended to gain more weight compared with subjects born with a normal birth weight. Weight gain alone was also associated with an increased risk for high blood pressure. Therefore, adult weight was seen as a potential confounder in the analysis, and adjustment for it became more common.<sup>6</sup> Some studies, however, found a significant association between birth weight and adult diseases only after adjustment for adult weight.<sup>7</sup> Therefore, the need for a multivariate regression model incorporating the effects of both birth weight and adult weight seemed to be the most promising statistical approach. Still, the interpretation of what was achieved by this adjustment remained unclear.

Lucas et al.<sup>4</sup> outlined the consequences of adjustment for adult weight (or length) in a multivariate regression analysis. They proposed using four regression models to analyze the data (Table 1), and stated that in the adjusted models the early and later size of the subjects can no longer be interpreted as stand-alone variables: adjusting early size for later size is a measure of change in size between the earlier and later measurement. In their terminology,

the *early model* describes the relation between early size (i.e., birth weight, or bw) and outcome ( $Y = \alpha_1 + \beta_1 X_{bw}$ ). In the *late model*, the relation between later size (i.e., adult weight, or aw) and outcome is studied ( $Y = \alpha_2 + \gamma_2 X_{aw}$ ). The *combined model* (adding later size to the early model) can be interpreted as describing the relation between change in size and outcome ( $Y = \alpha_3 + \beta_3 X_{bw} + \gamma_3 X_{aw}$ ), as argued by Lucas et al.<sup>4</sup> (see Table 1). Adding the interaction term of early and later size yields the *interaction model*, allowing exploration of whether early size affects the relation between later size and outcome ( $Y = \alpha_4 + \beta_4 X_{bw} + \gamma_4 X_{aw} + \delta_4 X_{bw} X_{aw}$ )<sup>4</sup>. Note, however, that the changing coefficients (in size and direction) in the combined and the interaction models compared to the early model result in a complicated interpretation. Indeed, the effect of later size is codetermined by the effect of early size on outcome, because adult weight is determined in part by birth weight, which influences the coefficients in the combined model. This also implicitly assumes a quadratic relation between birth weight and outcome in the interaction model, at least under the assumption that birth weight and adult weight are linearly related (Table 1).

**Table 1.** Interpretation of the multivariate regression model of Lucas et al.<sup>4</sup>

Model description	Equation
Early model, regression analysis of birth weight (bw) to outcome measure	$Y = \alpha_1 + \beta_1 X_{bw}$
Late model, regression analysis of adult weight (aw) to outcome measure	$Y = \alpha_2 + \gamma_2 X_{aw}$
Combined model, adding later size to early model	$Y = \alpha_3 + \beta_3 X_{bw} + \gamma_3 X_{aw}$
Interaction model, adding the interaction of early and adult size to the combined model	$Y = \alpha_4 + \beta_4 X_{bw} + \gamma_4 X_{aw} + \delta_4 (X_{bw} X_{aw})$
Interaction model, with subtraction of the means	$Y = \alpha_4 + \beta_4 X_{bw} + \gamma_4 X_{aw} + \delta_4 [(X_{bw} - \bar{X}_{bw})(X_{aw} - \bar{X}_{aw})]$

*Variables:*  $X_{bw}$  birth weight;  $X_{aw}$  adult weight;  $X_{bw} X_{aw}$  interaction of birth weight and adult weight;  $Y$  expected outcome;  $\alpha$  intercept;  $\beta$ ,  $\gamma$  and  $\delta$  coefficients.

### Which analysis meets the researcher's concerns?

Whether later size (e.g., adult weight) is a confounder in the analysis of early size (e.g., birth weight) and adult diseases, such as hypertension, or is rather a factor in the causal pathway is an ongoing debate in the literature. Adjustment for adult weight might not be justified after all.<sup>1-3</sup> Whatever the causal explanation, birth weight is positively correlated with adult weight and adult weight is correlated with adult blood pressure; therefore, we do first of all expect that any positive relation between birth weight and adult blood pressure will be attenuated upon adding adult weight to the model (the coefficient of birth weight will become closer to zero). Next, according to Lucas et al.,<sup>4</sup> it might be those who grew more than expected (i.e., attained greater adult weight for a given birth weight) who would develop the higher blood pressures. This would reverse the already attenuated relation with birth weight into a negative relation.

As researchers, we remain interested in the separate contribution of birth weight (reflecting prebirth influences) and change in weight from birth to adulthood (reflecting early life influences). Thus, we want to have an estimate of both. We want first an estimate of the effect of birth weight alone, and second, what we really want to know is the effect of someone growing more in weight than would be expected from a given birth weight. In a statistical analysis this can be accomplished in a single model by first calculating the expected adult weight, or  $eaw$ , based on birth weight ( $X_{eaw} = \alpha_0 + \beta_0 X_{bw}$ ), and then subtract expected adult weight from actual adult weight - which is in effect the calculation of a residual ( $X_{res} = X_{aw} - X_{eaw}$ ) (Table 2). Adding this residual increase in weight in a regression model of blood pressure on birth weight has three advantages. First, it leaves the coefficient of birth weight unchanged (because the effect of birth weight on adult weight is already taken out of the residual). Second, it gives us an insight into the additional influence of growing more in weight than expected upon the adult blood pressure. Third, the two variables in the regression model (birth weight and the residual increase in weight) are now independent, because the residual cannot be predicted from birth weight. Therefore, the interaction model does not assume a quadratic relation anymore. Li et al.<sup>8</sup> earlier described this model in the analyses of a Guatemalan study in which the association between prenatal and postnatal growth and adult body composition was studied; however, no algebraic explanation of this model was shown.

The proposed technique is not unique to the problems of interpreting regression in the fetal origins of adult diseases hypothesis. It has been used in social sciences literature under the name of *residualized gain score*.<sup>9,10</sup>



It should be noted that algebraically the combined model of Lucas et al.<sup>4</sup> is the same as the combined model using unexplained residuals (Appendix A); however, the effect of birth weight and residual postnatal growth is directly shown by the coefficients of the proposed unexplained residual regression model. In both models, for the interaction model we suggest to multiply not just the two variables, but first subtract the mean of that variable. In the model of Lucas et al.,<sup>4</sup> this becomes  $(X_{bw} - \bar{X}_{bw})(X_{aw} - \bar{X}_{aw})$ ; in the proposed model this becomes  $(X_{bw} - \bar{X}_{bw})(X_{res} - \bar{X}_{res})$ . As the mean of a residual is zero, this can be rewritten in  $(X_{bw} - \bar{X}_{bw})X_{res}$ .

Next to the model of Lucas et al.<sup>4</sup>, other simplified models are suggested to use in the analysis of the fetal origins of adult diseases hypothesis to measure the effect of change in weight. When researchers think about the problem, they often intuitively propose to subtract adult weight (standard deviation score; SDS) and birth weight (SDS) as a measure of change in weight and add this to birth weight (SDS) in a multivariate regression model. The problem

**Table 2.** Interpretation of unexplained residual regression model

Model description	Equation
Early model, regression analysis of early weight to outcome measure	$Y = \alpha_1 + \beta_1 X_{bw}$
Late unexplained residual model, regression analysis of residual of expected adult weight to outcome measure <sup>a</sup>	$Y = \alpha_2 + \gamma_2 X_{res}$
Combined unexplained residual model, adding the residual of the expected adult weight to early model	$Y = \alpha_3 + \beta_3 X_{bw} + \gamma_3 X_{res}$
Interaction unexplained residual model, adding the interaction the difference between birth weight and the mean birth weight and the difference between the residual and the mean residual of the expected later size to the combined unexplained residual model <sup>b</sup>	$Y = \alpha_4 + \beta_4 X_{bw} + \gamma_4 X_{res} + \delta_4 [(X_{bw} - \bar{X}_{bw})(X_{res} - \bar{X}_{res})]$ in which $\bar{X}_{res}$ is zero.

*Variables:*  $X_{bw}$  expected birth weight;  $X_{res}$  residual of expected adult weight, based on birth weight;  $(X_{bw} - \bar{X}_{bw})(X_{res} - \bar{X}_{res})$ , interaction of birth weight and residual of expected adult weight;  $Y$ , expected outcome;  $\alpha$ , intercept;  $\beta$ ,  $\gamma$ , and  $\delta$ , coefficients.

<sup>a</sup> First, expected adult weight  $X_{eaw}$  is calculated, based on birth weight ( $\alpha_0 + \beta_0 X_{bw}$ ). Then, the residual for expected adult weight is calculated as  $X_{res} = (X_{aw} - X_{eaw})$ . This leads to the equation in column 2.

<sup>b</sup> In the interaction unexplained residual model,  $\beta_1 = \beta_3 = \beta_4$  and  $\gamma_2 = \gamma_3 = \gamma_4$ .

with this model is the phenomenon of regression to the mean. The relative position of subjects with low birth weight will tend to increase and that of subjects with high birth weight will tend to decrease over time. This phenomenon is not present in the unexplained residual model, because in the calculation of adult weight residuals out of birth weight we force the residuals not to be related to birth weight. The coefficient of birth weight in a linear regression model of adult weight residuals is exactly zero (with very small confidence interval and a *P*-value of exactly 1).

Second, it has also been suggested to use population-based SD scores instead of calculating the residual of expected adult weight (SDS). However, the subjects studied in research concerning the fetal origins of adult diseases hypothesis are mostly not comparable to the general population, because of an overrepresentation of the low birth weight subjects. Subjects with low birth weight have different growing patterns. Therefore, for most studies it is not recommended to use population-based SD scores to calculate expected adult weight (SDS) and weight gain (SDS). In addition, it takes about 3 years after birth before an individual will track on his or her centile, especially in low birth weight infants. If the population-based reference standards were to be used as a measure for expected adult weight (SDS), in which the mean adult weight (SDS) will be zero, low birth weight (SDS) subjects will tend to have a negative residual for adult weight, because of their suboptimal growth. Then, the residual would not reflect the correct variable to answer our second question: what is the effect of someone growing more in weight than would be expected from a given birth weight? So, calculating the residual adult weight out of birth weight should be performed with the expected adult weight from the group of subjects that are used in the study.

## **Conclusion, and proposal**

Algebraically, the combined model of Lucas et al.<sup>4</sup> and our combined model with the residuals increase in weight can be rewritten in terms of each other, except for the situation where an interaction term is entered (see Appendix A). In the proposal by Lucas et al.<sup>4</sup>, however, one needs two separate models: first estimating the coefficient from the early model, and then looking at the coefficient for attained weight in the combined model (without paying attention to the coefficient of birth weight in that combined model, because the latter has become meaningless). For this reason, we prefer the proposed model with residuals because it permits in a more straightforward way to estimate the effect of birth weight and the effect of additional weight gain in a single model. We also prefer to use the interaction model containing the unexplained residuals, because no quadratic relation is assumed and because in principle all coefficients show their own effect without mutual influence (Table 2). Therefore, the interpretation of the model with the unexplained residuals is easier. An example with numerical data from an ongoing study in the Netherlands is given in Appendix B, including Tables B1 and B2.

In conclusion, we prefer to use regression model with unexplained residuals when the adjusted variable is in the causal pathway in the analyses of data referring to the fetal origins of adult diseases hypothesis.

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### Appendix A. Derivations

To rewrite the combination unexplained residual model in the combination model of Lucas et al.,<sup>4</sup> where  $Y$  is the expected outcome;  $\alpha$  is the intercept;  $\beta$  is a coefficient;  $X_{bw}$  is the birth weight;  $X_{aw}$  is the adult weight;  $X_{eaw}$  is the expected adult weight, based on early size ( $\alpha_0 + \beta_0 X_{bw}$ ); and  $X_{res}$  is the residual of expected adult weight ( $X_{aw} - X_{eaw}$ ):

$$Y = \alpha_1 + \beta_1 X_{bw} + \gamma X_{res} \quad (\text{the unexplained residual model})$$

$$Y = \alpha_1 + \beta_1 X_{bw} + \gamma [X_{aw} - (\alpha_0 + \beta_0 X_{bw})]$$

$$Y = \alpha_1 + \beta_1 X_{bw} + \gamma X_{aw} - \gamma \alpha_0 - \gamma \beta_0 X_{bw}$$

$$Y = (\alpha_1 - \gamma \alpha_0) + (\beta_1 - \gamma \beta_0) X_{bw} + \gamma X_{aw}$$

$$Y = \alpha' + \beta' X_{bw} + \gamma' X_{aw} \quad (\text{the Lucas et al.}^4 \text{ model})$$

$$\alpha' = \alpha_1 - \gamma \alpha_0$$

$$\beta' = \beta_1 - \gamma \beta_0$$

$$\gamma' = \gamma$$

To add the interaction term  $(X_{bw} - \bar{X}_{bw}) * (X_{aw} - \bar{X}_{aw})$  into the Lucas et al.<sup>4</sup> model, first suppose that  $X_{aw}$  is exactly linearly related to  $X_{bw}$ . Then, where  $\varepsilon$  is the residual:

$$X_{aw} = \alpha_0 + \beta_0 X_{bw} + \varepsilon$$

and

$$\bar{X}_{aw} = \alpha_0 + \beta_0 \bar{X}_{bw}$$

$$\text{So, } (X_{aw} - \bar{X}_{aw}) = (\alpha_0 + \beta_0 X_{bw} + \varepsilon) - (\alpha_0 + \beta_0 \bar{X}_{bw})$$

which can be rewritten as:

$$(X_{aw} - \bar{X}_{aw}) = \beta_0 (X_{bw} - \bar{X}_{bw}) + \varepsilon$$

Adding this to the interaction term

$$(X_{bw} - \bar{X}_{bw}) * (X_{aw} - \bar{X}_{aw}),$$

the equation will be:

$$(X_{bw} - \bar{X}_{bw}) * (\beta_0 (X_{bw} - \bar{X}_{bw}) + \varepsilon)$$

This can be rewritten as:

$$\beta_0 (X_{bw} - \bar{X}_{bw})^2 + (X_{bw} - \bar{X}_{bw}) * \varepsilon$$

Here, the quadratic relation between birth weight and outcome is shown.

To add the interaction term into the unexplained residuals model:

$$(X_{bw} - \bar{X}_{bw})(X_{res} - \bar{X}_{res}) = (X_{bw} - \bar{X}_{bw})X_{res}$$

In this model,  $X_{res}$  (the residual of expected adult weight) is independent of  $X_{bw}$  (birth weight).

All coefficients show the unadjusted effect of the variable on the outcome variable.

## Appendix B

Example of regression analysis according to Lucas et al.<sup>4</sup> and the *unexplained residual model* (Tables B1 and B2): In a prospective study the systolic blood pressure at adult age was measured. Birth weight standard deviation scores ( $BW_{SDS}$ ) and adult weight standard deviation scores ( $AW_{SDS}$ ) were known.

In Table B1, the change in estimated coefficients is shown in both the combined as the interaction model, both with and without the subtractions of means, when the model of Lucas et al.<sup>4</sup> is used. In the early model, birth weight (SDS) is related to blood pressure with a coefficient of 0.361. When adult weight (SDS) is added to the model the coefficient for birth weight (SDS) changed into a negative one (-0.0928). This is a result of the relation between birth weight (SDS) and adult weight (SDS). This change in the estimated coefficient is confusing for many authors; which coefficient is giving information about the relation between birth weight (SDS) and blood pressure?

In the combined unexplained residuals model, these estimated coefficients do not change (Table B2) when adult weight (SDS) is added to the model. The coefficient for birth weight and residual weight gain shift slightly in the interaction model in comparison with the combined weight residual model: probably this is due to non-exact-linear correlation between birth weight and weight gain.

The  $\delta_4$  coefficient does not change much in our example. The reason is that  $X_{bw}$  is not related to systolic blood pressure. Therefore, the  $\delta_4$  coefficient in the model of Lucas et al.<sup>4</sup> is comparable to the  $\delta_4$  coefficient in our model. When  $X_{bw}$  would be quadratically related to blood pressure, the  $\delta_4$  coefficient would differ much in both models.

**Table B1.** Estimated coefficients in our example when the Lucas et al.<sup>4</sup> model is used, with two types of interaction

		$\beta$	$\gamma$	$\delta$
<b>Model of Lucas et al. <sup>4</sup></b>	$\alpha$	$X_{bw}$	$X_{aw}$	$X_{bw}X_{aw}$
Early	122.943 ( $\alpha_1$ )	0.361 ( $\beta_1$ )		
Late	123.908 ( $\alpha_2$ )		2.069 ( $\gamma_2$ )	
Combined	123.743 ( $\alpha_3$ )	-0.0928 ( $\beta_3$ )	2.096 ( $\gamma_3$ )	
Interaction	123.771 ( $\alpha_4$ )	-0.0078 ( $\beta_4$ )	2.231 ( $\gamma_4$ )	0.120 ( $\delta_4$ )
Interaction with subtracted means	123.710 ( $\alpha_4$ )	$X_{bw}$	$X_{aw}$	$(X_{bw} - \bar{X}_{bw})(X_{aw} - \bar{X}_{aw})$
		-0.0766 ( $\beta_4$ )	2.125 ( $\gamma_4$ )	0.120 ( $\delta_4$ )

Variables:  $\alpha$ , intercept;  $\beta$ ,  $\gamma$ , and  $\delta$ , coefficients;  $X_{bw}$  expected birth weight (SDS);  $X_{aw}$  expected adult weight (SDS)

**Table B2.** Estimated coefficients in our example when the unexplained residual model is used

		$\beta$	$\gamma$	$\delta$
<b>Model unexplained residuals</b>	$\alpha$	$X_{bw}$	$X_{res}$	$(X_{bw} - \bar{X}_{bw})X_{res}$
Early	122.943 ( $\alpha_1$ )	0.361 ( $\beta_1$ )		
Late	123.623 ( $\alpha_2$ )		2.096 ( $\gamma_2$ )	
Combined	123.943 ( $\alpha_3$ )	0.361 ( $\beta_3$ )	2.096 ( $\gamma_3$ )	
Interaction	123.943 ( $\alpha_4$ )	0.361 ( $\beta_4$ )	2.121 ( $\gamma_4$ )	0.102 ( $\delta_4$ )

Variables:  $\alpha$  intercept;  $\beta$  coefficient;  $X_{bw}$  birth weight (SDS);  $X_{res}$  residual of expected adult weight (SDS);  $\bar{X}_{res}$  equals zero in interaction term  $(X_{bw} - \bar{X}_{bw})(X_{res} - \bar{X}_{res})$ . Expected adult weight ( $X_{eaw}$ ) = - 0.382 + 0.216  $X_{bw}$ . Residual of adult weight ( $X_{res}$ ) =  $X_{aw} - X_{eaw}$

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# 4

## **Reliability studies can be designed more efficiently by using variance components estimates from different sources**

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## **Abstract**

### **Objectives**

Reliability studies are frequently organized within the context of a large (multicenter) study, with only a small sample of subjects measured by the observers of the large study. To estimate interobserver reliability, data from the large study are not frequently used. In this article, the advantages of combining data from the reliability study and the large study to improve the estimation of intra-class correlation coefficients (ICCs) are highlighted.

### **Study design and setting**

This was done within the scope of estimating fat percentages in the Project On Preterm and Small-for-gestational-age infants-19 (POPS-19) study and with simulations. To calculate ICCs, three approaches were used: (1) the classical approach using data from a reliability study only, (2) the combined variances approach using inter-subject variances from the POPS-19 study, and (3) the maximum likelihood approach using all data.

### **Results**

The ICCs (95% confidence interval [CI]) for fat percentage calculated by the three approaches were 0.84 (0.57, 0.99), 0.94 (0.90, 0.97), and 0.94 (0.88, 0.97), respectively.

### **Conclusion**

The efficient use of data by combining data from a small reliability study with the data from the large study itself for the calculation of ICCs will lead to more precise ICCs.

## **Introduction**

The reliability of clinical measurements is an important issue in the design and interpretation of studies. A high degree of measurement error resulting in a poor reliability generally leads to underestimation of the strength of the associations studied. This affects the interpretation of results and can even lead to erroneous negative conclusions. To compensate for a lack of precision, sometimes a higher number of subjects is included or more repeated measurements per subject are obtained, but both are associated with less efficiency or more costs. In many large and often multicenter studies, reliability of clinical measurements can even be lower because multiple observers are involved in data collection.

Therefore, in large (multicenter) studies reliability of clinical measurements is sometimes assessed in special substudies to enhance the interpretation of the results of the main study. For example, Visser et al. studied the reliability of the Subjective Global Assessment of nutritional status<sup>1</sup> in a small substudy of the large multicenter NECOSAD cohort on risk factors for mortality in dialysis patients<sup>2</sup> whereas Klipstein-Grobusch et al. described the reliability of anthropometric measurements<sup>3</sup> assessed in the European Prospective Investigation into Cancer-Potsdam Study Cohort.<sup>4</sup> The classical approach in this situation is to perform a reliability study with a small, random sample of about at least 10 study participants (subjects) to be measured by all observers involved in the large study.<sup>5</sup> From the measurements in these reliability studies, indicators of reliability, for example intra-class correlation coefficients (ICCs), can be estimated.<sup>6</sup> In this approach, only data from the subjects participating in the reliability study are used, whereas the data from the large study are not used.

There are several methods to estimate ICCs by combining data from the reliability study and the large study. The first approach is to determine the interobserver and error variance in the reliability study and the inter-subject variance in the large study itself. This is in the line of Streiner and Norman who describe a formula to apply a known ICC to a different, more heterogenous population.<sup>7</sup> The second approach is to combine the data from both studies with maximum likelihood (ML) methods.

As these approaches are not frequently used in health science literature, the aim of this article was to highlight the advantages of combining data from a reliability study with data from the large study itself for the calculation of ICCs. For this purpose, we apply existing statistics to a novel context. The ICCs calculated in this way will be more accurate because of using data directly from the population of interest and also more precise because of the larger study population used. We will show this in a data set of the Project On Preterm and Small-for-gestational-age infants-19 (POPS-19) study,<sup>8</sup> and with simulations.

## Subjects and methods

### Study population

The POPS-19 study is a Dutch national prospective cohort study in young adults aged 19 years born before 32 weeks' gestation. Among other measurements, skinfold thickness was measured at four regions to determine fat mass and fat distribution in 403 19 years old. The POPS-19 study was organized as a multicenter study with 10 research centers all over the country and 15 observers.<sup>8</sup> When the POPS-19 study was started, a reliability study was organized with four healthy young adults who had their skinfolds measured in all 10 research centers by 13 out of the 15 POPS-19 observers. Due to practical circumstances (limited space in a small car for four people to travel about the whole country for various measurements, including time consuming ones), this reliability study only had a small sample size. In both studies, skinfold thickness measurements were performed in duplicate on the left side of the body at the triceps, biceps, subscapular, and iliacal regions. In the final analyses, the mean of each duplicate measurement was used. Fat percentage was computed from the sum of the four skinfolds.<sup>9</sup> The study was approved by the medical ethics committee of all participating centers, and written informed consent was obtained from all participants.

### Statistical analysis

Suppose that there are  $n$  subjects in the large study where each subject is measured by one observer. Furthermore, let  $J$  be the number of observers and  $I$  be the number of subjects in the reliability study. For some given variable  $X$ , we denote by  $X_{ij}$  the measurement of the  $j$ th observer made on the  $i$ th subject for  $i = 1, \dots, I, j = 1, \dots, J$ . We modeled the data as

$$Z_{ij} = \mu + \alpha_i + \beta_j + \varepsilon_{ij} \quad (1)$$

where  $\mu$  is some fixed parameter, and where  $\alpha_i$  the subject effect,  $\beta_j$  the observer effect and  $\varepsilon_{ij}$  are independent random effects, normally distributed with mean 0 and with between-subject variance  $\sigma_S^2$ ; interobserver variance  $\sigma_O^2$ ; and error variance  $\sigma_E^2$ ; respectively.

Interobserver reliability was measured with:

$$\text{ICC}_{\text{inter}} = \frac{\sigma_S^2}{\sigma_S^2 + \sigma_O^2 + \sigma_E^2} \quad (2)$$

We consider three different approaches to estimate the variance components  $\sigma_S^2$ ;  $\sigma_O^2$ ; and  $\sigma_E^2$  and  $\text{ICC}_{\text{inter}}$ . For all approaches logarithmical transformations of the skinfold measurements were performed because of the skewed distribution of errors of these variables.

*Classical approach*

In this approach, all variance components are estimated using only the data from the reliability study. The design of the reliability study is balanced (all subjects are measured by all observers) and variance components can be estimated using classical analysis of variance, which yields ICCs according to equation (2) and confidence intervals (CIs). See for details Shrout and Fleiss (formula 2, 1): ICC with random observer effect, single ratings.<sup>6</sup>

*Combined variances approach*

Here,  $\sigma^2_{\text{O}}$  and  $\sigma^2_{\text{E}}$  are estimated from the reliability study, and the inter-subject variability  $\sigma^2_{\text{S}}$  from the multi-center data. To estimate the inter-subject variability, we estimated the total variance  $\sigma^2_{\text{T}}$  of the variable X by the variance from the data of the large study. We assumed that  $\sigma^2_{\text{S}} = \sigma^2_{\text{T}} - \sigma^2_{\text{O}} - \sigma^2_{\text{E}}$ . Subsequently, estimates of ICCs were obtained by plugging-in estimates of variance components in equation (2). Ninety-five percent CIs of these ICCs can be obtained using the delta method (details are given in Appendix A), but is not straightforward to carry out because an estimate of the covariance matrix of the estimated variance components is needed.

*ML approach*

Both data sets are pooled and ML methods are used. Combining the data of both studies yields a data set with  $(n + l)$  subjects, where some of the subjects in this data set are measured by all observers, others by only one. In fact, one can see this as a very large reliability study with many missing observations (because not all subjects are measured by all observers). In this design, variance components can be estimated using ML or restricted maximum likelihood (REML). We used REML, as the REML estimator is known to be in general less biased than the ML estimator,<sup>10</sup> (page 66–69). This can be carried out with software for linear mixed models like SAS PROC mixed (SAS institute Inc., Cary, NC, USA). This yields estimates of  $\sigma^2_{\text{S}}$ ;  $\sigma^2_{\text{O}}$ ; and  $\sigma^2_{\text{E}}$  and of the covariance matrix of the estimates. The ICC is calculated by plugging these estimates into equation (2). Again 95% CI can be obtained using the delta method (see Appendix A).

In the Section 3, the three different approaches to the estimation of ICCs will be applied on the POPS-19 data. We also compare the efficiency of the different approaches in a simulation study using SAS version 8.2 (SAS institute Inc., Cary, NC, USA). We simulated data from model (1), with mean  $\mu=0$ , and with variance of the subject, observer and residual effect equal to  $\sigma^2_{\text{S}}=8$ ,  $\sigma^2_{\text{O}}=1$ , and  $\sigma^2_{\text{E}}=1$ , respectively. This implies that the ICC = 0.80. The parameter values were based upon the values of the triceps skinfold in the study example mentioned above, in which ICCs were all around 0.80 with quite similar observer and residual variances. Based on the POPS-19 example, we assumed a small reliability study with 4 subjects measured by 10 observers and a large study with 400 subjects each measured by only one

observer. Data were simulated 1,000 times from this setup. Because of the small number of subjects in the POPS-19 reliability study, we also repeated simulations with 10, 25, and 50 subjects in the reliability study.

## Results

General characteristics of the subjects from the POPS-19 study and the reliability study are displayed in Table 1. On average, the four subjects of the reliability study were somewhat older, and had greater body mass index (BMI) and sum of skinfolds than the POPS-19 participants. The anthropometric characteristics of all four subjects were well in the range of the POPS-19 participants.

**Table 1.** Characteristics of the study participants; means (SD)

Characteristics	POPS-19 study ( $n = 403$ )	Reliability study ( $n = 4$ )
Sex (% male)	46.4	50.0
Age	19.3 (0.18)	24.6 (3.6)
(Min, Max)	(19.1, 20.0)	(22.1, 30.0)
BMI (kg/m <sup>2</sup> )		
Males	21.7 (3.1)	25.3 (1.5)
(Min, Max)	(14.8, 34.7)	(24.3, 26.4)
Females	21.8 (3.4)	21.2 (1.5)
(Min, Max)	(15.6, 38.9)	(20.2, 22.3)
Sum of four skinfolds (mm)		
Males	41.2 (20.5)	81.2 (23.6)
(Min, Max)	(16.0, 130.5)	(64.6, 97.9)
Females	62.2 (22.6)	70.9 (0.57)
(Min, Max)	(7.3, 149.0)	(70.5, 71.3)

The variance components, ICCs, and 95% CIs of the triceps skinfold and fat percentage are presented in Table 2. Due to the small estimated between-subject variance in the reliability study, the classical approach yields lower ICCs compared with the two other approaches. This effect is more pronounced for the triceps skinfold than for the fat percentage. Both with the combined variances approach and with the ML approach, the obtained 95% CIs are much smaller than estimated with the classical approach. The ML approach yields larger estimates of both the between observer and measurement error variance with a slightly larger estimated 95% CI. The other skinfold measurements and derived estimates of body composition showed comparable results with regard to the differences between the various approaches (data not shown).

**Table 2.** Variance components and ICCs estimated in the POPS-19 data according to the various approaches

Outcome measure and method	$\sigma^2_S$	$\sigma^2_O$	$\sigma^2_E$	ICC	95% CI
Triceps skinfold thickness <sup>a</sup>					
Classical approach	0.00675	0.00249	0.00299	0.55	0.24 - 0.95
Combined variances approach	0.0442	0.00249	0.00299	0.89	0.82 - 0.93
REML approach	0.04151	0.00391	0.00354	0.85	0.74 - 0.91
Fat percentage					
Classical approach	22.0	2.85	1.48	0.84	0.57 - 0.99
Combined variances approach	70.9	2.85	1.48	0.94	0.90 - 0.97
REML approach	71.8	3.27	1.67	0.94	0.88 - 0.97

a For all approaches, logarithmical transformations were performed because of the skewed distribution of errors of the variables.

The variance components, ICCs, and 95% CIs of the triceps skinfold and fat percentage are presented in Table 2. Due to the small estimated between-subject variance in the reliability study, the classical approach yields lower ICCs compared with the two other approaches. This effect is more pronounced for the triceps skinfold than for the fat percentage. Both with the combined variances approach and with the ML approach, the obtained 95% CIs are much smaller than estimated with the classical approach. The ML approach yields larger estimates of both the between observer and measurement error variance with a slightly larger estimated 95% CI. The other skinfold measurements and derived estimates of body composition showed comparable results with regard to the differences between the various approaches (data not shown).

**Table 3.** Results of 1,000 simulations to compare the three estimation approaches with different numbers of subjects in the reliability study

Number of subjects in the reliability study	Estimation approach	$\sigma^2_S$	$\sigma^2_O$	$\sigma^2_E$	ICC
		True parameters	8	1	1
4 (POPS-19 example)	1. Classical approach	6.34 (0.99; 20.95)	0.91 (0.19; 2.17)	0.98 (0.62; 1.49)	0.76 (0.32; 0.92)
	2. Combined variances approach	7.89 (6.52; 9.25)	0.91 (0.19; 2.17)	0.98 (0.62; 1.49)	0.81 (0.69; 0.88)
	3. REML approach	8.01 (6.84; 9.10)	0.94 (0.27; 2.01)	0.99 (0.63; 1.46)	0.80 (0.71; 0.86)
10	1. Classical approach	7.42 (2.75; 14.73)	0.94 (0.29; 1.93)	0.99 (0.74; 1.27)	0.79 (0.57; 0.89)
	2. Combined variances approach	7.90 (6.69; 9.13)	0.94 (0.29; 1.93)	0.99 (0.74; 1.27)	0.80 (0.71; 0.87)
	3. REML approach	8.00 (6.97; 9.06)	0.94 (0.32; 1.91)	0.99 (0.75; 1.27)	0.80 (0.73; 0.87)
25	1. Classical approach	7.67 (4.69; 12.11)	0.91 (0.35; 1.96)	0.99 (0.86; 1.16)	0.80 (0.68; 0.88)
	2. Combined variances approach	7.89 (6.76; 9.07)	0.91 (0.35; 1.96)	0.99 (0.86; 1.16)	0.80 (0.72; 0.86)
	3. REML approach	7.96 (6.98; 9.00)	0.91 (0.35; 2.00)	0.99 (0.86; 1.16)	0.81 (0.73; 0.86)
50	1. Classical approach	7.83 (5.45; 10.50)	0.89 (0.35; 1.96)	1.00 (0.89; 1.11)	0.80 (0.70; 0.87)
	2. Combined variances approach	7.86 (6.77; 9.08)	0.89 (0.35; 1.96)	1.00 (0.89; 1.11)	0.81 (0.71; 0.86)
	3. REML approach	8.00 (6.99; 8.93)	0.90 (0.34; 1.97)	1.00 (0.89; 1.11)	0.81 (0.72; 0.86)

The median and (between brackets) 5th and 95th percentiles of the 1,000 estimates are given.

The results of the simulation analyses are summarized in Table 3. When the number of subjects is small ( $l = 4$ ), the 90% ranges of the ICCs from the combined variances and the REML approach are much smaller than that of the ICC estimated with the classical approach. The REML approach is a little more precise with a smaller 90% range compared to the combined variances approach. The median value of the estimated inter-subject variance as shown in Table 3 was 6.34, much smaller than the true value of 8.00. The median estimates of the ICCs were all close to the true value of 0.80.

With increasing numbers of subjects measured, the median of the estimated inter-subject variances comes closer to the true parameter 8.00. For both 10 and 25 subjects, the ICCs estimated with the combined variance approach and the REML approach still have a considerably smaller 90% range than those estimated with the classical approach. With 50 subjects, this effect is less pronounced. These simulations show that using the REML approach with 10 subjects in the reliability study (ICC, 90%; range, 0.73–0.87) is at least as precise as measuring 50 subjects and using the classical approach (ICC, 90%; range, 0.70–0.87).

## **Discussion**

In this article, two approaches are described which improve the precision of the estimation of ICCs in the context of a reliability study organized within a large study. These approaches were compared with the classical approach, that is, estimating all variance components in the small reliability study. With a relatively simple method, the inter-subject variance is estimated in the large study itself, whereas the other variance components are estimated in a reliability study. The other method, which is somewhat more precise, uses ML on the combined data from both studies.

The advantage of these approaches is that they obviate two possible shortcomings of the estimation of ICCs according to the classical approach. Firstly, due to chance the subjects in the reliability study might not form a representative sample of the subjects in the large study with a different inter-subject variance. This situation in which an ICC is applied to a different, more heterogeneous population has been described by Streiner and Norman<sup>7</sup> page 147, and before by Lord and Novick,<sup>11</sup> page 130. In combined variance and ML approaches data of the population of interest, namely the large study, are used to estimate the inter-subject variability, circumventing this problem. Secondly, a relatively small number of subjects is used in the classical approach, whereas with our approaches in which all available data are used a more precise estimation can be carried out with smaller CIs as a result.



A limitation of our study is the small sample size of four subjects we had to use in the reliability study due to practical circumstances. We assume that measurement error in skinfold thicknesses is not remarkably different in 19 and 20–30 years old, but still the small size could have influenced the value of the inter-subject variance found. In contrast, the interobserver variance was based on measurements of 13 observers. In the simulations, it can be seen that the estimated inter-subject variance with four subjects in the reliability study could differ much from the real parameter, which shows the advantages of our approaches. We studied the generalizability of our results by repeating simulations with larger numbers of subjects as commonly used in reliability studies<sup>3, 5, 12</sup> and.<sup>13</sup> With 10 or 25 subjects, the inter-subject variance and ICC did not differ much between all approaches, but the combined variances approach and the REML approach are still preferable to the classical approach regarding the precision of the estimated ICC as reflected in the smaller 90% ranges.

For clarity, in this article we used the means of duplicate measurements, and modeled the data as  $X_{ij} = \mu + \alpha_i + \beta_j + \varepsilon_{ij}$ . However, the described approaches of calculating ICCs can also be extended to a model using the separate duplicate measurements on a subject, subdividing the error variance into variance due to observer–subject variance and residual error variance. This will give comparable results.

In conclusion, we have shown the value of our novel approaches to estimate more precise ICCs with the efficient use of combined data in the POPS-19 study and we suggest that this approach can also be used in other studies concerning the reliability of outcomes in a large study. It is important to have precise information about the interobserver reliability of the outcome measurements, because this will influence the associations found between determinant and outcome in the large study. Low reliability will give noise and dilution, or even confounding of the associations found. With our approaches more precise estimations of ICCs are obtained, and we suggest to take this innovation into account when designing future reliability studies in the context of a large study.

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## Appendix A

In this appendix, it is shown how a confidence interval can be calculated for an intra class correlation, using the delta method.

The intra class correlation is defined as:

$$ICC = \frac{\sigma_S^2}{\sigma_S^2 + \sigma_O^2 + \sigma_E^2}$$

In the maximum likelihood approach, the variance components are estimated by either ML or REML, which also yields an estimate of the covariance matrix of the estimates.

To obtain a more closely normally distributed variate, the ICC is transformed using the Fisher-Z transformation:

$$z = \log\left(\frac{1+ICC}{1-ICC}\right) = \log\left(\frac{2\sigma_S^2 + \sigma_O^2 + \sigma_E^2}{\sigma_O^2 + \sigma_E^2}\right)$$

For convenience, we use matrix notations. Let  $\tau$  be the vector of variance components:  $\tau = (\sigma_S^2 \ \sigma_O^2 \ \sigma_E^2)^T$ , where the superscript T indicates a transposed vector. The delta method gives that

$$\text{var}(\hat{Z}) \approx \left(\frac{\partial Z}{\partial \tau}\right)^T \text{var}(\hat{\tau}) \frac{\partial Z}{\partial \tau}, \quad (*)$$

with  $\text{var}(\hat{\tau})$  the covariance matrix of the estimated variance components. It is straightforward to show that:

$$\frac{\partial Z}{\partial \tau} = \frac{1}{2\sigma_S^2 + \sigma_O^2 + \sigma_E^2} \begin{pmatrix} 2 \\ -2\sigma_S^2/(\sigma_O^2 + \sigma_E^2) \\ -2\sigma_S^2/(\sigma_O^2 + \sigma_E^2) \end{pmatrix}$$

and this can be plugged in (\*) to obtain the variance of  $\hat{Z}$ . A 95% confidence interval for Z can be calculated by:

$$(\hat{Z} - 1.96\sqrt{\text{var}(\hat{Z})} \ \hat{Z} + 1.96\sqrt{\text{var}(\hat{Z})})$$

This interval can be transformed back to an interval for ICC. If lwb and upb are respectively the lower and upper bound of the 95% CI for Z, the 95% CI for the ICC is given by:

$$\left( \left( \frac{e^{lwb} - 1}{e^{lwb} + 1} \right), \left( \frac{e^{upb} - 1}{e^{upb} + 1} \right) \right).$$

In the combined variances approach, the total variance  $\sigma_T^2$  was estimated from the large study, while independently  $\sigma_O^2$  and  $\sigma_E^2$  were obtained from the reliability study. By writing

$ICC = \frac{\sigma_T^2 - (\sigma_O^2 + \sigma_E^2)}{\sigma_T^2}$ , the delta method can be applied in the same way to obtain confidence

intervals in this situation.

## Appendix B Supplementary material

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# 5

## **A practical approach to Bland-Altman plots and variation coefficients for log transformed variables**

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## **Abstract**

### **Objective**

Indicators of reproducibility for log-transformed variables can often not be calculated straightforwardly and are subsequently incorrectly interpreted.

### **Methods and Results**

We discuss meaningful Coefficients of Variation (CV) for log-transformed variables, which can be derived directly from the standard error of the log-transformed measurements. To provide easy interpretable Bland and Altman plots, we calculated limits of inter and intraobserver agreement (LA) for log-transformed variables and transform them back to the original scale. These LAs for agreement are subsequently plotted on the original scale in a conventional Bland and Altman plot. Both approaches were illustrated in a clinical example on the reproducibility of skinfold thickness measurements.

### **Conclusion**

In reproducibility, it is important to calculate meaningful CVs, LAs, and Bland–Altman plots for log-transformed variables. We provide a practical approach in which existing statistical methods are applied in the field of reproducibility, thus leading to parameters of reproducibility which can be interpreted on the original scale.

## Introduction

Reproducibility can be described as the repeatability of measurements in time or by different observers.<sup>1,2</sup> Several indicators of reproducibility are applied in literature, with Intraclass Correlation Coefficients (ICC), Coefficients of Variation (CV), and limits of agreement (LA) being most frequently used. An ICC is a relative measurement of reliability, in which variation due to measurement error is compared with the variation between subjects. In a CV, reliability is expressed as the variation between measurements in relation to the mean value of all measurements. In contrast, LAs provide direct information about the absolute measurement error, which is plotted against the mean of the two measurements in a Bland and Altman Plot. This agreement forms an important measurement property by itself.<sup>2</sup>

Before reproducibility can be determined, data are frequently log transformed to approximate normality because of a skewed distribution of errors. Although ICCs after log transformation can still be calculated straight forward by estimating variance components on the log transformed data, a problem arises with the calculation and interpretation of other indicators of reproducibility, both for reliability and agreement measurements. CVs calculated in the conventional way have no natural interpretation anymore when estimated on a log-transformed scale without an actual zero. Bland and Altman describe the calculation of limits of agreement on log-transformed data.<sup>3</sup> However, the advantage of the Bland and Altman plot as an easy interpretable indicator of reproducibility expressed in the absolute units of measurement used in the clinical situation doesn't apply anymore.

In this article we discuss methods to calculate meaningful and interpretable CVs and LAs on log-transformed data, applied in an example from a clinical study on the reproducibility of skinfold thickness measurements.

## Methods

### Design and notations

In studies on reproducibility, one usually has observers (or instruments) measuring subjects. For simplicity, we start by assuming that each observer measures each subject once and focus on interobserver variability. Later on, we also consider the situation when more measurements are taken, which can be used to assess intraobserver variability. We denote the clinical measurement of interest by  $X$  and write  $X_{ij}$  for the measurement of the  $j$ th observer made on the  $i$ th subject ( $i = 1, \dots, I, j = 1, \dots, J$ ).



In this article, we consider the situation that the distribution of  $X$  is skewed and that a log transformation is performed to obtain an approximately normal distribution. The log-transformed measurement is denoted by  $Z$ . Although natural logarithms are mathematically more convenient, we consider here the 10-log transformation, because this is the transformation most frequently used in the applied field:  $Z = {}^{10}\log(X)$ .

### Random effect models

Linear random effect models are often used to analyze this kind of data. Here we assume that the log-transformed variable  $Z$  follows the following linear random effect model:

$$Z_{ij} = \mu + \alpha_i + \beta_j + \varepsilon_{ij} \text{ [Model a]}$$

where  $\mu$  is some fixed parameter, and where  $\alpha_i$ , the subject effect,  $\beta_j$ , the observer effect, and  $\varepsilon_{ij}$  are independent random effects, normally distributed with mean 0 and with between-subject variance  $\sigma_s^2$ , interobserver variance  $\sigma_o^2$ , and error variance  $\sigma_e^2$ , respectively. In studying interobserver reproducibility, the interobserver variance  $\sigma_o^2$  and error variance  $\sigma_e^2$  are expressed in relationship to the between-subject variance  $\sigma_s^2$ .

### Coefficient of variation

The coefficient of variation expresses the standard deviation as a percentage of the mean. It is a relative, unit-free measure, but it has only a useful interpretation if the measurement scale is positive, with value 0 the minimum value. For example, a CV for height or weight has a clear interpretation, but a CV for temperature measured in degrees Celsius or Fahrenheit not, because temperatures can be negative and the value 0 is not an absolute minimum.

When assessing the interobserver reproducibility, one would like to relate the mean of the observations to the spread of the measurements from different observers on the same subject. This measurement error between observations equals  $\sqrt{(\hat{\sigma}_o^2 + \hat{\sigma}_e^2)}$ , and is sometimes called the agreement standard error of the measurement:  $SEM_{\text{agreement}}$ .<sup>2</sup> In the linear random effects

model, the interobserver CV would be calculated by  $100\% \times \frac{\sqrt{(\hat{\sigma}_o^2 + \hat{\sigma}_e^2)}}{\bar{Z}}$ , with  $\bar{Z}$  the

sample mean of measurements of  $Z$  and  $\sigma$  indicates the estimate of  $\sigma$ . However, it makes no sense to calculate this CV for  $Z$ , since on the log scale, 0 is no absolute minimum. Values of  $X$  smaller than 1 correspond to values of  $Z$  smaller than 0, and it is well possible that  $Z$  is 0 or even negative.

Therefore, CV should be defined on the original scale. It can easily be shown, using Taylor expansion, that the standard deviation of a naturally log-transformed variable is approximately equal to the CV on the original scale. Therefore the  $SEM_{\text{agreement}}$  of the natural-log transformed measurement is quite commonly used as interobserver CV on the original scale. Here, we

use as interobserver coefficient of variation,  $CV_{\text{inter}} = 100\% \times \ln(10) \sqrt{(\hat{\sigma}_O^2 + \hat{\sigma}_E^2)}$ , where  $\sqrt{(\hat{\sigma}_O^2 + \hat{\sigma}_E^2)}$  is the spread of the log-transformed measurements from different observers on the same subject. The value  $\ln(10)$  is needed since we consider 10-log transformations. Bland and Altman<sup>4</sup> suggest a different CV for log-transformed variables. There are no strong arguments in favor of their way of calculating CVs and the two approaches will yield very similar results when the CV is not large.

### Limits of agreement and Bland–Altman plots

Assessing agreement between two observers or measurement methods can be done by using Bland and Altman plots and calculating limits of agreement. In a Bland and Altman plot, the difference between the two measurements per subject is plotted against the mean of the two measurements. In our situation, we have random observers, and assume that the mean difference between two arbitrary observers is 0. The limits of agreement are then defined as  $-1.96 s$  and  $+1.96 s$ , with  $s$  the observed standard deviation of the difference between the two measurements per subject. If the spread of the differences increases with increasing mean of the observations, the Bland Altman plot and limits of agreement should be calculated on a log scale. This is straightforward to do, but it is difficult to interpret log-transformed variables in clinical practice.

We transformed these limits of agreement back to the original scale by taking anti-logs. This yields an interval for the ratio between two measurements. If the limits of agreement for  $Z = {}^{10}\log(X)$  are between  $-a$  and  $a$ , with  $a = 1.96 s$ , this implies that the ratio between two measures on the original scale ( $X_1/X_2$ ) is between  $10^{-a}$  and  $10^a$ . Then, for a given value for  $\bar{X}$ , it can be shown that  $X_1 - X_2$  is between  $-2\bar{X}(10^a - 1)/(10^a + 1)$  and  $2\bar{X}(10^a - 1)/(10^a + 1)$ . Although a ratio of measures is still difficult to conceptualize, these LAs on the original scale can be plotted in a conventional Bland and Altman plot of  $X$  to clearly visualize the reproducibility of the measurement for each different value of  $\bar{X}$ .

So far, we considered only two observers. Rousson et al. extended the definition of limits of agreements to several observers by:  $LA_{\text{inter}} = 0 \pm 1.96 \cdot \sqrt{2(\sigma_O^2 + \sigma_E^2)}$ <sup>5</sup>. This upper limit of  $1.96 \cdot \sqrt{2(\sigma_O^2 + \sigma_E^2)}$  is also called the smallest detectable change,<sup>2</sup> that is, the smallest change in measurement, which is unlikely to occur by differences between observers. In the same way as described previously, the limits of agreement can be calculated for the log transformed variable  $Z$  and transformed back to the original scale. A Bland and Altman plot on the original scale of  $X$  can then be made by drawing these back transformed limits of agreement as function of the mean of  $X$ . An impression of the distribution of the individual data can be obtained by considering all possible pairs of observers and plotting the difference between the measurements per observer pair on the same subject versus the mean of the measurements of an observer pair on this subject.

**Intraobserver reproducibility**

To assess the intraobserver reproducibility, an observer has to measure a subject more than one time. Let  $Z_{ijk}$  be the  $k$ th measurement of observer  $i$  on subject  $j$ . Model [a] as described above can be extended to:

$$Z_{ijk} = \mu + \alpha_i + \beta_j + \gamma_{ij} + \varepsilon_{(ij)k} \text{ [Model b].}$$

The extra random term  $\gamma_{ij}$  models interaction between observer and subject and is assumed to be normally distributed, with mean 0 and variance  $\sigma_{OS}^2$ . The residual error term  $\varepsilon_{(ij)k}$  with variance  $\sigma_{ER}^2$  indicates the random error occurring within measurements made by one observer on one subject. For good intraobserver reproducibility this within-subject-observer variation should be as small as possible.

Following the same reasoning as described for the interreproducibility measures, for the Intra Coefficient of Variation of  $X$ , the  $CV_{intra} = 100\% \times \ln(10) \hat{\sigma}_{ER}$  can be used.

The intra-observer limits of agreement on the log scale are:  $LA_{intra} = 0 \pm 1.96 \cdot \sqrt{2\sigma_{ER}^2}$ , and can be transformed back to limits of agreement for the difference of two measurements made by the same observer on the same subject  $X_{ij1} - X_{ij2}$  being equal to  $-2\bar{X}(10^a - 1)/(10^a + 1)$  and  $2\bar{X}(10^a - 1)/(10^a + 1)$ , where  $a = 1.96 \cdot \sqrt{2\sigma_{ER}^2}$ .

**Clinical example**

To demonstrate the advantages of the methods described above, especially for the Bland and Altman plots, we will show data from a clinical study on the reproducibility of skinfold thickness measurements in young adults. In this study, skinfold thickness measurements at four locations (triceps, biceps, subscapular, and iliacal) were taken in duplicate on four subjects by 13 observers. Every subject was measured in duplicate at the four skinfold locations by all 13 observers. In the estimation of interobserver reproducibility, the mean of the two measurements by one observer was taken for every skinfold location. The objectives and methods of this study are described in detail elsewhere<sup>6</sup> and<sup>7</sup>. In this example, we take the data from the biceps skinfold measurement. Indicators of reproducibility and variance components and of the biceps skinfold measurement are displayed in Table 1.

**Coefficient of variation**

At first glance, one should be tempted to apply the normal formula for calculating an interobserver CV on the log-transformed data and thus divide  $\sqrt{\sigma_O^2 + \sigma_E^2} = \sqrt{(12.9 \cdot 10^{-3} + 7.142 \cdot 10^{-3})} = 0.142$  by the mean log-transformed biceps skinfold measurement, which is 1.14 (see Table 1).

**Table 1.** Indicators of reproducibility of the biceps skinfold measurement

Biceps skinfold	
Mean and range of all measurements on original scale (mm)	14.5 (range 7.3–29.0)
Mean and range of all measurements of <sup>10</sup> log transformed variable	1.14 (range 0.86–1.46)
Variance Components of <sup>10</sup> log transformed variable	
Intersubject variance $\sigma_s^2$	$2.904^{-3}$
Interobserver variance $\sigma_o^2$	$12.90^{-3}$
Error-variance* $\sigma_E^2$	$7.142^{-3}$
Observer-subject variance $\sigma_{os}^2$	$6.592^{-3}$
Residual-error variance $\sigma_{ER}^2$	$1.099^{-3}$
Limits of agreement	
Intraobserver LA of <sup>10</sup> log biceps	-0.092 to 0.092
Intraobserver LA of ratio of two biceps measurements	0.809 to 1.235
Intraobserver LA of difference of two biceps measurements as function of the mean $\bar{X}$	$-0.21\bar{X}$ to $0.21\bar{X}$
Interobserver LA of <sup>10</sup> log biceps	-0.392 to 0.392
Interobserver LA of ratio of two biceps measurements	0.400 to 2.499
Interobserver LA of difference of two biceps measurements as function of the mean $\bar{X}$	$-0.85\bar{X}$ to $0.85\bar{X}$
Coefficients of variation	
Intraobserver CV (%)	7.6%
Interobserver CV (%)	33.1%

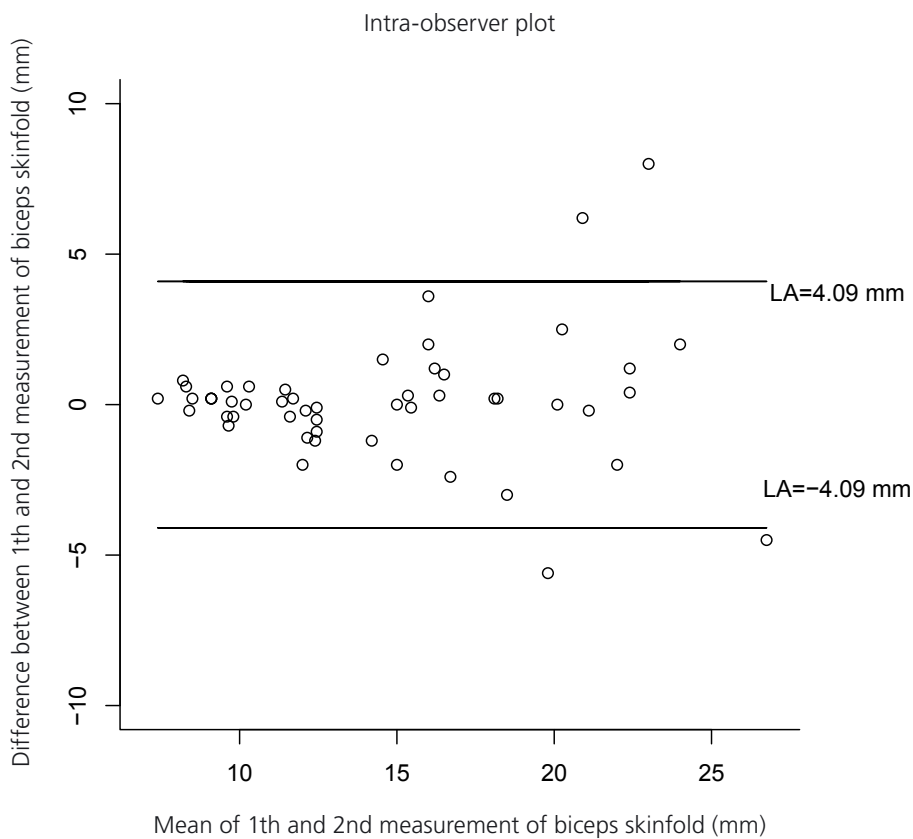
$a \cdot 10^{-3}$  was written as  $a^{-3}$ .

\* In this example  $\sigma_E^2 = \sigma_{os}^2 + \sigma_{ER}^2/2$ , since each observer measured a subject twice.

This yields an interobserver CV of 12.5%. The quantitative value of this CV might look attractive, but as explained above it is a completely meaningless value. Therefore, one should apply the formula for log-transformed data, which yields a CV of  $100\% \ln(10) \times 0.142 = 33.1\%$ . This is a true, meaningful value and indicates that the interobserver reproducibility of this skinfold is not that good compared with other literature on this topic.<sup>8</sup>

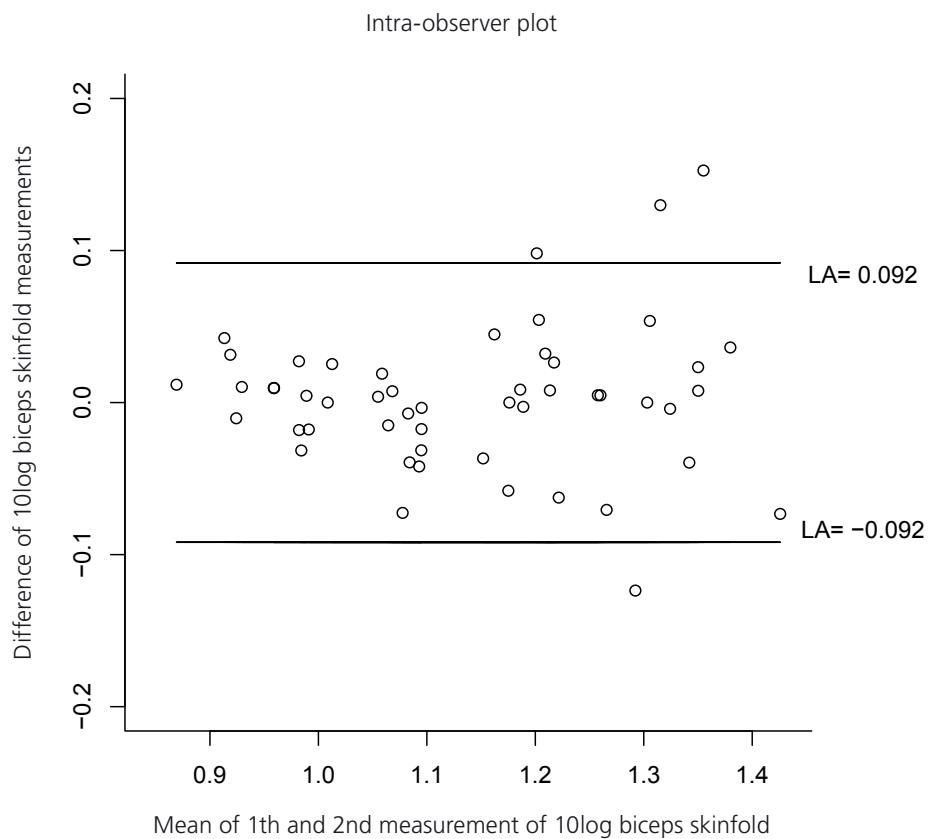
**Limits of agreement and Bland–Altman plots**

As can be clearly seen in the first conventional Bland and Altman plot, (Figure 1), the differences between the first and second measurement of the biceps skinfold by an observer are dependent of the skinfold thickness, with increasing intraobserver error with increasing



**Figure 1.** Conventional Bland and Altman plot. The differences between the first and second biceps skinfold measurement in relation to the mean of the two measurements of one observer on a subject. Lines are plotted indicating the limits of agreement ( $0 \pm 1.96$  S.D.).

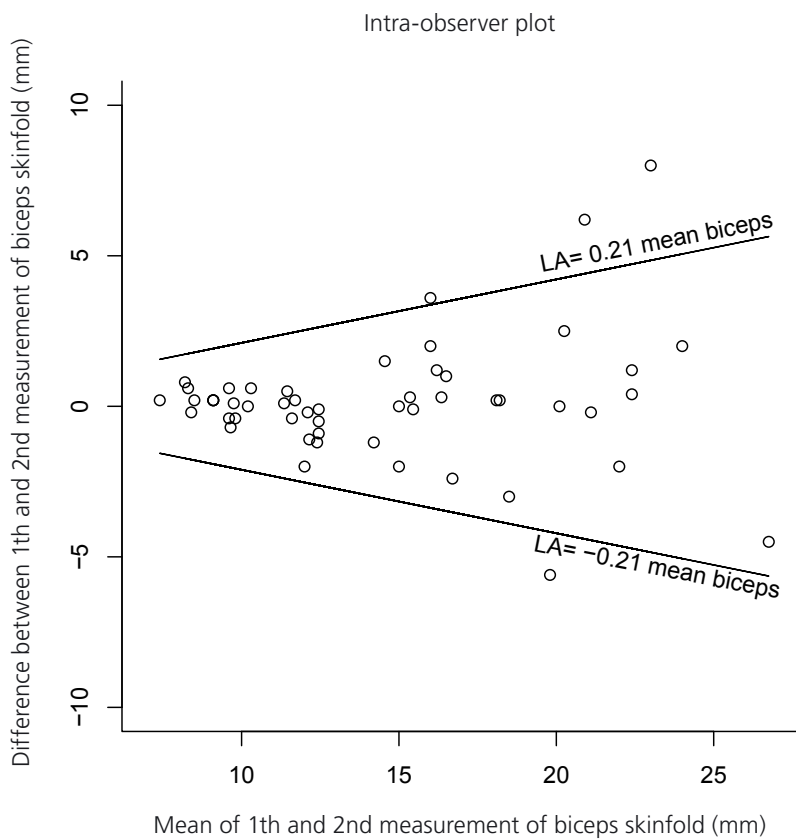
thickness of the biceps skinfold. Therefore, the conventional LAs do not well represent any of the measurements. In the second Bland and Altman plot, (Figure 2), on log-transformed data, the spread of observations on the left hand side is comparable to the spread on the right hand side. The LAs plotted do fit better, although some skewness remains. However, these log-transformed values are difficult to interpret for use in clinical practice. The values on the x and y-axis can be anti-logged, yielding the same plot but with more interpretable axes: geometric means on the x-axis and the ratio of measurements on the y-axis.<sup>4</sup> Still we prefer to study differences on the original scale and not ratios, because of their direct clinical interpretation. Therefore, in the third Bland and Altman plot, (Figure 3), we transformed the LAs (Table 1) back to the original scale using the methods described in



**Figure 2.** Bland and Altman plot of log-transformed data. The differences between the first and second 10 log biceps skinfold measurement in relation to the 10 log mean of the two measurements of one observer on a subject. Lines are plotted indicating the limits of agreement ( $0 \pm 1.96$  S.D.).

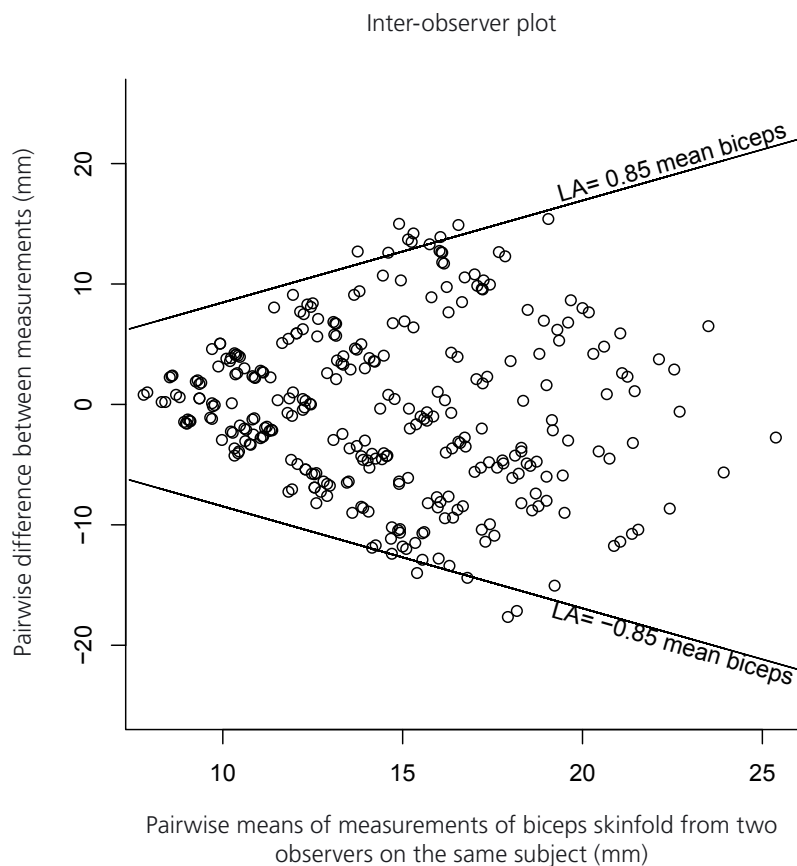
this article. We plotted these LAs into the conventional Bland–Altman plot on the original scale. This back transformation yields diagonal lines representing the intraobserver limits of agreement (formulas given in Table 1).

Note that the LAs for the differences are proportional to the mean. For example, a mean biceps value of 10 mm has limits of agreement between the measurements of two observers of  $-2.10$  and  $2.10$  mm, whereas if the mean biceps value increases to 20 mm, the LAs increase to  $-4.21$  and  $4.21$  mm (Figure 3).



**Figure 3.** Bland and Altman plot on the original scale with back transformed limits of agreement. The differences between the first and second biceps skinfold measurement in relation to the mean of the two measurements of one observer on a subject. Lines are plotted indicating the limits of agreement using the formulas in our paper.

Figure 4 shows the calculated interobserver LAs on the original scale for the difference between the measurements of two observers as function of the mean of the measurements of a pair of two observers on one subject. To illustrate the agreement between the 13 observers in our data set, we considered all possible pairs of observers and for each pair we plotted the differences between the measurements of biceps skinfold per subject versus the mean of the measurements. Whether the difference between two observers was positive or negative was decided arbitrarily, because there is no clear ordering of the observers. We should be careful not to overinterpret the observed patterns in this plot. Each observer here contributes



**Figure 4.** Bland and Altman plot on the original scale with back transformed limits of agreement. Interobserver variability is shown, with all observed pair wise differences between the measurements of biceps skinfold from two observers on the same subject. Lines are plotted indicating the limits of agreement using the formulas in our paper.



to 12 observer pairs. This explains the diagonal patterns of points in Figure 4 and results in downward trends for the smallest and largest mean values. Note that the downward trend for the observations with the largest mean values is caused by a small number of points and that the majority of the points is on the left side of the plot.

## Conclusion

In conclusion, we have shown that correct and meaningful indicators of reproducibility can be estimated for log-transformed variables, which can be interpreted straightforwardly. As log transformations are frequently applied in reproducibility studies, it is important to use the correct formula in calculating a meaningful and interpretable CV and to provide easy interpretable Bland and Altman plots and LAs on the original scale to assess agreement.

Apart from log transformations by which a scale without an absolute minimum arises, there are additional approaches to approximate normality in which an absolute minimum is preserved. For example, a square root transformation could normalize right skewed data while the null value remains zero. However, in clinical practice, log transformations are much more frequently applied. An important advantage of a log transformation is that differences on the logarithmic scale can be transformed back to ratios on the original scale, as shown in the calculated limits of agreement.

In Bland–Altman plots, it is also possible to express the difference between measurements as a percentage of the average of the measurements, as shown in an example by Dewitte et al.<sup>9</sup> However, with this approach the advantage of a direct overview of the exact value of both the measurement error and the corresponding limits of agreement in one plot is lost. In this situation, the absolute measurement error must be calculated from the mentioned percentages and means.

The approach of Bland and Altman plots for log-transformed data with back transformed limits of agreement, we provide here has almost never shown in literature on reproducibility of clinical measurements, apart from Dewitte et al. who briefly mentioned this method to be used in clinical chemistry.<sup>9</sup> Though the Bland and Altman plots obtained by this method might appear somewhat unconventional at first glance, they provide an easy and reliable tool to see the LAs for different values of the variable at once on a clinical relevant scale.

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# 6

## **Intrauterine growth restriction: no unifying risk factor for the metabolic syndrome in young adults**

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## **Abstract**

### **Background**

The validity and appropriateness of the metabolic syndrome as a cardiovascular risk factor is increasingly debated, partly due to the lack of a unifying underlying pathophysiological mechanism. Intra-uterine growth retardation (IUGR, low birth-weight by gender and gestational length) has been associated with several cardio-vascular problems and could be an important underlying risk factor for the metabolic syndrome.

### **Methods**

The association between IUGR (from the Norwegian Medical Birth Registry) and the metabolic syndrome in 7435 men and women aged 20-30 years from the population-based HUNT-2 study was studied with logistic regression using fractional polynomial models.

### **Results**

In men, there were significant associations with several of the separate components of the metabolic syndrome: central obesity (exponential,  $P<0.001$ ), raised triglycerides (negative linear,  $P=0.018$ ), reduced HDL-cholesterol (U-shaped,  $P=0.086$ ), raised blood pressure (negative linear,  $P=0.036$ ), and impaired glucose-tolerance (negative linear,  $P=0.036$ ). In women, there were significant associations with central obesity (positive linear,  $P<0.001$ ) and raised blood pressure (negative linear,  $P=0.003$ ) but not with the other components. When combining these components into the metabolic syndrome, an exponential association was found in men ( $P=0.017$ ), i.e. increased risk in subjects with high birth weight only. In women, there was no association at all ( $P=0.959$ ).

### **Conclusions**

Low birth weight was not associated with the metabolic syndrome at young adult age. Several associations between birth weight and the separate components of the syndrome were found, however, these associations were partly in different directions.

## **Introduction**

The clustering of central obesity, impaired glucose tolerance or overt diabetes mellitus type 2, dyslipidemia, and hypertension is often referred to as the metabolic syndrome.<sup>1</sup> The syndrome has a high prevalence worldwide, and it has been used widely in research and clinical practice as a cardiovascular risk factor.<sup>2</sup> However, the validity and appropriateness of the metabolic syndrome concept is increasingly debated.<sup>3-6</sup> Authorities have recently advised against its further use as much fundamental and clinical important information is missing.<sup>6</sup> Making the diagnosis does not improve clinical utility or pathophysiological understanding: it is not clear that the syndrome confers a cardiovascular risk that is different from the sum of its components, nor is a unifying underlying mechanism established.<sup>7</sup>

Intrauterine growth retardation (IUGR) leading to low birth weight has been suggested as an important risk factor for the development of the metabolic syndrome in analogy with associations established with adult cardiovascular disease.<sup>8</sup> For that reason, even 'the small baby syndrome' was proposed as a new name for the metabolic syndrome.<sup>9</sup> Later studies have often only studied separate components of the metabolic syndrome,<sup>10-12</sup> and the findings of the few studies considering the entire metabolic syndrome itself are not unequivocal: associations with both low,<sup>13,14</sup> and high birth weight<sup>15</sup> were found in some studies, while other studies showed no statistically significant association at all.<sup>16-18</sup> It is therefore unclear whether IUGR can be regarded as a common underlying risk factor for the metabolic syndrome. Most of these studies were relatively underpowered, and inappropriate statistical adjustment for current weight or BMI was applied in several studies.<sup>9,13,14,17,18</sup>

Hence, we studied the effect of birth weight on the metabolic syndrome and its individual components in young adults to avoid contamination of our study population with patients with frank diabetes or hypertension. The second Nord-Trøndelag Health study (HUNT 2) is a large population based study with birth weights available from the Norwegian Medical Birth Registry. We studied IUGR as a possible unifying underlying risk factor for the metabolic syndrome in the light of an increasing skepticism of defining its individual cardiovascular components as a specific syndrome.

## **Subjects and methods**

### **Study population**

The HUNT 2 study is a general health study conducted 1995-1997 in Nord-Trøndelag County, located in the middle of Norway with a population of 127,000 residents. All residents of this stable and homogeneous Caucasian population aged 20 years and older were invited for an

extensive questionnaire, a brief clinical examination, and a single venous blood specimen without specific instructions. Objectives, methods, and cohort retrieval of the HUNT 2 study are described in detail elsewhere.<sup>19</sup>

At birth, each neonate in Norway is assigned a unique identification number for life. By using this identifier, individual linkage could be performed between the data collected in the HUNT 2 study and perinatal data from the national Medical Birth Registry of Norway which exists since 1967. Therefore, all subjects aged 20-30 years living in Nord-Trøndelag county were eligible for the current study. Subjects with congenital malformations or women who were pregnant at the time of assessment were excluded because of possible influence on body composition and metabolism.

### **Measurements**

At birth, weight was measured in grams, and information on gestational age, congenital malformations, and pregnancy complications was registered by midwives and obstetricians. Birth weight was expressed as a standard deviation score (SDS) to correct for gestational age and sex using Scandinavian reference values.<sup>20</sup> Out-of-possible-range entries (gestational age <25 or >45 weeks, and/or birth weight <-5 SDS or >5 SDS) were considered as missing values.

In the HUNT 2 study information about diabetes and the use of antihypertensive drugs was obtained by questionnaire. Waist circumference was measured at the level of the umbilicus with a steel tape to the nearest 1.0 cm. Blood pressure was measured three times, and the means of the second and third measurement were taken. Time since last meal was recorded. Fresh serum samples were analyzed within three days.

### **Definitions**

The metabolic syndrome was defined according to the International Diabetes Federation (IDF) criteria: central obesity (waist circumference >94 cm (males) and >80 cm (females)) and at least two of the following four criteria: raised fasting triglyceride level (>1.7 mmol/l), reduced HDL cholesterol (<1.03 mmol/l (males) and <1.29 mmol/l (females)), raised blood pressure (systolic blood pressure  $\geq$ 130 mmHg and/or diastolic blood pressure  $\geq$ 85 mmHg, and/or use of antihypertensive drug treatment), and raised fasting plasma glucose ( $\geq$  5.6 mmol/l or previously diagnosed diabetes mellitus type 2).<sup>21</sup> We also used the American Heart Association / the revised US National Cholesterol Education Program Adult Treatment Panel (AHA / revised NCEP) criteria which differ from the IDF criteria only in defining an elevated waist circumference as  $\geq$ 102 cm in Caucasian males and  $\geq$ 88 cm in Caucasian females and at least any three out of the five criteria are required for the diagnosis.<sup>1</sup>

Serum glucose and triglycerides require a fasting state, which was not requested in the large-scale HUNT 2 study and therefore we adjusted them for time since the last meal. To that end, we used time specific percentiles for subjects with normal birth weight corresponding to the cutoff level used in the metabolic syndrome definition. For glucose we used the 95<sup>th</sup> percentile as this equals 5.6 mmol/l in the truly fasting group. For triglycerides we use the 87.5<sup>th</sup> percentile as this equals 1.7 mmol/l. This is analogous to adjustments suggested by others.<sup>22,23</sup> Glucose and triglyceride values did not need adjustment in 33% and 12% of subjects, respectively.

### **Statistical analysis**

Data were given by three categories of birth weight SDS using cut-off levels of -1.3 SDS and 1.3 SDS, compatible with the 10<sup>th</sup> and 90<sup>th</sup> sex and gestational age specific percentiles respectively. Birth weight < 10<sup>th</sup> percentile was considered Small for Gestational Age (SGA), birth weight between the 10<sup>th</sup> and 90<sup>th</sup> percentiles Appropriate for Gestational Age (AGA), and > 90<sup>th</sup> percentile Large for Gestational Age (LGA). The effect of birth weight SDS on the adult metabolic syndrome and its separate components was assessed by logistic regression analysis adjusting for the possible confounders age and being born after a pregnancy complicated by preeclampsia. To deal with non-linearity we used fractional polynomial functions in addition to the traditional approach of dividing continuous variables into categories.<sup>24</sup> To check our adjustments for serum glucose and triglycerides in non-fasting subjects, we also performed subgroup analyses in those subjects who could be classified as either having the metabolic syndrome or not having the metabolic syndrome without being dependent on the adjusted serum glucose and / or triglyceride values.

### **Results**

In total, 8596 subjects, i.e. 48% of all subjects born 1967-1977 in Nord-Trøndelag county, participated in the HUNT 2 study. There were no significant differences in birth weight or other perinatal characteristics between our study population and the non-participating young adults of Nord-Trøndelag county (data not shown), 513 subjects had missing data for gestational age and /or birth weight, and 131 had impossible values for these parameters. 318 pregnant women were excluded. Of the remaining 7634 subjects 136 had missing data on one or more components of the metabolic syndrome, so that data of 7498 subjects (3554 males and 3944 females) were analyzed. Birth weight ranged from 1020 to 5630 g, comprising 745 SGA, 5967 AGA, and 745 LGA subjects. Mean birth weight in these groups was 2733 (326), 3506 (415), and 4341 (401), respectively.



**Table 1.** Characteristics of HUNT 2 participants included by categories of intrauterine growth

	Total (n=7498)	SGA (n=750)	AGA (n=5999)	LGA (n=749)	P-values
Age (years)	24.7 (2.9)	24.6 (2.9)	24.8 (2.9)	24.7 (2.9)	0.42
Male gender (%)	47.4	47.7	46.9	51.4	0.15
High education <sup>a</sup> (%)	27.1	25.2	27.5	25.8	0.83
Height (cm)	173.0 (9.0)	169.9 (8.8)	173.0 (8.9)	176.2 (8.8)	<0.001
Weight (kg)	74.3 (14.2)	71.2 (13.7)	74.2 (14.1)	79.0 (14.5)	<0.001
Body Mass Index (kg/m <sup>2</sup> )	24.8 (3.9)	24.5 (4.0)	24.7 (3.9)	25.4 (3.9)	<0.001
Family history of DM or CVD <sup>b</sup> (%)	27.9	29.3	27.6	29.4	0.95
Physical inactivity <sup>c</sup> (%)	13.7	13.4	13.7	13.7	0.88
Current smoking (%)	28.3	31.2	28.0	28.6	0.29
Diabetes (%)	0.6	0.9	0.5	0.3	0.08
Antihypertensive treatment (%)	0.3	0.1	0.4	0.4	0.46
Time since last meal (h)	2.38 (2.30)	2.37 (2.42)	2.40 (2.31)	2.26 (2.11)	0.36
Waist circumference (cm)	80.7 (11.1)	79.6 (11.0)	80.5 (11.1)	82.8 (11.0)	<0.001
s-Triglycerides (mmol/l)	1.4 (0.9)	1.5 (0.9)	1.4 (0.9)	1.4 (0.9)	0.062
s-HDL cholesterol (mmol/l)	1.35 (0.34)	1.33 (0.34)	1.35 (0.34)	1.32 (0.33)	0.427
Systolic blood pressure (mmHg)	126.4 (13.2)	127.8 (13.5)	126.2 (13.1)	126.3 (13.2)	0.029
Diastolic blood pressure (mmHg)	71.3 (8.6)	72.1 (8.7)	71.2 (8.6)	71.1 (8.9)	0.039
s-Glucose (mmol/l)	4.9 (0.9)	5.0 (1.0)	4.9 (0.9)	4.8 (0.8)	0.013

Note: Variables are presented as mean (SD) or percentage. a: more than 15 years; b: DM = diabetes mellitus, CVD = cardiovascular disease, i.e. cerebral stroke or myocardial infarction before age 60; c: less than 1 hour per week of light physical activity. SGA (Small for Gestational Age) have birth weight adjusted for gestational age and sex below 10<sup>th</sup> percentile, AGA (Appropriate for Gestational Age) are between 10<sup>th</sup> and 90<sup>th</sup> percentiles, and LGA (Large for Gestational Age) are above 90<sup>th</sup> percentile. Differences between the three groups were checked with chi-square test in a 2 x 3 cross-table for binary variables and with one-way ANOVA for continuous variables.

**Table 2.** Adjusted associations between birth weight SDS and separate components of the metabolic syndrome

	Categories of birth weight (percentiles)						Over-all effect of birth weight		
	< 2.5 <sup>th</sup>	2.5-9 <sup>th</sup>	10-24 <sup>th</sup>	25-74 <sup>th</sup>	75-89 <sup>th</sup>	90-97.5 <sup>th</sup>	> 97.5 <sup>th</sup>	Functional form	P-value
<b>MEN (n=3535)</b>									
Central obesity <sup>†</sup>	1.22	1.03	0.86	1.00	1.23	1.45	2.06	Exponential	< 0.001
Raised TG level <sup>††</sup>	1.74	1.38	1.11	1.00	0.99	1.02	1.08	Neg. linear	0.018
Reduced HDL-cholesterol <sup>†</sup>	1.24	1.26	1.08	1.00	1.03	1.28	1.29	U-shaped	0.086
Raised blood pressure <sup>†</sup>	1.38	1.21	1.05	1.00	1.05	1.02	1.28	Neg. linear	0.036
Impaired glucose tolerance <sup>††</sup>	1.50	1.31	1.25	1.00	0.92	0.86	1.07	Neg. linear	0.036
<b>WOMEN (n=3922)</b>									
Central obesity <sup>†</sup>	0.72	1.01	0.97	1.00	1.13	1.07	1.31	Pos. linear	< 0.001
Raised TG level <sup>††</sup>	1.21	1.25	1.27	1.00	1.38	1.00	1.55	----	0.828
Reduced HDL-cholesterol <sup>†</sup>	1.19	1.04	1.15	1.00	0.99	0.98	1.18	---	0.879
Raised blood pressure <sup>†</sup>	1.60	1.15	1.08	1.00	0.89	1.03	0.76	Neg. linear	0.003
Impaired glucose tolerance <sup>††</sup>	1.25	1.25	1.15	1.00	1.13	0.69	0.97	---	0.738

Note: Logistic regression analysis showing the odds ratio for different components of the metabolic syndrome by categories of birth weight SDS. For studying the over-all effect of birth weight as a continuous variable we used fractional polynomial functions. P-values for the overall effect of birth weight and a description of the functional form are given. All analyses were adjusted for age and being born after a pregnancy complicated by preeclampsia. <sup>†</sup> The different components of the metabolic syndrome were dichotomized according to the International Diabetes Federation definition: central obesity if waist circumference >94 cm in men and >80 cm in women; reduced HDL-cholesterol if <1.03 mmol/l in men and <1.29 mmol/l in women; raised blood pressure if systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥85 mmHg and/or anti-hypertensive medication. <sup>††</sup> Cut-off depends on time since last meal, see text and Figure 1.

**Table 3.** Adjusted associations between birth weight SDS and the metabolic syndrome using different definitions and study groups

	MEN			WOMEN		
	MS y/n	Functional form	P-value	MS y/n	Functional form	P-value
IDF criteria, all included	343/3192	Pos. exponential	0.017	283/3639	---	0.959
IDF criteria, subgroup †	247/2878	Pos. exponential	0.004	197/2809	---	0.932
AHA / rNCEP criteria, all included	407/3128	Pos. exponential	0.130	215/3707	---	0.984
AHA / rNCEP criteria, subgroup †	131/1015	---	0.475	130/2085	---	0.956

Note: Logistic regression analysis with fractional polynomial functions was used to study the association between birth weight SDS as a continuous variable and the metabolic syndrome. P-values for the overall effect of birth weight and a description of the functional form are given. IDF = International Diabetes Foundation, AHA / r NCEP = American Heart Association / the revised US National Cholesterol Education Program Adult Treatment Panel. MS y/n gives the number of subjects with and without the metabolic syndrome. † Subgroup of subjects who could be classified as either having the metabolic syndrome or not having the metabolic syndrome without being dependent on the adjusted serum glucose and / or triglyceride values.

Characteristics of our study population as young adults, i.e. data from the HUNT 2 examination, are displayed in Table 1. Unadjusted broad categories of birth weight showed that body size was positively associated with birth weight, while other demographic, medical history variables, and the components of the metabolic syndrome were either not different or could indicate a non-linear effect. There were no differences in time since last meal by birth weight group, and no associations with age, sex, waist circumference, HDL cholesterol or blood pressure. Serum glucose and triglycerides were significantly associated with time after meal (test-for-trend 0.006 and <0.001, respectively).

Table 2 shows the gender specific associations between birth weight SDS and the separate components of the metabolic syndrome, adjusted for age and preeclampsia as no other variables were significantly associated. In men, the odds ratio for central obesity seemed to be increased in subjects with very low birth weight SDS (OR 1.22) and in subjects with higher birth weight (OR 1.23, 1.45, and 2.06). Using fractional polynomial functions we found a highly significant over-all association with birth weight ( $P<0.001$ ), but the functional form was a positive exponential function, i.e. no increased risk with lower birth weights. The expected negative linear effect, i.e. increased risk with lower birth weights, was found for raised triglycerides ( $P=0.018$ ), raised blood pressure, ( $P=0.036$ ) and impaired glucose tolerance ( $P=0.036$ ). For reduced HDL-cholesterol there was a U-shaped association with birth weight ( $P=0.086$ ). In women, there was a positive linear association between birth weight and central obesity, ( $P<0.001$ ) and a negative linear association with raised blood pressure ( $P=0.003$ ). Birth weight was not significantly associated with raised triglycerides, reduced HDL-cholesterol, or impaired glucose tolerance.

The prevalence of the metabolic syndrome according to the IDF criteria was 9.7% in men and 7.2% in women. Table 3 shows a significant association between birth weight and the metabolic syndrome in men ( $P=0.017$ ) with a positive exponential form, illustrated in Figure 1. This implies no increased risk among those with low birth weight SDS. Repeating the analyses in the subgroup of men not needing adjusted glucose and/or triglycerides cut-offs for the diagnosis of the metabolic syndrome gave very similar results. However, when metabolic syndrome was defined according to the AHA / revised NCEP criteria the association was weaker even in subjects with high birth weight. In women, there was no association between birth weight and the metabolic syndrome irrespective of syndrome definition and study group used (Figure 1).

**Figure 1.** Absolute risk for developing the metabolic syndrome in (A) men and (B) women at age 20-30 years associated with birth weight SDS. The risk is expressed as a probability with 95% confidence intervals using logistic regression analyses with fractional polynomial functions adjusted for age and preeclampsia in the pregnancy. The reference lines indicate the observed prevalence in men and women.

Figure 1A:

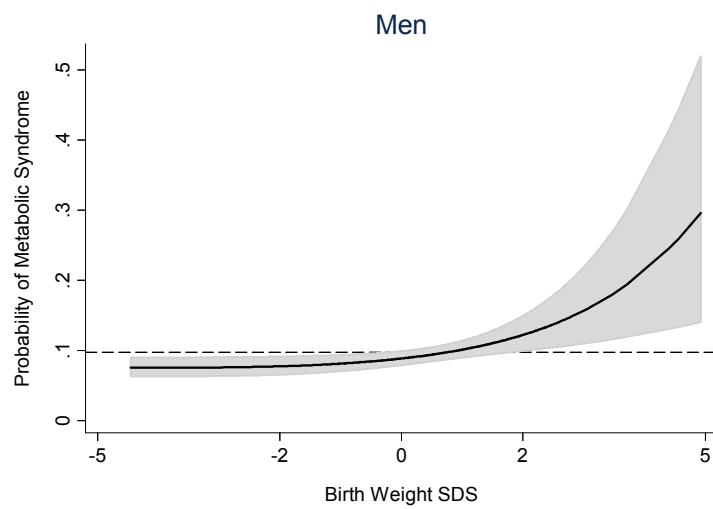
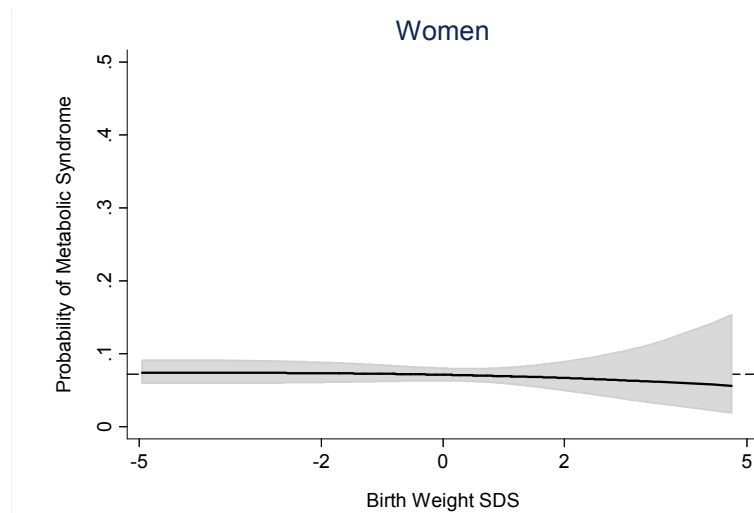


Figure 1B:



## **Discussion**

This large-scaled population-based study describes the relationship between birth weight and the metabolic syndrome at young adult age. Birth weight SDS was both negatively, not at all, and positively associated with the separate components of the metabolic syndrome. In both men and women, low birth weight was not significantly associated with the metabolic syndrome itself. This does not support IUGR as a common pathophysiological mechanism for the metabolic syndrome.

Our results might have been affected by limitations in study design or data collection. In the HUNT 2 study, subjects were not asked specifically to attend fasted. We therefore used different cut-offs for increased glucose and triglyceride depending on time after last meal, but some random misclassification can not be excluded. The effect of random misclassification is dilution of the observed effects, implying that we might have underestimated the true effect. However, repeating analyses in a smaller subgroup not relying on glucose or triglyceride values for diagnosing or excluding metabolic syndrome gave similar results. The participation rate in HUNT 2 for this age group was quite low (49%). However, there were no statistically significant differences in either birth weight or gestational age between participants and non-respondents. While non-response might have been related to the presence of metabolic syndrome, it is unlikely that this would result in bias, as bias requires selective non-response of a subgroup with both a certain birth weight category and a certain metabolic status. For example only a high non-response in those subjects with both a low birth weight and presence of the metabolic syndrome. This situation seems very unlikely. Another limitation is the absence of information about the possible confounders catch-up growth and breastfeeding. Finally, in non-linear relationship settings, low number of data points in the very low or very high range pose a special problem which is difficult to assess. We therefore cannot totally exclude lack of power as a possible cause of non-significant associations in our study, but our study did after all include 750 SGA subjects.

The large study population in combination with few missing data on birth weight forms a major strength of our study. Furthermore, both birth weight and gestational age were registered at birth, which avoids recall bias. We expressed birth weight in SDS, which adjusts for the possible interference of sex and gestational age. Besides, information on potential important confounders was taken into account. Though studying the effect of early origins in relatively young adults has the clear advantage that disturbing life-style effects have accumulated less frequently, it might have been too young to detect some possible associations as the prevalence of the metabolic syndrome increases with increasing age. Therefore, the current research question should also be examined in an older population in future.

Birth weight was inconsistently associated with the separate components of the metabolic syndrome in our study. The effect of high birth weight SDS on elevated waist circumference has also been described previously.<sup>13</sup> A negative association was found between birth weight and triglycerides in men, and even though it has been found in earlier studies, it was not in the majority of (small) studies on this topic.<sup>25</sup> However, most of these studies did not do separate analyses of men and women, and in those who did so a negative effect in men was found in five of six studies. We found a U-formed association between birth weight and HDL cholesterol in men. Most other studies have found no association,<sup>25</sup> which could be caused by the use of linear regression analysis and the joint evaluation of men and women. Like other studies, we found only a small effect of low birth weight on elevated blood pressure.<sup>26,27</sup> We found a negative association between low birth weight and glucose levels in males only, while a previous review found that most studies reported a negative association in both men and women.<sup>28</sup>

Contrary to most previous findings, we did not find a significant association between low birth weight SDS and the metabolic syndrome. This discrepancy could partly be explained by publication bias, a phenomenon that has also been described for studies on fetal origins of blood pressure.<sup>27</sup> Furthermore, a substantial part of the inverse associations found and published by others might also be explained by adjustments for current body size, mostly BMI. It is well known that BMI is positively related with risk factors for cardiovascular disease, and there is also a positive relation to birth weight.<sup>29</sup> High BMI should therefore be considered as an intermediate rather than a confounder, and thus, we think it is theoretically unjustified to adjust for indicators of adult body composition.<sup>30,31</sup>

A medical syndrome is usually defined as an aggregate of symptoms and signs conferring an increased risk unified by a common underlying pathophysiological process. The latter is important for a better understanding of the disease, both regarding prediction, diagnosis, and treatment. The metabolic syndrome was initially thought to be caused by insulin resistance, but more recent studies have shown that only 48% of insulin resistant subjects also have the metabolic syndrome.<sup>32</sup> As current knowledge is based on association studies only, it may well be that there is a more basic defect resulting in insulin resistance and other cardiovascular risk factors. IUGR could be such a basic unifying defect, as low birth weight has nowadays repeatedly been associated with adult cardiovascular disease<sup>8</sup> and its separate risk factors, both in this study as well as in other studies.<sup>13,26,27</sup> The early studies supported low birth weight as a risk factor for the metabolic syndrome,<sup>9,13,14</sup> but our data weigh against this hypothesis. Obviously, this does not exclude that a common pathological base for the metabolic syndrome might still be found in future, e.g. catch-up growth has been suggested to be such a risk factor.<sup>33</sup> However, like with low birth weight and the metabolic syndrome, the majority of the current studies supporting this hypothesis studied one or more separate components of the

syndrome only.<sup>33</sup> Furthermore, longitudinal data from population-based cohorts have recently shown that metabolic syndrome was only weakly associated with cardiovascular risk, and that the joint syndrome was not better than the sum of its components.<sup>34</sup> In this context, finding opposite effects of low birth weight on different components of the metabolic syndrome but no effect on the syndrome itself does not provide additional support for metabolic syndrome concept.

In conclusion, several significant but inconsistent associations were found between birth weight and the separate components of the metabolic syndrome. However, no significant association was found between low birth weight and the metabolic syndrome itself.

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# 7

## **Effect of intrauterine growth restriction on kidney function at young adult age: the Nord Trøndelag Health (HUNT 2) Study**

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## Abstract

### Background

The hypothesis of intrauterine origin of adult disease is debated. We tested whether intrauterine growth restriction is associated with later kidney function.

### Study design

Prospective cohort study.

### Setting and participants

7,457 Norwegian adults aged 20 to 30 years participating in the population based Nord Trøndelag Health Study (1995-1997) with data for birth weight, gestational age, and maternal and perinatal risk factors registered at the Medical Birth Registry of Norway.

### Predictor

Birth weight expressed as an SD score (SDS) to adjust for gestational age and sex. Subjects with a birth weight SDS less than -2.0, -2.0 to -1.3, and -1.3 to 1.3 were defined as very small, small, and appropriate for gestational age, corresponding to less than the 3rd, 3rd to 10th, and 10th to 90th percentiles, respectively.

### Outcome and measurements

Kidney function estimated using the Cockcroft-Gault and isotope dilution mass spectrometry-traceable 4-variable Modification of Diet in Renal Disease (MDRD) Study equation. Values less than the sex-specific 10th percentile were defined as low-normal kidney function.

### Results

Compared with men with birth weight appropriate for gestational age ( $n = 2,755$ ), odds ratios for low-normal creatinine clearance ( $<100$  mL/min) were 1.66 (95% confidence interval [CI], 1.16 to 2.37) if small for gestational age ( $n = 261$ ) and 2.40 (95% CI, 1.46 to 3.94) if very small for gestational age ( $n = 101$ ). Kidney function estimated using the MDRD Study equation gave similar results. Women ( $n = 3,126, 283, \text{ and } 112$ , respectively) had odds ratios of 1.65 (95% CI, 1.17 to 2.35) and 2.00 (95% CI, 1.21 to 3.29) for low-normal creatinine clearance ( $<80$  mL/min), whereas the association was not significant using the MDRD Study equation. Using linear regression, creatinine clearance decreased by 4.0 mL/min (95% CI, 3.3 to 4.6) in men and 2.9 mL/min (95% CI, 2.2 to 3.5) in women per 1-SDS decrease. Adjusting for possible confounders did not influence results.

### Limitations

Selection bias could be a problem because the participation rate was 49%, but there were no statistically significant differences between participants and nonparticipants regarding maternal and perinatal characteristics. Adjusting kidney function for body size can be a special problem in people with intrauterine growth restriction.

### Conclusions

Although effects were still small in young adulthood, intrauterine growth restriction was significantly associated with low-normal kidney function. The effect was weaker and less consistent in women compared with men.

## **Introduction**

Intrauterine growth restriction (IUGR) is increasingly proposed as a mechanism in the pathogenesis of cardiovascular disease. An increased risk of hypertension,<sup>1</sup> subclinical atherosclerosis assessed by using carotid intima-media thickness measurement,<sup>2</sup> nonfatal cardiovascular events<sup>3</sup> and cardiovascular death<sup>4</sup> were found in persons with low birth weight (BW). A few studies suggested that the propensity to chronic kidney disease may also be established in utero, and Brenner and Chertow<sup>5</sup> were the first to postulate that IUGR may cause a decreased number of nephrons, leading to hypertension and reduced kidney function.

Low kidney volume and nephron number were observed after IUGR in several animal models<sup>6,7</sup> and also in humans, newborns as well as adults, who died of nonrenal causes.<sup>8-10</sup> The clinical consequences of these alterations were investigated at different levels, and associations were found of IUGR with microalbuminuria,<sup>11,12</sup> faster progression of renal dysfunction in patients with specific kidney diseases,<sup>13,14</sup> and end-stage renal disease (ESRD).<sup>15,16</sup> Because IUGR also was associated with other diseases, such as type 2 diabetes mellitus, it is difficult to disentangle direct from indirect effects of IUGR on advanced renal failure. For that reason, follow-up studies of younger populations are necessary. A relationship between IUGR and renal function at 19 years of age was found in a prospective cohort study of subjects born very premature,<sup>17</sup> however, to date, no cohort study investigated the effect of IUGR on young adult kidney function in a general population.

We describe results from a large unselected cohort aged 20 to 30 years in which we assessed the relationship between BW (adjusted for sex and gestational age) and later kidney function to test the hypothesis that IUGR itself is primarily responsible for impaired kidney function. Because of the close relationship between kidney function and blood pressure, we also used blood pressure as a secondary outcome.

## **Methods**

### **Population**

The Health Survey of Nord-Trøndelag (HUNT 2 Study) is a general health survey conducted in 1995-1997 in Nord-Trøndelag County, Norway, with a population of 127,000. All residents of this stable and homogeneous population (97% whites) aged 20 years and older were invited for the survey. Objectives, methods, and participation in the HUNT 2 Study are described in detail elsewhere.<sup>18</sup> The present study also used data from the national Medical Birth Registry. Since 1967, midwives or attending physicians have been obliged to forward medical data for

each childbirth to the Medical Birth Registry.<sup>19</sup> Because all liveborns are assigned a unique identification number, linkage between databases is possible in Norway. The present study is based on an anonymized version of this record linkage and comprised a subgroup of the HUNT 2 Study, i.e., subjects born between 1967 and 1977. All participants gave written informed consent, and the study was approved by the Regional Committee for Medical Research Ethics, the National Data Inspectorate, and the Directorate of Health and Social Affairs. Chronic kidney disease has a high prevalence in Norway, as well as in other western countries (10%).<sup>20</sup> ESRD incidence is low (99 cases/million inhabitants per year), and the most frequent causes are hypertension (29%), glomerulonephritis (18%), and diabetes (15%).<sup>21</sup>

### Measurements

More than 99% of pregnant women in Norway receive standardized antenatal care.<sup>22</sup> Recording of live births is 100% complete in Norway. BW was recorded to the nearest 10 g, and gestational age was based on the last menstrual period. Data for congenital malformations, pregnancy complications, and maternal conditions were also recorded. Diagnostic criteria for preeclampsia fulfilled the 1972 recommendations of the American College of Obstetricians and Gynecologists, which defined preeclampsia as increased blood pressure ( $\geq 140/90$  mm Hg) after 20 weeks of gestation together with proteinuria, edema, or both.

Relevant data at a young adult age were obtained as part of the HUNT 2 Study: medical history, risk factors, education, and family history of cardiovascular disease. Height was measured to the nearest 1.0 cm, and weight, to the nearest 0.5 kg, with participants lightly clothed without wearing shoes. Blood pressure was measured by specially trained nurses or technicians using a Dinamap 845 XT (Critikon, Tampa, FL) based on oscillometry. Cuff size was adjusted after measuring arm circumference. Blood pressure measurements were performed after the participant had been seated for at least 2 minutes with the cuff around the arm with the arm resting on a table. Blood pressure was measured automatically 3 times at 1-minute intervals. For all analyses, mean values of the second and third systolic and diastolic measurements were obtained. Fresh serum samples were analyzed within 2 days on a Hitachi 911 Autoanalyzer (Hitachi, Mito, Japan), applying reagents from Roche (Roche Diagnostics, Mannheim, Germany). Serum creatinine was measured by using a blank-rate Jaffé method.

### Statistical Analysis

Subjects with congenital malformations and women pregnant at the time of assessment were not eligible for inclusion because of possible influences on body composition and renal function. There is controversy about how to index kidney function for body size.<sup>23</sup> Therefore, we used different estimates of kidney function. Creatinine clearance was estimated using the Cockcroft-Gault formula, and glomerular filtration rate (GFR) was estimated using the isotope dilution mass spectrometry (IDMS)-traceable 4-variable Modification of Diet in Renal

Disease (MDRD) Study equation. Results are presented as not adjusted for body surface area (in milliliters per minute) and adjusted for body surface area (in milliliters per minute per 1.73 m<sup>2</sup>) for both equations.<sup>24,25</sup>

Creatinine clearance (mL/min)

$$= (140 - \text{age}) / (\text{serum creatinine}[\text{mg/dL}] \times (\text{weight}[\text{kg}] / 72 \times 0.85 \text{ if female}))$$

GFR (mL/min / 1.73m<sup>2</sup>)

$$= 175 \times \text{serum creatinine (mg/dL)} - 1.154 \times \text{age} - 0.203 \times (\text{0.742 if female})$$

For the MDRD Study equation, now designed for use with IDMS-traceable serum creatinine values to avoid problems with interlaboratory calibration differences, we recalibrated our original Jaffè-based creatinine values to the Roche enzymatic method.<sup>26</sup>

To reflect intrauterine growth, we expressed BW as an SD score (BW-SDS) to correct for gestational age and sex by using Scandinavian references.<sup>27</sup> Very small for gestational age (VSGA) was defined as a BW less than the 3rd percentile for gestational age (< -2.0 SDS); small for gestational age (SGA), as a birth weight between the 3rd and 10<sup>th</sup> percentile (-2.0 to -1.3 SDS); and appropriate for gestational age (AGA), as a birth weight between the 10th and 90th percentile (-1.3 to 1.3 SDS). Similar categories were used for BW (2,450, 2,870, and 4,190 g, respectively) and gestational age (36, 38, and 42 weeks, respectively). We used low-normal kidney function, defined as values less than the sex-specific 10th percentile, as our primary outcome. Blood pressure was a secondary outcome.

Based on the Medical Birth Registry, we compared obstetric and neonatal characteristics of HUNT 2 participants and nonparticipants by using 2-sample *t*-test or Mann-Whitney *U* test, when appropriate. Nonlinear associations in our study population were then tested for by categorizing BWSDS, BW, and gestational age, and age-adjusted logistic regression analysis was used to assess the effect of IUGR. Linear regression was used if appropriate to assess the effect of IUGR as a continuous variable. Blood pressure was analyzed as a continuous variable. All analyses were performed separately for men and women,<sup>23</sup> and analyses were repeated with adjustment for maternal risk factors (age, preexisting diabetes and/or kidney disease, and preeclampsia), adult smoking, and educational level.

## Results

Forty-nine percent of all adults in Nord-Trøndelag County born between 1967 and 1977 participated in the HUNT 2 Study (n = 8,666). BW-SDS was missing for 490 participants, and



133 participants had improbable values BW-SDS < -5 or > 5), leaving 8,043 subjects eligible. As listed in Table 1, based on the Medical Birth Registry, there were no significant differences in BWs or other obstetric, neonatal, and maternal characteristics between study subjects and nonparticipants in Nord-Trøndelag County. The proportion of males was significantly lower among participants. Persons with congenital malformations (n = 126) and women pregnant at the time of the study (n = 323) were excluded, and 137 had missing data for serum creatinine or weight needed for estimating kidney function. Therefore, data from 7,457 subjects (3,534 males and 3,923 females) were analyzed. BWs ranged from 1,020 to 5,630 g, comprising 213 VSGA subjects, 544 SGA subjects, 5,881 AGA subjects, and 819 large-for-gestational-age subjects. Mean BWs in these groups were  $2,448 \pm 311$  (SD),  $2,851 \pm 253$ ,  $3,499 \pm 411$ , and  $4,321 \pm 391$  g, respectively. Table 2 lists characteristics of the study groups at the time of the HUNT 2 examination.

**Table 1.** Demographic, obstetric, and neonatal characteristics of all subjects born 1967-1977 in Nord-Trøndelag county, Norway

	Participants in HUNT 2 Study (n = 8043)	Nonparticipants (n = 8499)	P
Men (%)	45.4	59.0	<0.001
Dead after HUNT 2 (%)	0.5	0.7	0.04
Maternal hypertension (%)	0.1	0.1	0.9
Maternal chronic kidney disease (%)	0.7	0.8	0.4
Maternal diabetes mellitus (%)	0.1	0.1	0.9
Pregnancy-induced hypertension (%)	1.3	1.2	0.9
Preeclampsia (%)	4.6	4.5	0.8
Obstetric complications (%)	21.9	23.0	0.09
Gestational age (wk)	$39.9 \pm 1.8$	$39.9 \pm 1.9$	0.9
BW (g)	$3,510 \pm 539$	$3,515 \pm 535$	0.5
BW < 2,500 g (%)	3.4	3.4	0.9
BW > 4,000 g (%)	16.2	16.4	0.8
BW-SDS	$0.02 \pm 1.08$	$-0.01 \pm 1.08$	0.2
BW-SDS -2.0 to -1.3 (SGA) (%)	7.2	7.5	0.4
BW-SDS < -2.0 (VSGA) (%)	2.9	3.3	0.1

Note: Values expressed as mean  $\pm$  SD or percent. Binary variables compared by using chi-square test, continuous variables compared by using 2-sample *t*-test. Subjects born SGA and VSGA were defined by using BW-SDSs to also account for gestational age and sex.

Abbreviations: HUNT 2, Nord Trøndelag Health Study; BW, birth weight; SDS, SD score; SGA, small for gestational age; VSGA, very small for gestational age.

**Table 2.** Characteristics of HUNT 2 participants examined 1995-1997 by category of intrauterine growth

	VSGA (n = 213)	SGA (n = 544)	AGA (n = 5881)	P
Age (y)	24.4 ± 2.8	24.7 ± 2.9	24.7 ± 2.9	0.1
Men (%)	47.4	48.0	46.8	0.7
Low education* (%)	48.3	47.7	44.4	0.08
Height (cm)	169.4 ± 9.2	170.2 ± 8.5	173.0 ± 8.9	<0.001
Weight (kg)	70.0 ± 13.9	71.4 ± 13.5	74.2 ± 14.1	<0.001
Body surface area (m <sup>2</sup> )	1.80 ± 0.20	1.82 ± 0.19	1.87 ± 0.20	<0.001
Body mass index (kg/m <sup>2</sup> )	24.3 ± 4.0	24.6 ± 4.0	24.7 ± 3.9	0.3
Family history of DM or CVD (%)	33.8	27.0	27.6	0.2
Physical inactivity† (%)	13.5	13.1	13.6	0.8
Current smoking (%)	35.2	29.4	28.0	0.04
Diabetes (%)	0.9	0.9	0.5	0.2
Antihypertensive treatment (%)	0.0	0.2	0.4	0.3
Systolic blood pressure (mm Hg)	128.7 ± 12.7	127.4 ± 13.8	126.2 ± 13.1	<0.01
Diastolic blood pressure (mm Hg)	73.1 ± 9.0	71.7 ± 8.6	71.2 ± 8.6	<0.01

Note: Variables presented as mean ± SD or percentage. VSGA birth weight adjusted for gestational age and sex less than 3rd percentile, SGA birth weight adjusted for gestational age and sex between 3rd and 10th percentiles, and AGA birth weight adjusted for gestational age and sex between 10th and 90th percentiles. Binary variables compared by using the linear-by-linear test for trend in a 2 × 3 cross-table; continuous variables compared using 1-way analysis of variance.

Abbreviations: HUNT 2, Nord Trøndelag Health Study; SGA, small for gestational age; VSGA, very small for gestational age; AGA, appropriate for gestational age; DM, diabetes mellitus; CVD, cardiovascular disease (i.e. cerebral stroke or myocardial infarction age < 60 years).

\* Less than 12 years.

† Less than 1 hour per week of light physical activity.

**Table 3.** Odds Ratios for low-normal kidney function estimated using different methods at a young adult age by intrauterine growth observed in HUNT 2 participants born 1967-1976

Intrauterine growth	Men					Women				
	Cockcroft-Gault* (mL/min)	Cockcroft-Gault† (mL/min/1.73 m <sup>2</sup> )	MDRD Study Equation‡ (mL/min)	MDRD Study Equation§ (mL/min/1.73 m <sup>2</sup> )	Cockcroft-Gault* (mL/min)	Cockcroft-Gault† (mL/min/1.73 m <sup>2</sup> )	MDRD Study Equation‡ (mL/min)	MDRD Study Equation§ (mL/min/1.73 m <sup>2</sup> )	Cockcroft-Gault* (mL/min)	Cockcroft-Gault† (mL/min/1.73 m <sup>2</sup> )
<b>Birth weight</b>										
<3rd percentile (<2,450 g)	2.42 (1.43-4.08)	2.00 (1.15-3.49)	2.70 (1.61-4.51)	2.68 (1.58-4.51)	1.40 (0.80-2.44)	0.89 (0.45-1.72)	1.07 (0.58-1.97)	1.01 (0.54-1.90)	1.40 (0.80-2.44)	0.89 (0.45-1.72)
3rd-10th percentile (2,450-2,870 g)	1.80 (1.20-2.69)	1.43 (0.92-2.21)	1.52 (0.99-2.34)	1.19 (0.73-1.92)	1.61 (1.14-2.29)	1.33 (0.92-1.94)	1.24 (0.85-1.82)	1.19 (0.81-1.77)	1.61 (1.14-2.29)	1.33 (0.92-1.94)
10th-90th percentile (2,870-4,190 g)	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
<b>Multiaadjusted birth weight</b>										
<3rd percentile (<2,450 g)	2.43 (1.39-4.25)	1.86 (1.00-3.44)	2.21 (1.23-3.96)	2.35 (1.30-4.24)	1.71 (0.97-3.01)	1.07 (0.55-2.09)	1.19 (0.62-2.25)	1.08 (0.55-2.11)	1.71 (0.97-3.01)	1.07 (0.55-2.09)
3rd-10th percentile (2,450-2,870 g)	1.84 (1.21-2.80)	1.51 (0.95-2.40)	1.41 (0.88-2.25)	1.06 (0.62-1.82)	1.84 (1.28-2.64)	1.50 (1.01-2.20)	1.31 (0.87-1.96)	1.23 (0.81-1.86)	1.84 (1.28-2.64)	1.50 (1.01-2.20)
10th-90th percentile (2,870-4,190 g)	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
<b>Gestational age</b>										
<3rd percentile (<36 wk)	1.81 (1.02-3.20)	1.99 (1.14-3.48)	2.17 (1.26-3.75)	1.60 (0.87-2.94)	1.25 (0.64-2.46)	0.72 (0.31-1.66)	0.99 (0.47-2.09)	0.62 (0.25-1.55)	1.25 (0.64-2.46)	0.72 (0.31-1.66)
3rd-10th percentile (36-38 wk)	1.22 (0.80-1.85)	1.00 (0.64-1.56)	1.06 (0.68-1.65)	1.03 (0.66-1.63)	0.95 (0.60-1.52)	1.11 (0.71-1.73)	1.08 (0.69-1.70)	1.40 (0.92-2.12)	0.95 (0.60-1.52)	1.11 (0.71-1.73)
10th-90th percentile (38-42 wk)	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
<b>Multiaadjusted gestational age</b>										
<3rd percentile (<36 wk)	1.75 (0.97-3.17)	1.83 (1.01-3.31)	2.00 (1.12-3.56)	1.41 (0.73-2.73)	1.17 (0.57-2.37)	0.61 (0.24-1.52)	0.74 (0.32-1.73)	0.50 (0.18-1.38)	1.17 (0.57-2.37)	0.61 (0.24-1.52)
3rd-10th percentile (36-38 wk)	1.20 (0.78-1.87)	0.94 (0.57-1.54)	0.99 (0.61-1.60)	1.04 (0.64-1.68)	1.08 (0.67-1.74)	1.21 (0.76-1.90)	1.11 (0.69-1.77)	1.39 (0.89-2.17)	1.08 (0.67-1.74)	1.21 (0.76-1.90)
10th-90th percentile (38-42 wk)	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
<b>Birth weight by gestational age</b>										
<3rd percentile (<-2.0 SDS)	2.40 (1.46-3.94)	1.90 (1.11-3.25)	2.74 (1.68-4.48)	2.10 (1.22-3.60)	2.00 (1.21-3.29)	1.08 (0.58-1.99)	1.07 (0.58-1.98)	0.99 (0.52-1.85)	2.00 (1.21-3.29)	1.08 (0.58-1.99)

**Table 3. (continued)**

Intrauterine growth	Men					Women				
	Cockcroft-Gault* (mL/min)	Cockcroft-Gault† (mL/min/1.73 m <sup>2</sup> )	MDRD Study Equation‡ (mL/min)	MDRD Study Equation§ (mL/min/1.73 m <sup>2</sup> )	MDRD Study Equation¶ (mL/min)	Cockcroft-Gault* (mL/min)	Cockcroft-Gault† (mL/min/1.73 m <sup>2</sup> )	MDRD Study Equation‡ (mL/min)	MDRD Study Equation§ (mL/min/1.73 m <sup>2</sup> )	MDRD Study Equation¶ (mL/min)
3rd-10th percentile (-2 to -1.3 SDS)	1.66 (1.16-2.37)	1.19 (0.80-1.78)	1.65 (1.14-2.39)	1.50 (1.02-2.19)	1.54 (1.08-2.19)	1.21 (0.83-1.77)	1.17 (0.80-1.71)	0.90 (0.59-1.37)	1.00	1.00
10th-90th percentile (-1.3 to 1.3 SDS)	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Multiadjusted birth weight by gestational age										
<3rd percentile (<-2.0 SDS)	2.67 (1.59-4.48)	2.04 (1.14-3.63)	2.22 (1.26-3.89)	1.70 (0.90-3.20)	2.44 (1.46-4.07)	1.29 (0.69-2.39)	1.34 (0.72-2.48)	1.20 (0.63-2.28)	1.00	1.00
3rd-10th percentile (-2 to -1.3 SDS)	1.63 (1.11-2.39)	1.22 (0.80-1.87)	1.72 (1.16-2.52)	1.62 (1.09-2.43)	1.46 (1.00-2.14)	1.19 (0.79-1.78)	1.19 (0.79-1.79)	0.87 (0.55-1.37)	1.00	1.00
10th-90th percentile (-1.3 to 1.3 SDS)	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00

Note: Values expressed as odds ratio (95% confidence interval). Age-adjusted logistic regression analysis on the effect of categories of birth weight, gestational age, and birth weight by gestational age on kidney function. Kidney function was estimated by using different methods, and low-normal kidney function was defined as values less than the sex-specific 10th percentile with cutoff values as noted. Regression analyses were also adjusted for maternal risk factors (age, diabetes, kidney disease, and preeclampsia) and potential confounders at adult age (smoking and education). To convert creatinine clearance in mL/min to mL/s, multiply by 0.01667; glomerular filtration rate in mL/min/1.73 m<sup>2</sup> to mL/s/1.73 m<sup>2</sup>, multiply by 0.01667. Abbreviations: HUNT, Nord Trøndelag Health; SDS, SD score; MDRD, Modification of Diet in Renal Disease.

\* Cutoff value: 101 mL/min in men and 80 mL/min in women.

† Cutoff value: 92 mL/min/1.73 m<sup>2</sup> in men and 85 mL/min/1.73 m<sup>2</sup> in women.

‡ Cutoff value: 104 mL/min in men and 86 mL/min in women.

§ Cutoff value: 92 mL/min/1.73 m<sup>2</sup> in men and 86 mL/min/1.73 m<sup>2</sup> in women.

**Table 4.** Association between kidney function estimated using different methods at a young adult age and intrauterine growth observed in HUNT 2 participants born 1967-1976

Intrauterine Growth	Men						Women					
	Cockcroft-Gault (mL/min)	Cockcroft-Gault (mL/min/1.73 m <sup>2</sup> )	MDRD Study Equation (mL/min)	MDRD Study Equation (mL/min/1.73 m <sup>2</sup> )	Cockcroft-Gault (mL/min)	Cockcroft-Gault (mL/min/1.73 m <sup>2</sup> )	MDRD Study Equation (mL/min)	MDRD Study Equation (mL/min/1.73 m <sup>2</sup> )	Cockcroft-Gault (mL/min)	Cockcroft-Gault (mL/min/1.73 m <sup>2</sup> )	MDRD Study Equation (mL/min)	MDRD Study Equation (mL/min/1.73 m <sup>2</sup> )
Birth weight (1 kg)												
Age adjusted	7.3 (6.0-8.6)	2.8 (2.0-3.6)	6.1 (4.8-7.4)	1.7 (0.6-2.7)	5.5 (4.2-6.8)	1.8 (1.0-2.7)	3.8 (2.5-5.1)	-0.1 (-1.3-1.1)				
Multiadjusted	7.2 (5.8-8.6)	2.6 (1.8-3.4)	5.5 (4.1-6.9)	1.0 (-0.1-2.1)	5.7 (4.3-7.0)	2.0 (1.1-2.9)	3.9 (2.5-5.2)	0.0 (-1.2-1.2)				
Gestational age (1 wk)												
Age adjusted	0.3 (-0.1-0.7)	0.2 (-0.1-0.4)	0.3 (-0.1-0.7)	0.2 (-0.2-0.5)	0.2 (-0.2-0.6)	0.1 (-0.1-0.4)	0.2 (-0.2-0.6)	0.2 (-0.2-0.5)				
Multiadjusted	0.2 (-0.2-0.6)	0.1 (-0.1-0.4)	0.2 (-0.2-0.7)	0.2 (-0.2-0.5)	0.1 (-0.3-0.5)	0.1 (-0.1-0.4)	0.2 (-0.2-0.6)	0.2 (-0.2-0.6)				
Birth weight by gestational age (1 SDS)												
Age adjusted	4.0 (3.3-4.6)	1.5 (1.1-1.9)	3.2 (2.6-3.9)	0.8 (0.3-1.3)	2.9 (2.2-3.5)	0.9 (0.5-1.3)	1.9 (1.3-2.6)	-0.1 (-0.7-0.5)				
Multiadjusted	4.0 (3.3-4.7)	1.4 (1.0-1.8)	3.0 (2.3-3.7)	0.4 (-0.2-1.0)	3.1 (2.4-3.7)	1.0 (0.6-1.5)	2.0 (1.4-2.7)	-0.1 (-0.7-0.5)				

Note: The effect (95% confidence interval) of intrauterine growth on kidney function was first adjusted for subject age in a linear regression analysis. In the multiadjusted analysis, we also adjusted for maternal risk factors (age, diabetes, kidney disease, and preeclampsia) and potential confounders at adult age (smoking and education). To convert creatinine clearance in mL/min to mL/s, multiply by 0.01667; glomerular filtration rate in mL/min/1.73 m<sup>2</sup> to mL/s/1.73 m<sup>2</sup>, multiply by 0.01667.

Abbreviations: HUNT 2, Nord Trøndelag Health; SDS, standard deviation score; MDRD, Modification of Diet in Renal Disease.

Table 3 lists risks for low-normal kidney function, defined as estimates less than the 10<sup>th</sup> percentile, for different categories of BW, gestational age, and BW by gestational age. In men, crude BW less than the 3rd percentile (< 2,450 g) was associated with at least a 2 times greater risk of low-normal kidney function independent of how kidney function was estimated. Similar results were found for those born with a gestational age less than 36 weeks. When assessing intrauterine growth as BW adjusted for gestational age, we found that those born SGA (3rd to 10<sup>th</sup> percentile) also had significantly increased risk. Defining low-normal kidney function as Cockcroft-Gault estimates less than 100 mL/min (< 1.67 mL/s), men born VSGA (< 3rd percentile) had an odds ratio (OR) of 2.40 (95% confidence interval [CI], 1.46 to 3.94) compared with those born appropriate for gestational age. Men born SGA (3rd to 10th percentile) had an OR of 1.66 (95% CI, 1.16 to 2.37) for low-normal kidney function. A significant trend for increasing risk with decreasing BW-SDS scores was found ( $P < 0.001$ ). In women, the association with IUGR was much less consistent and highly dependent on how kidney function was estimated. Defining low-normal kidney function as Cockcroft-Gault estimates less than 80 mL/min (< 1.33 mL/s), a significant association was found with BW adjusted for gestational age for women born VSGA (OR, 2.00; 95% CI, 1.21 to 3.29) and SGA (OR, 1.54; 95% CI, 1.08 to 2.19), and there was also a significant test for trend ( $P < 0.001$ ). However, there was no significant association with BW or gestational age. When using other estimates for kidney function, no significant association was found.

Table 4 lists the effect of IUGR on kidney function as a continuous variable by using linear regression analysis. In men, there was a significant association between BW and all kidney function estimates. When BW increased by 1 kg, creatinine clearance increased by 7.3 mL/min (0.12 mL/s; 95% CI, 6.0 to 8.6). However, there was no association with gestational age, and the association with BW adjusted for gestational age was weaker than with crude BW. Creatinine clearance increased by 4.0 mL/min (0.07 mL/s; 95% CI, 3.3 to 4.6) per 1-SDS increase in BW. Adjustment for potential confounders, such as maternal risk factors (age, diabetes, kidney disease, and a preeclamptic pregnancy), adult smoking, and educational level did not change the strength of the observed associations. In women, there was also a significant, but less strong, association between BW and kidney function. When BW increased by 1 kg, creatinine clearance increased by 5.5 mL/min (0.09 mL/s; 95% CI, 4.2 to 6.8). There was no association with gestational age, and the association with BW adjusted for gestational age was weaker: creatinine clearance increased by 2.9 mL/min (0.05 mL/s; 95% CI, 2.2 to 3.5) per 1-SDS increase in BW. There was no significant association when estimating kidney function using the MDRD Study equation (in milliliters per minute per 1.73 m<sup>2</sup>). Results of multiaadjusted analyses were very similar to those of age-adjusted analyses.

Table 5 lists the effect of BW on blood pressure. Systolic blood pressure decreased by 0.74

**Table 5.** Association between birth weight and blood pressure at a young adult age observed in HUNT 2 participants born 1967-1976

	Change in Blood Pressure			
	Men		Women	
	/1 kg BW	/1 BW-SDS	/1 kg BW	/1 BW-SDS
Systolic blood pressure (mm Hg)				
Adjusted for age	-0.74 (-1.45 to -0.02)	-0.38 (-0.75 to -0.01)	-1.27 (-1.96 to -0.59)	-0.57 (-0.91 to -0.24)
Adjusted for age and potential confounders	-0.51 (-1.26 to 0.25)	-0.24 (-0.63 to 0.15)	-1.50 (-2.22 to -0.79)	-0.69 (-1.05 to -0.34)
Adjusted for age, potential confounders, and adult weight	-1.52 (-2.26 to -0.77)	-0.81 (-1.19 to -0.43)	-2.35 (-3.05 to -1.65)	-1.15 (-1.50 to -0.81)
Diastolic blood pressure (mm Hg)				
Adjusted for age	-0.16 (-0.68 to 0.36)	-0.16 (-0.43 to 0.10)	-0.68 (-1.18 to -0.17)	-0.42 (-0.66 to -0.17)
Adjusted for age and potential confounders	0.05 (-0.50 to 0.60)	-0.05 (-0.33 to 0.23)	-0.69 (-1.21 to -0.16)	-0.41 (-0.67 to -0.15)
Adjusted for age, potential confounders, and adult weight	-0.49 (-1.04 to 0.06)	-0.35 (-0.64 to -0.07)	-1.10 (-1.62 to -0.57)	-0.64 (-0.90 to -0.38)

Note: The association (95% confidence interval) between BW-SDS and blood pressure was assessed in an age-adjusted linear regression analysis. Maternal risk factors (age, diabetes, kidney disease, and preeclampsia) and current smoking and education were considered as potential confounders and adjusted for. We also adjusted for adult weight to illustrate the effect of considering this variable as a confounder.

Abbreviations: HUNT 2, Nord Trøndelag Health; BW, birth weight; SDS, SD score.

mm Hg (95% CI, 0.02 to 1.45) for each 1-kg increase in BW in men and by 1.27 mm Hg (95% CI, 0.59 to 1.96) in women after adjustment for age at the HUNT 2 examination. The decrease was 0.38 mm Hg (95% CI, 0.01 to 0.75) for each 1-SDS increment in BW adjusted for gestational age in men and 0.57 mm Hg (95% CI, 0.24 to 0.91) in women. Diastolic blood pressure did not decrease significantly in men, but in women, it decreased 0.68 mm Hg (95% CI, 0.17 to 1.18) for each 1-kg increase and 0.42 mm Hg (95% CI, 0.17 to 0.66) for each 1-SDS increment in BW. Exclusion of subjects administered antihypertensive medication did not change results. Adjustment for maternal risk factors (age, diabetes, kidney disease, and preeclampsia), current smoking, and education at adult age resulted in only minor changes in the observed associations, whereas adjustment for adult weight increased the coefficients significantly.

## **Discussion**

In this population-based study, we found that subjects born after IUGR had an increased risk of low-normal kidney function at a young adult age. When adjusting BW for gestational age, creatinine clearance decreased by 4.0 mL/min (0.07 mL/s) in men and 2.9 mL/min (0.05 mL/s) in women per 1-SDS decrease. If intrauterine growth was expressed as crude BW, creatinine clearance decreased by 7.3 mL/min (0.12 mL/s) in men and 5.4 mL/min (0.09 mL/s) in women per 1-kg decrease in BW.

Several method issues need discussion. Kidney function was not measured directly, and although the methods used for estimating kidney function previously were found to be unbiased in the present study group,<sup>26</sup> their accuracy is only moderate and misclassification can occur. Urine albumin is another important marker of kidney damage, but this was available for only a subgroup of participants and could not be used in our analyses. An optimal diagnosis of IUGR requires repetitive measurements of fetal growth parameters by using ultrasound. However, in epidemiological studies of larger numbers of pregnancies, such as ours, this procedure was not feasible; therefore, the concept of SGA was used as a proxy of IUGR. Because this reflects only the situation at birth, there will be some misclassification because not all SGAs result from IUGR and some non-SGAs experienced IUGR.

It is well documented that subjects with IUGR have lower adult height, lower muscle mass, and higher fat content.<sup>28,29</sup> Because of this body composition, they might have serum creatinine values that are underestimated and weights that are overestimated relative to height. Because the Cockcroft-Gault formula is based on the product of these 2 variables, it is conceivable that they balance each other and therefore give a reliable estimate of kidney function. However, overestimation or underestimation is also possible. The MDRD Study equation



might overestimate kidney function in subjects with IUGR, and a possible low-normal kidney function will be veiled, rendering the observed ORs conservative. Formulas including lean body mass could have been well suited for this research question,<sup>30</sup> but information for lean body mass was not available.

Furthermore, instead of expressing kidney function traditionally per surface area, some recommend to adjust for body size in the regression analysis.<sup>31-33</sup> This is controversial in “fetalorigin” studies because such body size variables as extracellular volume, body surface area, and body mass index are influenced by central obesity, which must be considered as an intermediate variable in the causal pathway between IUGR and later kidney function. Adjustment for height is suggested because smaller body size might require less absolute kidney filtration, but the use of noncorrected kidney function estimates is recommended until these problems are clarified further.<sup>23</sup> We therefore used Cockcroft-Gault estimates (milliliters per minute) as our primary outcome, but also used other estimates of kidney function. Especially in men, all outcome variables were consistently associated with BWSDS, indicating that the relation between BW and kidney function probably is not caused by chance finding or bias. However, in women, associations were less strong. Nonresponse may lead to selection bias. However, participants and nonparticipants did not differ in perinatal characteristics, thereby making an effect of selection bias less likely. Estimating gestational age based on date of last menstrual period is prone to error, but sonographic estimates were not routinely performed in Norway in the 1970s. A major strength of our study is the prospective design. Furthermore, the completeness of the perinatal registration enabled us to adjust BW for gestational age, which is considered important to obtain a valid measure of a subjects’s exposure to IUGR.<sup>7,34-36</sup>

We found that IUGR was associated with low-normal kidney function in young adults from the general population. This is consistent with findings in subjects born very prematurely<sup>17</sup>. A low nephron number was observed in low-BW subjects at autopsy. This could explain associations of low BW with such clinical outcomes as albuminuria, low-normal kidney function, and ESRD.<sup>6-17,37</sup> However, these are only a few studies, sometimes with a weak design, and the effects found were not strong. Case-control studies showed an OR of 1.5 for ESRD in subjects with BWs less than 2,500 g, but data for BW were missing in half the cases.<sup>15,37</sup>

Blood pressure was used as a secondary outcome because of the central role of the kidneys in blood pressure regulation, and IUGR is also postulated to lead to hypertension and reduced kidney function through a decreased number of nephrons.<sup>5</sup> We found that systolic blood pressure increased by 0.7 to 1.3 mm Hg per 1-kg decrease in BW. This is in accordance with 2 large meta-analyses that found systolic blood pressure increased by 1 to 2 mm Hg per 1-kg decrease in BW<sup>38,39</sup> and strengthens the external validity of our results. Earlier studies reported much larger associations, eg, an increase in systolic blood pressure of 11

mm Hg per 1-kg lower BW in middle-aged subjects.<sup>1</sup> These early more radical conclusions most likely reflect random error, publication bias, and inappropriate adjustment for current weight.<sup>38</sup> Theoretically, if there was no correlation between BW and adult blood pressure, but both positively correlated with adult body size, adjusting for adult body size could induce a negative correlation between BW and blood pressure.<sup>40</sup> Our study shows that such adjustment clearly increased the magnitude of the association, but did not create it. Others also found similar results,<sup>39</sup> and noting that low BW is associated with low adult weight, which in turn is associated with lower blood pressure, it is not yet clear how to solve this problem.

Sex was reported to modulate the effect of IUGR in many experimental animal models.<sup>41-43</sup> In different species and using different methods for creating an adverse fetal environment, male offspring consistently experienced worse outcomes. Our findings are in accordance with these results. The analysis of discrete outcomes showed nearly no association between IUGR and low normal kidney function in women, but analysis of continuous outcomes showed a general effect, although weaker, in women as well, which can be related to the greater power present with continuous data. Consequently, the intrauterine origin of adult disease hypothesis may be of greater importance in men than women. Still, bias caused by kidney function estimation methods veiling an effect also in females cannot be ruled out; the effect of IUGR on blood pressure was present in both men and women.

The impact of low BW on public health in developed countries has been questioned.<sup>44</sup> The question remains whether IUGR causes adult disease or IUGR is caused by a factor that also causes adult disease, either of genetic or permanent environmental nature. In the latter case, IUGR predicts rather than causes adult disease. Irrespective of mechanisms, our findings, even if effects are small, may have important implications. Small effects found at a young adult age may progress to larger effects at older ages because the kidney and vasculature no longer may be able to compensate with hyperfiltration, vasodilatation, and antioxidant pathways. Such amplification throughout life was clearly shown for blood pressure.<sup>39,45</sup>

Moreover, the potential effect of intervention can be different in developing countries. Mean BW is nearly 1 kg less in South Asia compared with western Europe.<sup>46</sup> Modifiable factors, such as shortage of food, micronutrient deficiencies, sex discrimination, and intentionally decreased food intake during pregnancy because of cultural beliefs may be of greater importance for BW than racial differences *per se*.<sup>35,47,48</sup> Although most fetal origins of adult disease studies were conducted in white populations, an increasing number of studies from China and India confirm the influence of low BW on adult blood pressure, glucose metabolism, and other cardiovascular risk factors.<sup>49-52</sup> Mortality and morbidity from coronary artery disease, diabetes mellitus, and chronic kidney disease are expected to increase by 200% to 400% in developing countries during the next 30 years because of increased longevity and adverse

lifestyle changes.<sup>53,54</sup> These estimates, which are based on changes in demographic and lifestyle factors alone, could even be too conservative because a large proportion of these populations were exposed to IUGR.

In conclusion, we found that IUGR was associated with low-normal kidney function in this large Norwegian population-based cohort study. The association was stronger in men than women and persisted after adjusting for potential important perinatal confounders. Although the absolute effects found were small, our results may have important etiologic implications.

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# 8

## **Associations between prenatal and infancy weight gain and BMI, fat mass, and fat distribution in young adulthood: a prospective cohort study in males and females born very preterm**

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## **Abstract**

### **Background**

Increasing evidence indicates that adult body composition is associated with prenatal and infancy weight gain, but the relative importance of different time periods has not been elucidated.

### **Objective**

The objective was to study the association between prenatal, early postnatal, and late infancy weight gain and body mass index (BMI), fat mass, and fat distribution in young adulthood.

### **Design**

We included 403 men and women aged 19 y from a Dutch national prospective follow-up study who were born at <32 wk of gestation. BMI, waist circumference, and waist-to-hip ratio SD scores and subscapular-to-triceps ratio, percentage body fat, fat mass, and fat-free mass at age 19 y were studied in relation to birth weight SD scores, weight gain from preterm birth until 3 mo postterm (early postnatal weight gain), and weight gain from 3 mo until 1 y postterm (late infancy weight gain).

### **Results**

Birth weight SD scores were positively associated with weight, height, BMI SD scores, and fat-free mass at age 19 y but not with fat mass, percentage body fat, or fat distribution. Early postnatal and late infancy weight gain were positively associated with adult height, weight, BMI, waist circumference SD scores, fat mass, fat-free mass, and percentage body fat but not with waist-to-hip ratio SD scores or subscapular-to-triceps ratio.

### **Conclusions**

In infants born very preterm, weight gain before 32 wk of gestation is positively associated with adult body size but not with body composition and fat distribution. More early postnatal and, to a lesser extent, late infancy weight gain are associated with higher BMI SD scores and percentage body fat and more abdominal fat at age 19 y.

## **Introduction**

Obesity is a major health problem throughout the world. Numerous studies have shown an association between obesity and various cardiovascular disease risk factors, such as diabetes, hypertension, and dyslipidemia.<sup>1-3</sup> Obesity is also associated with an increased risk of death.<sup>4</sup>

Fetal life and the early postnatal period have been suggested to be important for the development of adult obesity.<sup>5,6</sup> The Dutch famine studies have shown that reduced maternal calorie intake during the first 2 trimesters of pregnancy might increase the risk of adult obesity.<sup>7,8</sup> The association between birth weight, mainly an indicator of fetal growth during the third trimester, and adult obesity is equivocal.<sup>9</sup> In several studies, a linear positive association was found,<sup>10-12</sup> whereas in others a J- or U-shape association<sup>13,14</sup> or no association<sup>15</sup> was observed. In these studies, obesity was expressed as body mass index (BMI; in kg/m<sup>2</sup>), which includes both fat mass and fat-free mass.

In studies about fat mass and fat distribution, low birth weight has been associated with a more central pattern of fat distribution<sup>16,17</sup> and a lower BMI, mostly because of a lower lean body mass and not a lower fat mass<sup>18-22</sup>. In addition, a rapid rate of weight gain during early infancy has been associated with both a higher BMI<sup>23</sup> and more fatness and a more central pattern of fat distribution in childhood.<sup>6</sup> In certain specific populations, early growth has been positively associated with obesity and lean body mass in adulthood.<sup>24,25</sup> However, the associations between birth weight and adult body composition have not been consistently found in all populations,<sup>26,27</sup> and in various studies the associations became significant only after adjustment for adult BMI.<sup>16,17,21,22</sup> It is still unclear whether the associations found between early postnatal weight gain and fat mass and fat distribution in childhood persist into adulthood, and even less is known about fetal growth during the first 2 trimesters of pregnancy and subsequent adult body composition in humans.

We studied the relation between birth weight and early postnatal weight gain and adult BMI, fat mass, and fat distribution within the scope of the Project On Preterm and Small-for-gestational-age infants (POPS), a national cohort of individuals born very preterm. In this prospective study, birth weight could be used as an indicator of fetal growth during the first 2 trimesters, whereas growth during the third trimester and the period thereafter could be monitored well ex utero. We studied the relative predictive value of weight gain before 32 wk of gestation, during the period from preterm birth until 3 mo postterm (early postnatal weight gain), and from 3 mo until 1 y postterm (late infancy weight gain) for BMI, fat distribution, and body composition at age 19 y.

## Subjects and methods

### Study population

The subjects were participants of the POPS study. The POPS cohort comprises 94% of all live born infants in the Netherlands between 1 January and 31 December 1983 after a gestation of <32 completed weeks, with a birth weight of <1500 g, or both<sup>28</sup>. The physical and psychosocial outcomes of the POPS cohort have been intensely studied over the years.<sup>28,29</sup> In the current study, conducted when the subjects were 19 y of age, only those subjects with a gestational age <32 wk were studied. Subjects with congenital malformations leading to changes in body proportions and body composition (eg, focomely, amely, chromosomal abnormalities, and inborn errors of metabolism) were not eligible for inclusion. The study was approved by the medical ethics committee of all participating centers, and written informed consent was obtained from all participants.

### Measurements

Weight (g), length (cm), and head circumference (cm) were measured at birth and expressed as SD scores to correct for gestational age and sex with the use of Swedish references for very preterm infants.<sup>30</sup> At the ages of 3 mo and 1 y postterm, weight and length were measured at the outpatient clinics of the participating centers by trained physicians and nurses. These measurements were expressed as SD scores with the use of Dutch reference values.<sup>31</sup> Weight gain between birth and the age of 3 mo postterm (early postnatal weight gain) and between the ages of 3 mo and 1 y postterm (late infancy weight gain) were computed as  $\Delta$ -SD scores.

Anthropometric measurements were performed in 10 centers in the Netherlands by 15 nurses and physicians according to standardized procedures when the subjects had reached the age of 19 y. All assessors had received extensive training before the start of the study; during the study, retraining and standardization were carried out at 2-mo intervals to maximize interobserver reliability. The assessors were blinded with respect to the birth weight or duration of gestation of the subjects.

Subjects were measured barefoot while wearing underclothing. Weight was measured on a balance scale to the nearest 0.1 kg. Height was measured to the nearest 0.1 cm with a fixed stadiometer. BMI was calculated as weight in kg/height squared in cm.<sup>2</sup> Waist circumference was measured at the level of the umbilicus after full expiration and hip circumference at the level of the greater trochanter, both with the use of a flexible tape measuring to 0.1 cm accuracy. The waist-to-hip ratio was calculated. Four skinfold-thickness measurements were taken in duplicate with a calibrated skinfold caliper on the left side of the body at the triceps, biceps, subscapular, and iliacal regions according to guidelines of the World Health

Organization (biceps and subscapular)<sup>32</sup> and Falkner and Tanner (triceps and iliacal).<sup>33</sup> The sum of the 4 skinfold thicknesses was used as a measurement of overall subcutaneous fatness. The ratio of subscapular-to-triceps-skinfold thickness was calculated as an index of truncal to peripheral adiposity.<sup>34</sup> Fat mass and the corresponding fat-free mass were computed by using the equations of Durnin and Rahaman.<sup>35</sup> All outcome measures at age 19 y, except for the derived outcomes, were expressed as SD scores according to recent Dutch references.<sup>31,36,37</sup>

Multivariate linear regression analyses were performed with SPSS 11.0 software (SPSS Inc, Chicago) to assess associations between prenatal, early postnatal, and late infancy weight gain and the outcome measures at age 19 y. To disentangle the effects of birth weight, early postnatal weight gain, and late infancy weight gain on adult outcomes, early postnatal weight gain was corrected for birth weight, and late infancy weight gain was corrected for both the effect of birth weight and the effect of early postnatal weight gain. This correction was performed by entering the variables mentioned above into multivariate regression models. An interaction term, computed as the product of birth weight (SD scores) and early postnatal weight gain ( $\Delta$ -SD scores) and late infancy weight gain ( $\Delta$ -SD scores), respectively, was introduced to assess whether the effect of early postnatal and late infancy weight gain on outcome measures at age 19 y was different for those individuals with low birth weights compared with those with higher birth weights. The relative importance of weight gain during the various time periods was studied by comparing the changes in explained variance ( $R^2$ ) for each period.

Because it was not possible to use an SD score for variables derived from skinfold thicknesses, regression analyses with these outcome measures were corrected for sex. The analyses with waist and hip circumferences, fat mass, and fat-free mass at age 19 y as outcomes were also adjusted for variations in adult body size by adjusting for current height (SD scores). The analyses with height (SD scores) at age 19 y as the outcome measure were adjusted for target height (SD scores) computed as (midparental height  $\pm$  6.5 cm) + 4.5 cm (estimated secular trend per generation). All analyses were repeated with adjustment for the possible confounders race (white versus nonwhite), socioeconomic status (measured on a 6-point scale in which 1 was lowest and 6 was highest), and physical activity (measured on a 3-point scale).

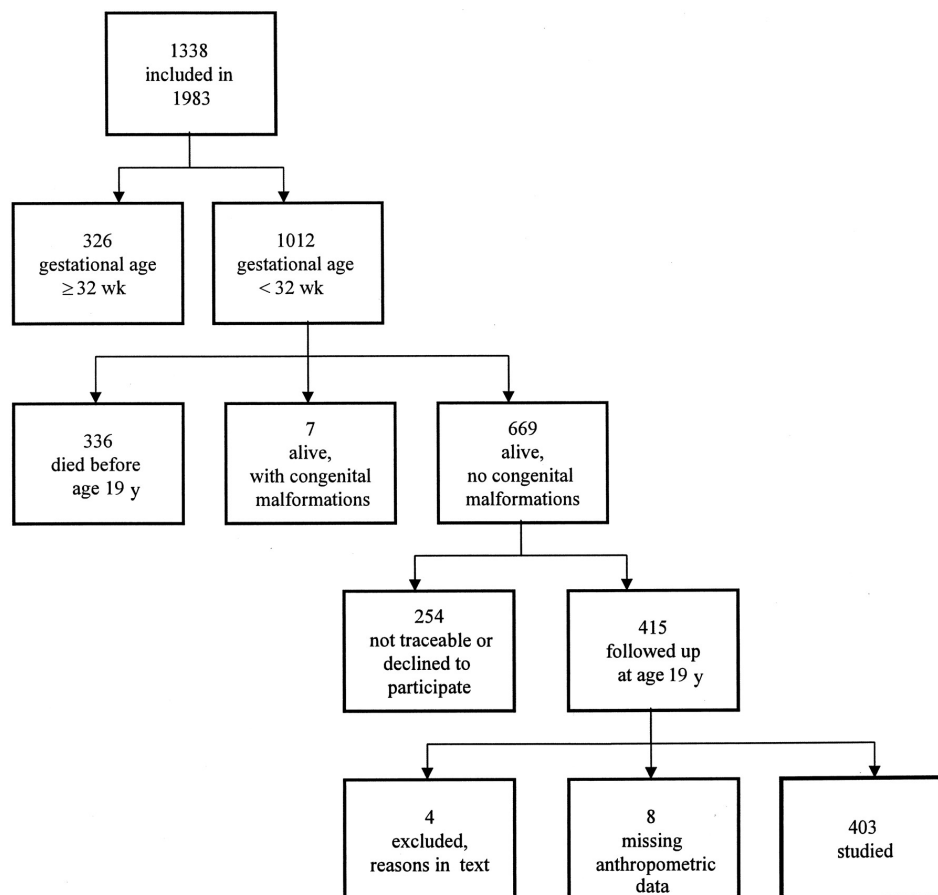
## **Results**

In 1983, 1012 infants who were born before 32 wk of gestation were included in the POPS cohort; 669 without congenital malformations were still alive at age 19 y. Of these subjects, 415 (194 males and 221 females) gave informed consent for the present study (response rate

62%). No anthropometric measurements were performed in 8 subjects either because these subjects were wheelchair bound or because no calibrated instruments were available. Four subjects were excluded from the analyses because of medical conditions or because they were taking medication that could lead to aberrations in body proportions and body composition: 2 subjects used oral corticosteroids, 1 woman had anorexia nervosa, and 1 woman was pregnant at the time of the study. The study population thus included 403 subjects in whom anthropometric measurements were performed at age 19 y (Figure 1).

Characteristics of the subjects are given in Table 1. Nonresponse was higher among males, nonwhites, and those with a mother with a low educational level. Mean birth weight (SD scores) and gestational age did not differ significantly between responders and nonresponders.

**Figure 1.** Flow chart of the study sample



The anthropometric characteristics of the response group are provided in Table 2 as absolute values and SD scores. For both males and females, the mean values for height, weight, and BMI were lower than the means of the Dutch reference population of 19-y-olds, whereas the mean values for waist circumference, waist-to-hip ratio, and the sum of the skinfold thicknesses were greater than the Dutch population means.

**Table 1.** Birth and neonatal characteristics of infants born very preterm

Characteristic	Responders ( <i>n</i> = 403) <sup>1</sup>	Nonresponders ( <i>n</i> = 254) <sup>1</sup>
Demographic		
Sex (% male)	46.4	65.7 <sup>2</sup>
Race (% white)	87.7	80.2 <sup>3</sup>
Low-educational-level mother (%)	38.9	56.5 <sup>2</sup>
Obstetric		
Multiple birth (%)	22.8	21.7
Hypertension during pregnancy (%)	17.6	15.7
Diabetes mellitus gravidarum (%)	5.0	4.3
Smoking during pregnancy (%)	28.0	29.5
Drugs and alcohol intoxication (%) <sup>4</sup>	52.0	52.0
Elective delivery (%)	19.4	13.4 <sup>3</sup>
Birth		
Gestational age (wk)	29.7 ± 1.5 <sup>5</sup> (25.7–31.9) <sup>6</sup>	29.8 ± 1.5 (25.4–31.9)
Birth weight (g)	1316 ± 336 (560–2580)	1347 ± 274 (610–2000)
(SD score)	−0.13 ± 1.0 (−2.98–2.70)	−0.091 ± 0.88 (−3.60–1.66)
Birth length (cm)		
(cm)	39.1 ± 3.4	39.6 ± 2.9 <sup>3</sup>
(SD score)	−0.12 ± 1.2	−0.062 ± 1.13
Head circumference at birth		
(cm)	27.4 ± 2.1	27.6 ± 1.9
(SD score)	0.029 ± 1.2	−0.091 ± 1.0
Postnatal		
Weight at 3 mo		
(kg)	5.1 ± 0.90	5.3 ± 0.88
(SD score)	−0.94 ± 1.3	−0.90 ± 1.4
Weight at 1 y		
(kg)	8.9 ± 1.2	9.1 ± 1.4
(SD score)	−0.98 ± 1.2	−0.94 ± 1.4

- 1 The sample size was slightly less for some variables.
- 2,3 Significantly different from responders (chi-square test for dichotomous variables and two-sample *t* tests for continuous variables): 2 ; *P* < 0.001, 3 ; *P* < 0.05.
- 4 Smoking, drinking alcohol, or using soft drugs, hard drugs, or methadone during pregnancy.
- 5  $\bar{x} \pm SD$  (all such values).
- 6 Range (all such values).

**Table 2.** Characteristics of the response group at age 19 year by sex

	Males ( <i>n</i> = 187) <sup>a</sup>	Females ( <i>n</i> = 216) <sup>a</sup>	<i>P</i> <sup>b</sup>
Height			
(cm)	179.4 ± 7.9 <sup>c</sup>	166.4 ± 7.1	0.001
(SD score)	-0.55 ± 1.1	-0.60 ± 1.1	0.633
Weight			
(kg)	69.9 ± 12.1	60.5 ± 10.6	0.001
(SD score)	-0.41 ± 1.2	-0.48 ± 1.4	0.583
BMI			
(kg/m <sup>2</sup> )	21.7 ± 3.1	21.8 ± 3.4	0.659
(SD score)	-0.10 ± 1.2	-0.17 ± 1.2	0.569
Waist circumference			
(cm)	80.2 ± 8.9	76.6 ± 7.9	0.001
(SD score)	0.24 ± 1.1	0.73 ± 0.92	0.001
Hip circumference			
(cm)	92.1 ± 8.1	94.2 ± 9.4	0.017
(SD score)	-0.22 ± 1.2	0.025 ± 1.1	0.037
Waist-to-hip ratio	0.87 ± 0.054	0.82 ± 0.063	0.001
Waist-to-hip ratio (SD score)	0.72 ± 0.92	0.90 ± 0.93	0.055
Sum of skinfold thicknesses			
(mm)	41.3 ± 20.6	62.6 ± 22.4	0.001
(SD score)	1.7 ± 2.8	1.1 ± 1.6	0.012

a The sample size was slightly less for some variables.

b Two-sample *t* tests.

c  $\bar{x} \pm$  SD (all such values).

### Prenatal, early postnatal, and late infancy weight gain and adult anthropometry

The associations between prenatal, early postnatal, and late infancy weight gain and the anthropometric outcomes at age 19 y are shown in Table 3. Birth weight (SD scores) was positively associated with adult height, weight, BMI, and waist circumference (SD scores), although the 95% CIs for the latter 2 variables almost included zero. There was also a positive association between birth weight (SD scores) and both fat mass and fat-free mass but not between birth weight (SD scores) and percentage body fat at age 19 y. When adjusted for current height (SD scores), the association between birth weight (SD scores) and waist circumference disappeared. The regression coefficient of the association between birth weight (SD scores) and fat-free mass decreased, and the association between birth weight (SD scores) and fat mass became nonsignificant after correction for current height (SD scores). No significant associations were found between birth weight (SD scores) and the waist-to-hip ratio (SD scores), the sum of skinfold thicknesses (SD scores), and the subscapular-to-triceps ratio at age 19 y.

**Table 3.** Linear regression analyses of anthropometric measures at age 19 y with birth weight (SD score), early postnatal weight gain, and late infancy weight gain<sup>1</sup>

Outcome measures at age 19 y	Birth weight (SD score)			Early postnatal weight gain (Δ-SDS) adjusted for birth weight (SD score)			Late infancy weight gain (Δ-SDS) adjusted for birth weight (SD score) and for early postnatal weight gain (Δ-SD score)		
	N	β	95% CI	N	β	95% CI	N	β	95% CI
Height (SD score)	403	0.366	0.265 to 0.466	373	0.238	0.150 to 0.325	351	0.422	0.310 to 0.535
Height (SD score) adjusted for target height (SD score)	401	0.299	0.218 to 0.381	371	0.202	0.132 to 0.273	351	0.240	0.143 to 0.337
Weight (SD score)	403	0.369	0.248 to 0.489	373	0.321	0.215 to 0.427	351	0.445	0.311 to 0.580
BMI (SD score)	403	0.152	0.036 to 0.268	373	0.196	0.092 to 0.300	351	0.215	0.078 to 0.356
Waist circumference (SD score)	399	0.106	0.005 to 0.207	369	0.173	0.082 to 0.263	347	0.218	0.096 to 0.339
Waist circumference (SD score) adjusted for height at age 19 y (SD score)	399	0.00546	-0.098 to 0.109	369	0.111	0.020 to 0.203	347	0.138	0.009 to 0.267
Hip circumference (SD score)	399	0.155	0.042 to 0.268	369	0.173	0.072 to 0.273	347	0.288	0.153 to 0.424
Hip circumference (SD score) adjusted for height at age 19 y (SD score)	399	0.0208	-0.093 to 0.135	369	0.0879	-0.012 to 0.188	347	0.166	0.025 to 0.307
Sum of 4 skinfold thicknesses (SD score)	390	0.0535	-0.170 to 0.277	361	0.190	-0.015 to 0.394	340	0.286	0.011 to 0.561
Fat mass (kg) <sup>2</sup>	390	0.826	0.264 to 1.389	361	0.873	0.370 to 1.376	340	1.275	0.614 to 1.936
Fat mass (kg) adjusted for height at age 19 y (SD score) <sup>2</sup>	390	0.331	-0.252 to 0.914	361	0.599	0.091 to 1.108	340	0.961	0.258 to 1.665
Fat-free mass (kg) <sup>2</sup>	390	2.181	1.582 to 2.779	361	1.639	1.116 to 2.161	340	2.429	1.178 to 3.081
Fat-free mass (kg) adjusted for height at age 19 y (SD score) <sup>2</sup>	390	0.811	0.310 to 1.312	361	0.855	0.420 to 1.290	340	1.202	0.605 to 1.798
Percentage body fat (%) <sup>2</sup>	390	0.176	-0.329 to 0.682	361	0.479	0.022 to 0.936	340	0.651	0.033 to 1.269

<sup>1</sup> Waist-to-hip ratio (SD score), subscapular-to-triceps ratio, and the interaction terms between birth weight and later weight gain were not significant and thus were not reported.

<sup>2</sup> Adjusted for sex.



**Table 4.** Explained variance ( $R^2$ ) and change in explained variance ( $R^2$  change) for the outcome measures at age 19 y, which were significantly associated with birth weight (SD score), early postnatal weight gain, and late infancy weight gain ( $\Delta$ -SDS), or both according to a stepwise model in which the independent variables were included in chronologic order

Outcome measures at age 19 y	n	$R^2$ change (%)			Sex	Total $R^2$ (%)
		Target height (SD score)	Height at age 19 y (SD score)	Birth weight (SD score)		
Height (SD score)	351	37.5 <sup>a</sup>	—	6.2 <sup>a</sup>	—	51.5
Weight (SD score)	351	—	—	9.6 <sup>a</sup>	—	28.0
BMI (SD score)	351	—	—	2.7 <sup>a</sup>	—	10.1
Waist circumference (SD score)	347	—	8.8 <sup>a</sup>	0.0	—	12.2
Sum of 4 skinfold thicknesses (SD score)	340	—	—	0.1	—	3.1
Fat mass (kg)	340	—	5.4 <sup>a</sup>	0.2	25.2 <sup>a</sup>	34.0
Fat-free mass (kg)	340	—	18.1 <sup>a</sup>	0.7 <sup>a</sup>	60.1 <sup>a</sup>	80.8
Percentage body fat (%)	340	—	—	0.0	64.7 <sup>a</sup>	65.8

<sup>a</sup>  $P < 0.05$ .

Early postnatal weight gain and late infancy weight gain were both positively associated with height, weight, BMI, and waist circumference (SD scores), fat mass, fat-free mass, and percentage body fat at age 19 y. Late infancy weight gain was also positively associated with the adult sum of skinfold thicknesses (SD scores). The coefficients of waist circumference, fat mass, and fat-free mass in relation to early postnatal and late infancy weight gain diminished after correction for current height (SD scores) but remained significant. When adjusted for target height (SD scores), the associations between prenatal, early postnatal, and late infancy weight gain and adult height (SD scores) remained significant but decreased in magnitude. No significant associations were found between early postnatal and late infancy weight gain and the waist-to-hip ratio (SD scores) or subscapular-to-triceps ratio in young adulthood.

No significant interaction was found between birth weight (SD scores) and early postnatal weight gain or between birth weight (SD scores) and late infancy weight gain with regard to any of the outcome measures at age 19 y. Correction for race, socioeconomic status, sex, and physical activity did not significantly change the results of the abovementioned analyses (data not shown).

#### **Relative contributions of weight gain during different time periods**

For the anthropometric outcomes at age 19 y that were associated with weight gain during early life, the percentages of variance explained by weight gain during the different time periods are presented in Table 4. For current height (SD scores), 37.5% of the variance was explained by target height (SD scores). Birth weight explained 6.2% of the variance in current height not explained by target height, whereas early postnatal weight gain explained another 4.5% of current height variance not explained by target height or birth weight. Late infancy weight gain explained 3.3% of the variance of current height not explained by the abovementioned variables. So, for current height (SD scores), adjusted for target height (SD scores), the largest change in  $R^2$  values was observed for the effect of birth weight (SD scores).

For adult weight, the effect of birth weight on  $R^2$  change equaled the effect of early postnatal weight gain. For BMI and waist circumference (SD scores) and fat mass, fat-free mass, and percentage body fat, the largest increase in  $R^2$  - apart from adjustments for sex and current height (SD scores) - was observed with the input of early postnatal weight gain into the model. The percentages of variance explained by early postnatal and late infancy weight gain were larger for adult fat mass than for adult fat-free mass.

## Discussion

This study describes the results of a large-scale prospective study on the relation between birth weight, postnatal weight gain, and anthropometric variables at the age of 19 y in subjects born very preterm and provides exclusive information about the predictive value of weight gain during the first 2 trimesters of pregnancy for adult body composition.

In our study there might have been an interference of the effects of possible programming (ie, the lifelong changes in structure or function of body systems that follow a specific insult in early life) and the effects of prematurity on BMI and body composition in young adulthood. We studied only children with a gestational age <32 wk and corrected birth weight for gestational age, which facilitated a valid comparison within the cohort. The results may not be generalizable to infants born at term but do provide useful information about fetal growth restriction in infants born very preterm. We did not separately address the effect of gestational age on adult outcomes, because this interesting issue provides sufficient data for a different study.

Inherent to the population studied, perinatal mortality was high, especially in those infants with a shorter gestational age and to a lesser extent in those with a lower absolute birth weight. However, no significant difference in birth weight (SD scores) was found between those who died and those who survived; therefore, confounding by selective mortality seems unlikely. The same reasoning can be applied to the response and the nonresponse groups. Some subjects had missing data on weight at 3 mo or 1 y, but these missing data were not related to any of the outcome measures.

We found some differences between anthropometric characteristics at age 19 y between the male and the female participants. Whereas the differences in absolute values were expected, the different SD scores for a few outcomes were not. However, because these sex differences were found in unplanned post hoc analyses, the results should be interpreted very cautiously. Adjustment for sex did not change the conclusions of the study.

To determine fat mass and distribution we used skinfold thicknesses, which are known to be prone to interobserver variation.<sup>38</sup> However, although skinfold-thickness measurements tend to overestimate fat mass somewhat compared with a direct method such as dual-energy X-ray absorptiometry (DXA), Fewtrell et al<sup>39</sup> concluded from their study on prematurity and body fatness at ages 8–12 y that the same associations were found with both methods. The correlations between the anthropometric data of Durnin and dual-photon absorptiometry are 0.76 and 0.83 for males and females, respectively.<sup>40</sup> A study of the reproducibility of the skinfold-thickness measurements used in the POPS-19 study

showed that the reliability of the skinfold-thickness measurements was relatively low, but the reliability of the derived estimates of body composition was much higher (intraclass correlation coefficients ranged from 0.55 to 0.98), with a high intraobserver reliability (intraclass correlation coefficient > 0.99) (AM Euser, MJJ Finken, S le Cessie, JM Wit, FW Dekker, unpublished observations, 2004). Because the birth weights of participants did not substantially differ between centers, this relatively low interobserver reliability will have only attenuated the associations between birth weight and body composition at age 19 y.

We found that birth weight was positively associated with weight, height, and BMI at age 19 y. These findings are consistent with those of studies in populations born at term.<sup>11,12</sup> Our study indicates that the positive association between birth weight and adult BMI is determined as early as the first 2 trimesters of pregnancy. This finding conflicts with the results of the Dutch famine studies, which suggest that maternal malnourishment during early gestation predisposes to later obesity in the offspring.<sup>7,8</sup> Our study does not confirm the J- or U-shape relation between birth weight and adult BMI found in some studies,<sup>13,41,42</sup> which might form a biological link between low birth weight and adult diseases. This suggests that either the associations mentioned above are established during the third trimester of pregnancy or that there is another link between fetal growth and adult disease. Singhal et al<sup>18</sup> proposed that this link might be formed by fat-free mass. However, though fat-free mass was significantly associated with birth weight, our data show no significant association between birth weight and percentage body fat in adulthood.

Although prenatal weight gain was not associated with percentage body fat, more early postnatal weight gain was associated with both a higher BMI and a higher percentage body fat at age 19 y. The higher BMI found agrees with the findings of earlier studies in which a positive association between early growth and adult BMI and obesity was found.<sup>13,43</sup> Our study showed that this association was independent of birth weight and that the higher BMI was partly accounted for by a higher percentage body fat, at least in premature infants. So far, only a few studies have addressed the relation between early growth and adult fat mass and distribution. From our results it may be concluded that the positive associations found by Ong et al<sup>6</sup> and Stettler et al<sup>24</sup> between early catch-up growth and fatness in childhood persist into young adulthood. This agrees with a study by Li et al<sup>25</sup> about early postnatal growth in length and adult fat-free mass in a Guatemalan population.

Moreover, we also found that a greater postnatal weight gain was associated with a higher adult waist circumference, both when adjusted and unadjusted for current height (SD scores). Fetal weight gain was also positively associated with waist circumference (SD scores), but after adjustment for current body height (SD scores), the association completely disappeared;

this finding indicates that the increase in waist circumference with higher birth weight reflects mainly an increase in body size and not solely an increase in visceral fat. Prenatal and postnatal weight gain were not significantly associated with waist-to-hip ratio or subscapular-to-triceps ratio, although a tendency for low birth weight to be associated with a higher waist-to-hip ratio and a subscapular-to-triceps ratio was observed. This finding agrees with the results of Fall et al<sup>13</sup> and Li et al<sup>25</sup>. In some studies, low birth weight and early growth have been associated with a more truncal and abdominal fat pattern<sup>13,16,17</sup> but only after adjustment for current BMI. Although adjustment for current body size in fetal origins studies should always be interpreted cautiously, it might be arguable for some adult disease outcomes.<sup>44</sup> However, we think it is theoretically incorrect to adjust for current BMI -which includes current fat mass- in analyses with fat mass and fat distribution as outcomes. If correction for current body proportions is applied, an index independent of body fat should be used.

The associations found between birth weight, early postnatal weight gain, and late infancy weight gain and adult BMI and body composition might be explained by perinatal programming.<sup>45</sup> However, it is also possible that genes that influence prenatal, perinatal, and adult determinants underlie the associations found. More research is required about the possible mechanisms of programming of body proportions and body composition.

In conclusion, gestation, the period from birth until 3 mo postterm, and the period from 3 mo until 1 y postterm seem to be important predictors of body size and body mass in young adulthood in infants born very preterm. Greater weight gain during these periods is associated with greater height, weight, BMI, and fat-free mass at age 19 y. Birth weight in infants born very preterm is not associated with fat distribution. However, early postnatal weight gain and late infancy weight gain are -independently of birth weight or current height- associated with a more abdominal pattern of fat distribution and a higher percentage body fat. The relative effect of weight gain from birth until 3 mo postterm on adult fat mass and fat distribution is more pronounced than is the effect of weight gain from 3 mo until 1 y postterm.

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## Chapter 8

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# 9

## General discussion



## General discussion

The general aim of the studies described in this thesis was of two sorts; in the first place to study the effects of prenatal and early postnatal growth on various adult health outcomes in individuals born preterm or with a low or very low birth weight, and in the second place to address methodological issues closely related to early origins of adult disease studies. In this chapter we will consider the results found in these studies in a more extensive perspective, both theoretically and clinically. At first, we will reflect on the broad scope of definitions, associations, and pathology that lies behind the term 'metabolic syndrome'. Next, we will briefly relate this to the early origins hypothesis and its putative underlying etiological mechanisms. Subsequently, we will consider the sequence of posing research questions, building regression models, and interpreting results in early origins studies. This will be followed by several methodological issues inherently intertwined with the populations studied, after which we will address our main findings in relation to the recent literature about these topics. Finally, clinical relevance and future research perspectives will be discussed.

### A metabolic syndrome?

The metabolic syndrome and some of its separate components form important outcome measures in our clinical studies in the HUNT and POPS populations. However, at first glance it becomes evident that this so called metabolic syndrome has no universally accepted definition, and that a confusion of tongues seems to exist. Numerous names and definitions coexist for the syndrome, of which those of the World Health Organization, the American Heart Association, the International Diabetes Federation, and the National Cholesterol Education Program are most widely used.<sup>1-4</sup> While those definitions agree in considering central obesity, impaired glucose tolerance, dyslipidemia, and hypertension as essential components, they differ about corresponding cut-off levels, for these traits are all continuous variables artificially cut into the binary variable physiological versus pathological. Besides, the definitions differ in the algorithm used to cluster components to a syndrome, in how to measure glucose tolerance and obesity, in the appliance or non-appliance of different cut-offs for anthropometric values in different ethnic populations, and in the inclusion of the additional components microalbuminuria in the WHO definition.<sup>1</sup> The result of this excessive number of definitions is a decreased generalizability of results found, and a thwarted comparison of the prevalence of the metabolic syndrome in different populations, for prevalences in the same population vary impressively depending on the syndrome definition used.<sup>5,6</sup>

The original WHO definition of the metabolic syndrome is unique in the inclusion of microalbuminuria,<sup>1</sup> which is the earliest clinical manifestation of obesity-associated kidney

damage and diabetic nephropathy in humans. The association between the kidney, obesity, and the metabolic syndrome is complex and might be pathologically mediated by both type II diabetes and hypertension.<sup>7</sup> Though not undisputed, microalbuminuria has repetitively been found as a marker of insulin resistance and glucose intolerance that becomes evident before diabetes, and may thus serve as a marker of disease activity.<sup>8</sup> However, even in non-diabetic adults the metabolic syndrome has been shown to be independently associated with an increased risk for chronic kidney disease.<sup>9</sup> So, apart from functioning as a complementary marker of insulin resistance only, the damaged kidney has a dual role with regard to the metabolic syndrome. This might be due to the fact that the kidney is closely associated with hypertension as well. On one hand, the kidney can raise blood pressure by several mechanisms hence provoking hypertension, while on the other hand hypertension aggravates the progression of renal disease.<sup>10</sup> This hypertension found in obesity, another component of the metabolic syndrome, appears to be closely linked to abnormal kidney function caused by simultaneous activation of the renin angiotensin system, of the sympathetic nerve system, and by physical compression of the kidneys when visceral obesity is present.<sup>7</sup> However, despite increased pathophysiological understanding, the precise interaction between the kidneys and the metabolic syndrome has not been unraveled yet.

In the pediatric field as well a tangle of definitions for the metabolic syndrome used in parallel exists, with the definition of the International Diabetes Federation being the most recent one.<sup>11</sup> This abundance is not surprising, for in children and adolescents defining 'the metabolic syndrome' is even more complex than in adults. In the first place, several components of the syndrome, e.g. waist circumference and blood pressure, increase with age, and part of them are also influenced by puberty, like fat distribution and insulin sensitivity.<sup>12</sup> Secondly, the end points for which the syndrome might give an increased risk are still far away in time and usually do not occur until in late adulthood. Therefore, direct evidence for the predictive value of the syndrome in childhood for increasing the risk of adult cardiovascular death or even disease is lacking, and instead only surrogate end points are reported.<sup>13</sup> However, the international increase in overweight and obese infants and adolescents<sup>14</sup> has led to an urge to define the syndrome in this young and dynamic population as well, and numerous definitions coexist.<sup>15</sup> Partly, the problems mentioned above have been resolved by classifying children into age groups with different definitions, and by using age- and sex-specific percentiles or Z-scores in most definitions.<sup>15</sup> However, it should be stressed that anthropometric reference charts generally have a descriptive origin and not a normative one, so when the population as a whole becomes more obese during the years, the same percentile lines represent increased BMI values. This has been clearly shown in the Netherlands between 1980 and 1997.<sup>16</sup> This knowledge should be kept in mind when defining which percentile should serve as cut-off point. Besides, as reference charts tend to result from cross-sectional data collection, the inter-individual variance in the onset of puberty is intertwined in the reference values of individual ages.

The reason that 'The Metabolic Syndrome' as such does not exist, neither in adults nor in children, is partly inherent to it being a syndrome, as the definition of a syndrome is rather vague. The word 'syndrome' in Greek means 'the confluence', and this confluence is the only basis of a syndrome, which is usually defined as: "a symptom complex of unknown etiology, which is characteristic of a particular abnormality" (MeSH term), or: 'a pattern of multiple anomalies thought to be pathologically related'.<sup>17</sup> However, while the etiology per definition is still unknown in the initial decision of calling a constellation of symptoms a syndrome, it is implicitly expected that this unifying pathological relation will be found in subsequent research. Nevertheless, a satisfying unifying pathological base for the metabolic syndrome has not yet been found, despite intensive research, while the concept of the metabolic syndrome has been used for decades.<sup>18</sup> Various hypotheses have been postulated, of which the insulin resistance hypothesis with glucose intolerance as central key player to explain the pathology of the other features of the syndrome is the most profoundly worked out and generally accepted one.<sup>19</sup> However, it is possible to have the metabolic syndrome without being insulin resistant, and the association of insulin resistance with some of the other components of the syndrome is rather weak, while other more closely related features are excluded from the definition.<sup>20</sup> Other complementary and alternative hypotheses with a more prominent role for central obesity,<sup>3</sup> inflammation,<sup>21</sup> or neurobiology<sup>22</sup> have been proposed, but have not led to a satisfying single underlying etiology, which is, together with the ill-defined dichotomous criteria, grist to the mill of the opponents of the existence of a metabolic syndrome.<sup>20,23</sup>

In addition to the physiologist's point of view from which a unitary causation is lacking, the metabolic syndrome is also criticized from an epidemiologist's point of view. Regardless if the expected common etiology has already been unraveled or not, the practical usefulness of working with a syndrome construct is the improved prediction of disease or complications compared with the sum of its separate components. And this, in turn, can be used in policy making and daily clinical practice. Originally, the metabolic syndrome has been defined because it should predispose to diabetes and cardiovascular disease (CVD).<sup>1</sup> Indeed, the metabolic syndrome is associated with an increased risk of type two diabetes.<sup>24,25</sup> However, as impaired fasting glucose, impaired glucose tolerance, or even overt diabetes form all components of the different definitions, this finding does not really strike like a bolt from the blue. The metabolic syndrome predicts future cardiovascular events in men and women as well.<sup>6,26</sup> But again, objections can be raised; in the first place, the various definitions of the metabolic syndrome do not seem to predict better than existing risk scores for Cardio Vascular Disease (CVD) like the Framingham risk score.<sup>27,28</sup> And more important, they do not predict better than the sum of the separate components.<sup>5,29,30</sup> As the syndrome is composed of components which do all form well established, undisputed risk factors for CVD, a more than additive risk in case of clustering of components ought to form the mere advantage of taking them together in one definition. Taken all this criticism together, the usefulness

of the concept “metabolic syndrome” for the clinician seems to be little, as establishing the diagnosis improves neither pathophysiological understanding nor clinical utility.

While indications for a common underlying etiology of the metabolic syndrome are often searched for in basic research as in animal models, or statistical models like factor analyses, another form of circumstantial evidence can be found in the classical logic form of *modus tollens*, i.e. “denying the consequent”. In science this form became well known when it was used by Karl Popper, who postulates that falsifiability is a prerequisite for a scientific theory. And though no rockbottom of knowledge exists, the best theory is that with the highest empirical content combined with the highest degree of corroboration.<sup>31</sup> With our study on the metabolic syndrome in the HUNT we tested the hypothesis that the metabolic syndrome is a true syndrome with one common underlying etiology. If this first premise is true, the second premise is that all components of the metabolic syndrome should show the same kind of association with this underlying cause. Part of the underlying etiology of the metabolic syndrome - including that of the insulin resistance component – is likely to be formed by early life experiences, for small but recurring effects have been found for several of the separate components e.g. hypertension and glucose intolerance.<sup>32,33</sup> In that case all separate components of the metabolic syndrome should have the same kind of association with an early life parameter, e.g. birth weight. However, we found several statistically significant but inconsistent associations of birth weight with the separate components of the so called metabolic syndrome. Though alternative explanations are imaginable, this result does not corroborate the metabolic syndrome as a true syndrome with one single underlying etiology.

### Early origins

Underneath this level of epidemiological associations, several mechanisms have been proposed with regard to the explanation of the replicated associations between early growth and various adult metabolic diseases. Typically, the major contrast is formed by the ‘thrifty phenotype’ hypothesis which was first postulated by Barker et al. on one hand, and the ‘thrifty genotype’ hypothesis on the other hand. In the first theory, the fetus is thought to adapt to intrauterine shortage of nutrients by a reduced capacity for insulin production by the pancreas, and insulin resistance, which results in reduced somatic growth *in utero*, and subsequent an increased adult disease sensitivity when growing up in a nutrient rich postnatal environment.<sup>34</sup> In the second theory, reduced insulin-mediated fetal growth and adult insulin resistance, type II diabetes, and disease susceptibility are all regarded as phenotypes corresponding to the same insulin-resistance genotype.<sup>35</sup> Adjacent to these two opposites, other hypotheses have been generated, like the “catch-up growth” hypothesis in which early postnatal catch-up growth is thought to be the pathogeneus link between fetal and adult life by causing over-activation of

the IGF system which in turn will result in secondary insulin resistance.<sup>36</sup> Further, in the “fetal salvage” hypothesis the importance of insulin resistance is stressed while in contrast to the fetal insulin hypothesis beta cell hypoplasia is not thought to play a role in the development of adult disease in this theory.<sup>37</sup> Finally, also increased fetal exposure to cortisol mediated by decreased maternal enzyme activity is suggested to connect low birth weight and adult disease, especially hypertension.<sup>38</sup>

Recently, there is increasing evidence that epigenetic mechanisms, which concern the regulation of gene activity without affecting the genetic DNA code itself, might underlie the associations between early life parameters and adult disease. Epigenetic mechanisms tend to be gene specific and cell specific, and though it is unclear when they exert their effects on human developmental plasticity and subsequent disease susceptibility, this window might well extend from before conception until early postnatal life.<sup>39</sup> Though much has still to be unravelled about epigenetic mechanisms and their role in the early origins of adult disease, they might well form a union between in former partly contradicting hypotheses.

### **Methodological reflections**

Originally, only the effect of birth weight as a proxy for prenatal growth and influences on adult health outcomes was presented,<sup>40</sup> which is quite straightforward. However, it is well known that adult metabolic outcomes, e.g. blood pressure, are strongly positively associated with current adult weight.<sup>41,42</sup> Besides, birth weight and subsequent adult weight are also positively associated.<sup>43</sup> With this triad of associations in mind, researchers have subsequently almost invariably adjusted associations between birth weight and adult outcome for current adult weight with different explanations. Some of them just do so without any explanation,<sup>44</sup> most of them consider current weight or BMI as a potential confounder.<sup>45</sup>

Subsequently, a debate arose about whether this adjustment for current weight in early origin studies was justified, for it might well be an intervening variable in the causal pathway. This controversy was fuelled by Huxley et al. who showed in a meta-analysis that there was little or no relationship between birth weight and adult blood pressure without adjustment for current weight. She postulated the extreme statement that “adjustment for current weight might produce a spurious inverse association even if birth weight and current blood pressure are uncorrelated”.<sup>46</sup> Theoretically, this situation might indeed occur as described more formally by Hernán et al. who propagate the use of causal diagrams to encode a priori subject matter knowledge before deciding whether a variable is a confounder that should be adjusted for in the analyses.<sup>47</sup>



Finally, Lucas et al. transposed the main point of the discussion from the interpretation of the changing prenatal weight component to the interpretation of the current weight component. The effect of adding current weight into a regression model with early weight and adult outcome is intricate. Lucas et al. suggests that such a model should be interpreted as the effect of change in weight between birth and adulthood (postnatal centile crossing), rather than the effect of restricted fetal growth.<sup>48</sup> Moreover, it might be that especially those individuals with the lowest birth weights and the highest postnatal weight change have the highest changes on adult diseases.<sup>49,50</sup>

A well defined research question should be considered before building and interpreting any model. Given that the relationship between adult weight as such and adult metabolic diseases has already been sufficiently established, three separate research questions remain. The first one is the one it all started with: what is the effect of birth weight on adult disease? We think it theoretically unjustified to adjust for current adult weight in assessing this association, for adult weight is situated in the causal pathway. Birth weight is a proxy measurement of a dynamic process; prenatal growth (which once more might be considered to be a proxy variable as well, but this falls beyond the scope of this discussion). Birth weight itself alters at the very first day of life, as weight changes rapidly in small infants. Therefore, this potential risk indicator for adult disease should exert its effect through other, biological pathways. Adult size - which is as well a measurement of growth, though postnatal - might be one intervening mechanism, as it is related to birth weight. Since small infants tend to be small adults and large adults have an increased risk of adult metabolic disease, statistical 'adjustment' for adult size will incorrectly inflate the association between birth weight and adult disease.

The second question is: what is the effect of postnatal growth on adult disease? As we first started with determining the effect of birth weight on adult disease, this subsequent question should be refined to: What is the effect of "growing more than expected from a given birth weight" on adult disease? Therefore in this case it is theoretically justified to build a regression model with adjustment for the effect of birth weight in the statistical model, because the effect of birth weight is known, it lies earlier in time, and we are not longer interested in it for this new, second research question. However, one should not look at the coefficient of birth weight in this model, let alone interpret it, for it is meaningless. If one wants to interpret both separate research questions in one model, one should use our proposed unexplained residual model.

Finally, the third question is: does the effect of postnatal growth on adult disease differ between subjects with a low or a high birth weight? In this case a third model should be built with a third variable to test statistical interaction and one should look at all three coefficients for a proper interpretation of the results found. In this case we especially propagate the

unexplained residual model in contrast to the model of Lucas et al., for the former does not assume an underlying quadratic relation between birth weight and adult disease anymore. This question should be investigated, even if with the first question no association has been found, for the effects found in smaller subgroups might be overruled by the main group analysis.

### **Reliability**

Another problem frequently encountered, especially in multi-center studies, is the reliability of measurements. In our studies about reliability we try to provide practical approaches for two problems: reliability indicators and log transformed variables, and the assessment of reliability in a small study within the context of a large clinical study. It should be stressed that especially the latter should not be regarded as an illegitimate statistical "solution" to improve the reliability by inflating its coefficient, like estimating an intra-class correlation coefficient in a much more heterogeneous population than the study population it will be used in. On the contrary; the point estimate of the reliability coefficient remains exactly the same, but the precision of the estimate improves, or, if one takes the point of view that this precision could also be effectuated by increasing the number of subjects in the reliability study, the efficiency increases. Still, the clinical question about the reliability of skinfold measurements, and consequently the accuracy of its use in the POPS-19 study, remains open. At this point the methodological and clinical studies confluence and the reliability study shows that the reliability of the solitary skinfold measurements was poor. The sum of the four skinfolds however, had a better reliability and therefore this measure was subsequently used in the POPS-19 study to calculate the corresponding fat percentage, to which end it was first log transformed. At last, the decision if in situations like this special reliability indicators for log transformed variables are needed, should always be based solely on the (skewed) distribution of the errors and not of the distribution of the variable itself.

### **Population related issues**

The populations in which the main effect on adult health outcomes is expected to be found consist largely of infants with a low birth weight or born preterm. However, analyses in this population are complicated at different levels, most of methodological origin. The major problem is formed by different definitions applied in the literature to form a cohort; classification by gestational age<sup>51</sup> or by birth weight.<sup>52</sup> This has important consequences for the subsequent postnatal growth characteristics in the cohorts formed. Besides, no consensus has been reached about the optimum reference grow chart,<sup>53</sup> which complicates comparisons

both between different preterm study populations, and comparison with infants with normal birth weight and gestational age range. Finally, as improvements in neonatal care have only recently facilitated the survival of very preterm and very low birth weight infants, systematic literature about the consequences of early growth in adulthood is lacking in this population thus far.

Together with others,<sup>54</sup> we suggest classification of small infants by gestational age, for in this population this is a better predictor of survival than birth weight.<sup>55</sup> Next, in every gestational age category a classification of appropriate for gestational age (AGA) or small for gestational age (SGA) can be made. For an optimal distinction between AGA and SGA, preferably an up-to-date growth chart from the same population should be available. To avoid bias of non-random missing data at lower gestational ages, when the timing of delivery is strongly related to poor growth, a combination of anthropometry of live born infants and intra-uterine ultrasound growth estimates of fetuses of the same gestational age not born yet has been proposed.<sup>53</sup> However, fetal ultrasound has systematic and random inaccuracies, which seem both to be related with birth weight.<sup>56</sup>

Taken in account these limitations encountered early in the follow up of cohorts of low birth weight or preterm subjects, new problems are likely to accumulate in the same cohorts at adult follow up. First, selection bias might be introduced by a high mortality in the perinatal period leading to selective survival. In the POPS cohort, 27% of the infants died within the first year of life,<sup>55</sup> and 28% were deceased before the age of 19 years.<sup>57</sup> The in-hospital mortality was strongly associated with gestational age, and hence with the incidence and severity of the respiratory distress syndrome.<sup>55</sup> It is plausible that metabolic parameters affecting perinatal survival also affect the metabolic profile, including body composition, at age 19. For example, while in small infants born very preterm hypoglycemia and hypotension are important life threatening conditions to overcome, at age 19 right the opposite conditions of insulin resistance and hypertension are considered to be a health disadvantage. At low gestational ages and low birth weights, infants with a protective metabolic profile will have a better survival, while at higher gestational ages and birth weights metabolic profile does not influence survival anymore and infants with all metabolic profiles will have equal changes to survive till age 19. However, while selective mortality might form an explanation for associations found, it should not be considered as a bias in this case, for survival until adult age is a prerequisite for developing disease at adult age, and hence might be considered to be 'in the causal pathway' of low birth weight and adult disease.

A second issue, closely related to the first, might affect both the internal and internal validity of studies in the cohort. This concerns the effect of medical treatment on survival and the changes in neonatal care during the years. One keystone of treatment of infants born very

preterm is antenatal corticosteroid (betamethasone) administration, which significantly reduces neonatal mortality (RR 0.69, 95% CI 0.58 to 0.81).<sup>58</sup> Antenatal corticosteroids exert a major effect by reducing the incidence of Infant Respiratory Distress Syndrome (IRDS), but the effects are likely to be pleiotropic, possibly also affecting metabolic systems<sup>59,60</sup>. In this way its use in certain individuals could have changed the effects of the selective survival of certain metabolic profiles as described above. While the first trial with corticosteroids in humans took place in 1972,<sup>61</sup> the first structured review about this subject was published only in 1990.<sup>62</sup> This means that in 1983 when the POPS cohort was started, the prescription of antenatal corticosteroids was still dependent on the personal views of the gynecologists. However, it does not seem likely that this non-randomized allocation of a treatment has led to confounding, for it was random with regard to other risk factors that may have influenced the outcome studied, i.e. metabolic profile.

Nowadays antenatal corticosteroids are standard treatment in impending preterm delivery and synthetic surfactant has a widespread application after its initial introduction in the early 1980s.<sup>63</sup> Compared with the POPS cohort of 1983, this has led to an increase in survival of very preterm infants, but not in a change in disease free survival, because at present, the sicker infants survive as well.<sup>64</sup> For this reason the generalizability of the results found in studies in the POPS cohort, including those in this thesis, to the current generation of infants born very preterm is unclear. While for the incidence of handicaps or bronchopulmonary disease a distinct trend can be shown, this is harder to predict for the adult metabolic outcomes. While on the one hand the availability of surfactant has decreased the importance of pulmonary function to survive the first days of life and thereby placing more weight on the importance of a suitable metabolic profile of the neonate to survive, on the other hand the effect of antenatal corticosteroids is likely to be more pleiotropic as explained above and act on both pulmonary and metabolic systems. However, it is inherent to the introduction of a new treatment that the long-term effects, both intended and unintended cannot be studied until late future has turned into present.

Finally, selection bias could have been introduced by a low response rate, which was the case in both the POPS-19 and the HUNT 2 studies. In POPS non-response was associated with male sex, non-Dutch origin, low maternal education, and severe handicaps,<sup>57</sup> while in the HUNT study the main reasons for non-participation in the age group studied were having moved out of the county or lack of time.<sup>65</sup> However, in neither of the two studies non-response was associated with birth weight or gestational age. For this reason, as an association with determinant i.e. birth weight and non-response is lacking, non-response can not have introduced bias in this situation, irrespective of the unknown outcome of the missing subjects.

Apart from all these deliberations, an interesting remaining question is whether differences found in the association between early growth and adult metabolic disease in the POPS population compared with the HUNT study might be (partly) explained by the prematurity of the first subjects. It would be tempting to say so, for the mean gestational age forms a major difference between the two populations and unfortunately a control group for the POPS has never been recruited in the past. But, on the other hand, gestational age is not the only difference between the populations, apart from the age of the adult health assessment, the studies are also conducted in two different countries i.e. the Netherlands and Norway. To distort the hypothesized effect of prematurity on the association between early growth and adult disease, factors that differ between the different countries should have an influence on both prematurity and the relation between early growth and adult disease. One of the most important factors that might have these specific multiple effects will be the national level of prosperity that among others will work through in the mean birth weight, quality of neonatal care, and the development and treatment of adult diseases as well. This national level of prosperity, for example expressed as the gross national product, is similar, so it is not likely to overshadow the possible effect of prematurity in this context. However, as the level of overlap between the two populations was too limited for proper comparison – only 28 very preterm subjects in the HUNT, we can not be certain.

### **Main results in relation to the literature**

With regard to prenatal growth and the adult metabolic syndrome, we found that birth weight was inconsistently associated with the separate components of the syndrome in men and women. In general, these findings are in agreement with recent systematic reviews about the association between birth weight and these individual outcomes.<sup>32,66-70</sup> However, contrary to most previous findings<sup>66,71-76</sup> we did not find a significant association between low birth weight SDS and the metabolic syndrome as a composite construct. There are several explanations for this discrepancy. First it might partly be explained by publication bias. Second, inappropriate statistical adjustment for current weight or BMI was applied in several studies<sup>25,75 66</sup> as we explained in chapter 6. Third, in these previous studies often only separate components of the metabolic syndrome were analyzed, while in the conclusions report about 'the metabolic syndrome'.<sup>72-74</sup> All together, this weakens the validity of low birth weight as a unifying risk factor for the metabolic syndrome.

We found that IUGR was associated with low-normal kidney function in young adults from the general population. This is consistent with a recent systematic review of observational studies (including ours) in which an Odds Ratio of 1.8 was found for the effect of low birth weight on low adult glomerular filtration rate. This effect size was relatively consistent for

other renal outcomes reviewed like end stage renal disease or albuminuria.<sup>77</sup> Our results are also in agreement with findings in subjects born very prematurely from the POPS cohort.<sup>78</sup> A pathological basis supporting these clinical findings has been found in autopsy studies in which a low nephron number was observed in low-BW subjects.<sup>79-81</sup>

Regarding the effect of early growth on adult body composition we found in infants born very preterm that prenatal growth was positively associated with weight, height, and BMI at age 19; i.e. mainly with body size. These findings are consistent with studies in term born populations<sup>43,82</sup> and indicate that the positive association between birth weight and adult BMI is already determined in the first two trimesters of pregnancy. We did not confirm the J- or U-shape relation between birth weight and adult BMI found in some other studies.<sup>45,83,84</sup> This suggests that either these associations are established during the third trimester of pregnancy, or that there is another link than BMI between reduced fetal growth and adult disease. Fat-free mass has been proposed,<sup>85</sup> but our data do not support this. More early postnatal weight gain however, was associated with both a higher BMI and a higher percentage body fat at age 19 y. Our results confirm studies in adults,<sup>83,86,87</sup> and it may be concluded from our data that the positive associations found between early catch-up growth and fatness in childhood<sup>88,89</sup> persist into young adulthood. Our study adds that the higher BMI found was partly accounted for by a higher percentage body fat, at least in premature infants, and that the association was independent of birth weight. Finally, we also found that a greater postnatal weight gain was associated with a higher adult waist circumference, both when adjusted and unadjusted for current height (SD scores). This finding agrees with the results of Fall et al<sup>83</sup> and Li et al.<sup>86</sup> In some studies, both low birth weight and early growth have been associated with a more truncal and abdominal fat pattern<sup>83,90,91</sup> but only after adjustment for current BMI. Again, we think it is theoretically incorrect to adjust for current BMI -which includes current fat mass- in analyses with fat mass and fat distribution as outcomes.

### **Clinical relevance and future perspectives**

In contrast with the methodological studies that can be applied directly in future research, the clinical studies in this thesis are mainly of a descriptive nature. With regard to the effect of prematurity a less favorable adult body composition was found, while low birth weight was associated with reduced kidney function and a slightly less favorable metabolic profile at young adult age. Therefore, prevention of prematurity and low birth weight should be stressed. However, when prematurity or low birth weight is already an accomplished fact, the focus should be on systematic screening of these infants and adults for the sake of prevention, life style advices, and early treatment of metabolic diseases. With regard to recommendations about early catch-up growth even more caution is warranted, for at first

place it is not proven that preventing this catch-up growth in low birth weight or (very) preterm infants also prevents adult metabolic disease and, more important, early catch-up growth is considered to be important for neurodevelopmental outcome.<sup>92-94</sup> In general, growth should be considered as a proxy measurement for early life influences, not as the causal agent itself. In this context, the associations we found, though of small size, signify that lifelong effects of early life influences seem to exist in these specific populations as well, and that more research on underlying mechanisms is required.

As mentioned before, the outcomes of the POPS-19 study might not be fully generalizable to the current generation of preterm infants. Therefore, ideally a new research cohort should be formed for a prospective study, with special attention for an appropriate term control group, prenatal ultrasound measurements, and drawing cord blood. However, follow-up in the POPS (and HUNT) should be continued as well, for age 19 is still young to develop a full blown metabolic syndrome, let alone cardiovascular events, and this should be studied at older age. At subsequent follow-up, new focuses could be the acquiring of DNA of sibs and parents for the role of genetics and epigenetics in prematurity, growth, and disease, and the reproduction and offspring of the POPS infants. An imaging technique like a DEXA body scan should also be desirable as part of this follow-up, to study more precisely the adult body composition of subjects born preterm, and in second place for the external validation of skinfold measurements in this population. A related issue that could be studied in this context is the supposed altered body composition of SGA and preterm subjects which seems to continue in adulthood that will exert an effect on the estimation of GFR by using formulas dependent on creatinin and body weight. Finally, when in the same subjects body composition, renal function, and possible intermediate hormones like adiponectin are assessed, this might unravel more of the association between metabolic diseases and kidney disease.

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# 10

**Summary**

**Samenvatting**

**Dankwoord**

**Curriculum Vitae**

**List of publications**



## Summary

Cardiovascular disease forms a major health problem world wide and often results from an aberrant metabolic profile. Numerous 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. According to recent hypotheses an interaction between genetic, epigenetic, and environmental influences leads to intra-uterine programming of metabolic systems like the insulin system to become adapted to scarcity. This programming remains in postnatal life, leading to obesity and disease when food supply is abundant here. However, several unresolved questions in this field remain. In this thesis the effects of prenatal and early postnatal growth on metabolic disease at young adult age are addressed in both a population of subjects born at term, and in a population born very preterm, together with some closely intertwined methodological issues.

As infants born (very) preterm usually have a very typical growth pattern, the available literature about the growth of these infants until adulthood is reviewed in **chapter 2**. In the early postnatal period, they almost invariably show a substantial growth failure, which is usually followed by catch-up growth over two to three years. Generally, subjects born (very) preterm achieve a slightly shorter height and lower weight than term born peers at adulthood. Disproportionate catch-up growth in height and weight may lead to an altered body composition in adulthood, especially in females. While catch-up growth in this population is beneficial for neurodevelopmental outcome, recent literature indicates that it might have adverse effects on metabolic health in adult life.

In **chapter 3** various (linear) regression models are compared to study the effect of prenatal growth - expressed as birth weight - and the effect of subsequent postnatal growth on adult health outcome simultaneously in one model. This method implicates a proper research question and a careful interpretation of the coefficients found. A regression model based on unexplained residuals resulting from the equation of predicting later growth from birth weight was preferred. In this model the regression coefficients of birth weight and later growth can both be directly interpreted in the same model, and besides this model doesn't assume a quadratic relationship in testing for interaction between birth weight and later growth on adult disease.

As in early origins studies probably small effects are searched for over a long time span during which a lot of variables like life style are likely to exert their effects on metabolic profile, large study populations are required. These are often characterized by a multi-center design in which accurate information about reliability of the measurements is very important, for low reliability might lead to bias or dilution of the results found. In **chapter 4** a method is discussed



to optimize reliability studies by combining variance components found in a small reliability study with variance components found in the large multi-center itself when estimating intra-class correlation coefficients. This method leads to a more precise and efficient estimation of reliability.

When reliability indicators are log transformed because of a skewed distribution of errors, the interpretation of the indicators of reliability Bland-Altman method (BA) and Coefficients of Variation (CV) is not straight forward anymore. In **chapter 5** practical methods are addressed to obtain meaningful parameters of reliability on the original scale of measurement by applying existing statistical methods in the field of reproducibility. Regarding BA plots anti-logs are utilized for back transformation of log-transformed limits of agreement which can subsequently be plotted into the BA plot on original scale. CVs can be derived directly from the standard error of the log-transformed measurements.

The metabolic syndrome is an adult health outcome that has been repeatedly associated with early growth, but has been almost never been analyzed as the entire syndrome in literature. In **chapter 6** the association between birth weight and the metabolic syndrome according to international definitions was studied in a Norwegian population based prospective cohort study of males and females aged 20 to 30 years old (HUNT 2). It was found that the metabolic syndrome as a whole had no association with birth weight in females, and a small u-shaped association with birth weight in males, so a slightly increased risk for both a lower and a higher birth weight than the reference category. When addressing the separate components of the syndrome, various associations were found in both men and women, but of different directions. This might indicate that low birth weight is not a unifying etiological base for the metabolic syndrome, thereby also weakening the appropriateness of the metabolic syndrome concept.

Another important organ that is likely to be influenced in its function by early life experiences, but not included in most metabolic syndrome definitions is the kidney. In **chapter 7** this association between birth weight and kidney function was studied in the Norwegian cohort mentioned above. A small effect of low birth weight being associated with low-normal kidney function in young adulthood was found. This effect was stronger and more consistent in men than in women.

In contrast to term born infants, in infants born (very) preterm growth during the first two trimesters can be estimated directly by measuring their birth weights, thus providing information about timing of early life influences on adult outcome. In **chapter 8** the effects of prenatal and early postnatal growth on young adult body composition were studied in a nationwide Dutch cohort of infants born <32 weeks of gestation (POPS-19). For both

males and females, mean height and weight were below the means of the Dutch reference population of 19-year olds, while mean values for waist circumference, waist-to-hip ratio, and the sum of four skinfold thicknesses were greater than the Dutch population means. In these infants, weight gain before preterm birth was positively associated with adult body size, but not with fat mass or fat distribution. In contrast, more early postnatal growth was associated with both a higher adult BMI, and a higher percentage body fat, and more abdominal fat at age 19.



## Samenvatting in het Nederlands

### Hoofdstuk 1. Inleiding

Hart- en vaatziekten vormen wereldwijd een groot gezondheidsprobleem. Een belangrijke risicofactor voor het krijgen van hart- en vaatziekten is een afwijkend stofwisselingspatroon (metabool syndroom). Tot dit metabool syndroom behoren overgewicht - met name een te grote buikomvang -, een verhoogde bloeddruk, een verhoogde bloedsuikerspiegel en een verstoorde vethuishouding.

Uit eerder onderzoek is bekend dat de kans op het krijgen van hart- en vaatziekten mede bepaald wordt door gebeurtenissen in het zeer vroege leven, zowel binnen als buiten de baarmoeder. Dit wordt de 'early origins of adult disease hypothesis' genoemd. Vroege groei, bijvoorbeeld uitgedrukt als geboortegewicht, is een belangrijke en goed meetbare afspiegeling van deze gebeurtenissen. Binnen het *early origins* onderzoeksveld zijn echter nog veel onbeantwoorde vragen. Ook de manier waarop *early origins* onderzoek methodologisch het best verricht kan worden is onderwerp van discussie.

Dit proefschrift betreft twee typen onderzoek. In een aantal hoofdstukken wordt het verband tussen vroege groei en het ontstaan van het metabool syndroom en daarmee samenhangende gezondheidsproblemen op jongvolwassen leeftijd onderzocht. Dit onderzoek vindt zowel plaats in een op tijd geboren populatie (de Noorse HUNT-studie) als in een populatie van veel te vroeg geboren (de Nederlandse POPS-studie). Daarnaast is er een aantal hoofdstukken waarin ingegaan wordt op diverse methodologische vraagstukken die zich voordoen bij deze vorm van epidemiologisch onderzoek.

### Hoofdstuk 2. De groei van te vroeg geboren kinderen

Kinderen die veel te vroeg geboren zijn, dat wil zeggen na een zwangerschapsduur van minder dan 32 weken in plaats van 40 weken, vertonen vaak een kenmerkend groeipatroon. Het is bekend dat dit groeipatroon doorgaans afwijkt van dat van de normale populatie, maar deze groei van geboorte tot volwassenheid is nog nooit systematisch op grote schaal beschreven. Een vergelijking tussen de bestaande artikelen over de groei van te vroeg geboren wordt bemoeilijkt doordat de Amerikaanse indeling van kleine pasgeborenen is gebaseerd op lichaamsgewicht in plaats van zwangerschapsduur zoals in Europa.

In dit hoofdstuk wordt een systematisch overzicht gegeven van de bestaande literatuur over de groei van te vroeg geboren tot aan de volwassenheid. In de periode kort na de geboorte vertonen deze kinderen nagenoeg allemaal een forse groeiachterstand. Vervolgens begint

de meerderheid van de kinderen aan een periode van inhaalgroei tot ongeveer het tweede à derde levensjaar. Uiteindelijk zijn veel te vroeg geboren kinderen zowel in hun kindertijd als in de puberteit wat kleiner en lichter dan hun leeftijdsgenoten die geboren zijn na een voldragen zwangerschap. Door een verschil in inhaalgroei in lengte en gewicht kan bij een deel van de kinderen een verstoorde lichaamssamenstelling ontstaan wat zowel kan leiden tot over- als ondergewicht. Dit lijkt vooral het geval te zijn bij meisjes.

Het is aangetoond dat de vroege inhaalgroei gunstig is voor de neurologische ontwikkeling van veel te vroeg geborenen. Er zijn echter ook aanwijzingen dat dezelfde inhaalgroei ongunstig is voor het stofwisselingsprofiel op jong volwassen leeftijd. De literatuur hierover is echter nog zeer beperkt.

### **Hoofdstuk 3. Een regressiemodel met 'restgroei' heeft de voorkeur in het analyseren van early origins of adult disease hypothesis vraagstukken**

Het effect van vroege groei op het ontstaan van het metabool syndroom op volwassen leeftijd kan worden onderzocht met behulp van een lineair regressie model. Deze aanpak is vrij rechttoe rechtaan. Indien echter naast het effect van vroege groei ook naar het effect van latere groei wordt gekeken, zijn er twee variabelen in het model. Deze zullen elkaar beïnvloeden, waardoor de uitkomsten van het model gemakkelijk verkeerd geïnterpreteerd kunnen worden. Het ligt namelijk voor de hand om het effect van latere groei te corrigeren voor vroege groei, aangezien latere groei wordt beïnvloed door vroege groei. Indien daarentegen naar het effect van vroege groei zelf wordt gekeken, is het theoretisch meestal onjuist om voor het effect van latere groei te corrigeren. Dit laatste gebeurt echter automatisch in een regressiemodel met twee variabelen.

Eén oplossing voor dit probleem is om twee aparte regressiemodellen te gebruiken voor de twee afzonderlijke vraagstellingen. Eén met alleen vroege groei in het model voor het effect van vroege groei, en één met beide variabelen in het model voor het effect van latere groei, waarbij men dan de door het model gegenereerde uitkomst voor de vroege groei moet negeren. Dit is een nadeel van deze eenvoudige en overzichtelijke benadering met twee modellen.

Een tweede oplossing die wij in dit hoofdstuk beschrijven, biedt de mogelijkheid om beide uitkomsten voor vroege en late groei wel op correcte wijze uit één model af te lezen. Hiervoor wordt eerst met behulp van een regressiemodel late groei voorspeld vanuit vroege groei. Zo ontstaat een derde variabele, namelijk de 'restgroei' die overblijft als van de gehele late groei het effect van vroege groei is weggenomen. De restgroei, wiskundig beschreven als 'unexplained residuals', is onafhankelijk van de vroege groei. Indien nu vroege groei en de

restgroei samen in één lineair regressiemodel worden gevoegd, kunnen rechtstreeks de juiste uikomsten voor zowel vroege als late groei op het ontstaan van ziekte op volwassen leeftijd afgelezen worden. Dit model is ontwikkeld binnen het kader van de POPS-studie, maar kan breed worden toegepast in toekomstige studies naar 'early origins' in andere populaties.

#### **Hoofdstuk 4. Reproduceerbaarheidsstudies kunnen efficiënter worden opgezet door variantiecomponenten uit verschillende studies te combineren**

Het effect van vroege groei op ziekte op volwassen leeftijd is vermoedelijk klein. Dit effect wordt gemakkelijk overschaduwd door andere effecten zoals levensstijl, vooral omdat het metabool syndroom pas later in het leven optreedt. Om toch een mogelijk effect van vroege groei te kunnen aantonen, zijn vaak grote studies met verscheidene deelnemende centra nodig. In deze grote studies waarbij veel proefpersonen moeten worden onderzocht, wordt uit het oogpunt van effectiviteit vaak gekozen voor snelle en eenvoudige onderzoeksmethoden. De prijs die hiervoor soms betaald wordt, is een verminderde nauwkeurigheid van de bepaling, mogelijk veroorzaakt door verschillen in metingen tussen onderzoekers en tussen centra.

Het is voor het beantwoorden van de oorspronkelijke vraagstelling: "is er een verband tussen vroege groei en het ontstaan van het metabool syndroom op volwassen leeftijd?" van groot belang om te weten hoe nauwkeurig de bepaling is verricht. Als er systematische verschillen tussen onderzoekers of centra gevonden worden, kan hiervoor gecorrigeerd worden. Indien er veel 'toevalsvariatie' tussen metingen gevonden wordt, geeft dit ruis in de gegevensverzameling. Als er vervolgens geen verband kan worden aangetoond tussen vroege groei en ziekte op latere leeftijd, wil men kunnen uitsluiten dat dit uitsluitend werd veroorzaakt door deze toevalsvariatie c.q. ruis. En indien er wel een verband wordt aangetoond wil men kunnen vermelden in welke mate dit mogelijk nog versterkt wordt indien er gecorrigeerd zou worden voor toevalsvariatie in de metingen.

In een reproduceerbaarheidsstudie naar de herhaalbaarheid van metingen worden de verschillen tussen onderzoekers en centra vastgelegd. Vaak worden deze verschillen (meetfout) uitgedrukt in verhouding tot de verschillen tussen proefpersonen onderling (de echte verschillen waarin de onderzoeker geïnteresseerd is). In deze reproduceerbaarheidsstudies worden dezelfde proefpersonen meerdere malen gemeten door verschillende onderzoekers. In tegenstelling tot de grote studie zijn deze reproduceerbaarheidsstudies juist vaak kleinschalig van opzet, anders zou dit de gewonnen efficiëntie van de grote studie teniet doen. Tegelijkertijd is een bepaald aantal mensen vereist om nog betrouwbare uitspraken te kunnen doen, wat de nodige logistiek vereist bij een studie met verscheidene centra.

In dit hoofdstuk beschrijven wij een methode waarbij de verschillen tussen personen geschat worden in het grote oorspronkelijke onderzoek en de verschillen tussen onderzoekers en centra in de kleine reproduceerbaarheidsstudie. Dit wordt beschreven aan de hand van een voorbeeld van de huidplooiemetingen uit de POPS-19 studie. De methode verandert niet de uitkomst, namelijk hoe herhaalbaar de meting is, maar wel hoe betrouwbaar men dit kan schatten. Zo worden ook reproduceerbaarheidsstudies efficiënter en hoeven minder proefpersonen meerdere keren te worden gemeten. Deze methode wordt hier gedemonstreerd in de POPS-19 studie, en is overall toepasbaar waar sprake is van een relatieve fout - die meestal gepaard gaat met grotere verschillen bij grotere meetwaarden - in plaats van een absolute fout.

### **Hoofdstuk 5. Een praktische aanpak voor het toepassen van Bland-and-Altman grafieken en Variatie Coëfficiënten op log-getransformeerde variabelen**

Meetfout kan op diverse manieren worden uitgedrukt. Als boven beschreven is het belangrijk om een beeld te hebben van de meetfout in de uitkomst van een studie. Eén methode om meetfout te beschrijven is door middel van een Bland-and-Altman-grafiek. In deze grafiek wordt het verschil tussen twee metingen afgezet tegen het gemiddelde van de twee metingen, samen met de grenzen van overeenstemming waarbinnen 95% van de gevonden verschillen zich bevindt. Dit is een overzichtelijke, grafische maat voor de herhaalbaarheid van metingen, waarbij de onderzoeker of clinicus zelf kan afleiden hoe relevant hij het verschil vindt ten opzichte van de gemeten waarde. Deze waarden zijn namelijk direct af te lezen op de beide assen van de grafiek.

Als een uitkomstmaat een scheve verdeling heeft, wordt doorgaans een transformatie naar een normale verdeling verricht, vaak een log-transformatie. Dit is bijvoorbeeld het geval voor de huidplooien gemeten in de POPS-19 studie, waarmee uiteindelijk het vetpercentage van de deelnemers is bepaald. Na log-transformatie vervalt echter een groot voordeel van de Bland-and-Altman-grafiek, namelijk dat de verschillen en gemiddelden direct afleesbaar zijn op de schaal waarop ook klinisch is gemeten.

In dit hoofdstuk beschrijven wij hoe de grenzen van overeenstemming kunnen worden berekend op de logaritmische schaal, met als uitkomst een ratio. Door vervolgens een terugtransformatie toe te passen, kunnen deze grenzen van overeenstemming als verschillen worden ingetekend in de Bland-and-Altman-grafiek op de oorspronkelijke schaal. Dit geeft voor elk getal op de oorspronkelijke schaal aparte grenzen van overeenstemming die rechtstreeks kunnen worden afgelezen uit de figuur. Dit wordt geïllustreerd aan de hand van de huidplooiemetingen uit de POPS-19 studie.

Een soortgelijke toepassing wordt uitgewerkt voor de Variatie Coëfficiënt, een maat voor de meetfout waarin de meetfout wordt uitgedrukt ten opzichte van het gemiddelde van de meting. Deze maat is nietszeggend indien rechtstreeks toegepast op een logaritmische schaal, aangezien hier een absoluut nulpunt ontbreekt. Door het schatten van de standaard fout van de log-getransformeerde waarden kan wel een interpreteerbare Variatie Coëfficiënt berekend worden.

### **Hoofdstuk 6. Groeivertraging in de baarmoeder: geen verbindende onderliggende risicofactor voor het ontstaan van het metabool syndroom bij jong volwassenen**

In verscheidene studies is reeds een verband aangetoond tussen vroege groei en het ontstaan van het metabool syndroom op volwassen leeftijd. Bij nadere beschouwing blijkt echter dat in de meerderheid van deze studies alleen de afzonderlijke componenten van het metabool syndroom zijn bestudeerd en niet de gehele uitkomst metabool syndroom volgens de internationaal gedefinieerde criteria. Daarnaast wordt geregeld gecorrigeerd voor huidig lichaamsgewicht, terwijl (over)gewicht deel is van het metabool syndroom en dus van de uitkomstmaat zelf. Dit is dan ook onjuist.

Daarom beschrijven wij in dit hoofdstuk het verband tussen vroege groei en het ontstaan van het metabool syndroom op jong volwassen leeftijd. Als maat voor vroege groei wordt het geboortegewicht gecorrigeerd voor de zwangerschapsduur gebruikt, en het metabool syndroom wordt gedefinieerd volgens internationale criteria. De onderzoekspopulatie betreft de Noorse HUNT-studie; een grootschalig gezondheidsonderzoek waaraan ongeveer 8000 mannen en vrouwen tussen de 20 en 30 jaar oud deelnamen. Naast de in deze studie verkregen gegevens over hun huidige gezondheid, is van alle deelnemers ook een nauwkeurig geboortegewicht en zwangerschapsduur bekend uit het Noors nationaal geboorteregister.

Het metabool syndroom was niet geassocieerd met geboortegewicht binnen de vrouwelijke onderzoekspopulatie, terwijl voor de mannen een zwak U-vormig verband werd gezien. Dit betekent een licht verhoogd risico op het metabool syndroom zowel voor mannen met een lager als een hoger geboortegewicht dan gemiddeld. Bij bestudering van de afzonderlijke componenten van het metabool syndroom werden zowel voor mannen als voor vrouwen diverse significante verbanden gevonden voor het effect van geboortegewicht, maar in tegengestelde richtingen. Deze tegengestelde verbanden voor de diverse componenten van het syndroom in relatie tot dezelfde aannemelijke risicofactor - namelijk vroege groei - doen de toegevoegde waarde van het concept 'metabool syndroom' afnemen.



### **Hoofdstuk 7. Het effect van groeivertraging in de baarmoeder op de nierfunctie op jong volwassen leeftijd: de Nord Trøndelag Gezondheidsstudie (HUNT 2)**

Uit dierstudies en onderzoek bij overledenen is gebleken dat de nier een orgaan is dat erg kwetsbaar is voor de nadelige effecten van groeivertraging. Daarnaast is de nierfunctie gerelateerd aan het metabool syndroom door regulatie van de bloeddruk door de nier enerzijds, en schade aan de nier door suikerziekte en hoge bloeddruk anderzijds.

De relatie tussen geboortegewicht en nierfunctie op jong volwassen leeftijd is eerder onderzocht in de POPS populatie van veel te vroeg geboren. In dit hoofdstuk beschrijven wij het verband tussen geboortegewicht en het ontstaan van een laag-normale nierfunctie op jong volwassen leeftijd in de algemene populatie die voornamelijk bestaat uit mensen geboren na een voldragen zwangerschap. Dit wordt onderzocht in de Noorse HUNT-studie bij ongeveer 8000 mannen en vrouwen van 20 tot 30 jaar.

Uit dit onderzoek blijkt dat een verlaagd geboortegewicht voor de zwangerschapsduur leidt tot een licht verhoogd risico op een laag-normale nierfunctie op jong volwassen leeftijd. Dit verband was sterker en eenduidiger voor mannen dan voor vrouwen.

### **Hoofdstuk 8. Associaties tussen groei voor en kort na de geboorte en BMI, vetmassa en vetverdeling op jong volwassen leeftijd: een prospectieve cohort studie in veel te vroeg geboren mannen en vrouwen**

Lichaamsgewicht en lichaamssamenstelling vormen mogelijk een belangrijke link tussen vroege groei en het ontstaan van hart- en vaatziekten op latere leeftijd. In dit hoofdstuk wordt het verband beschreven tussen geboortegewicht, groei in de eerste maanden na de geboorte en lichaamsgewicht en lichaamssamenstelling op jong volwassen leeftijd. Dit is onderzocht in de POPS-19 studie: een groep van ongeveer 400 19-jarigen geboren na een zwangerschapsduur van minder dan 32 weken.

Normaal gesproken vormt het geboortegewicht een afspiegeling van de totale groei tijdens de gehele zwangerschap. In deze specifieke populatie van veel te vroeg geboren vormt het geboortegewicht echter een directe afspiegeling van de groei tijdens de eerste twee trimesters van de zwangerschap en kan de groei daarna rechtstreeks in kaart worden gebracht. Zo kan tevens het effect van de timing van groeivertraging op volwassen lichaamsgewicht en lichaamssamenstelling worden onderzocht.

Gemiddeld hadden de POPS-19 deelnemers een lager gewicht en een lagere body mass index (BMI) dan hun leeftijdsgenoten geboren na een voldragen zwangerschap. Hun gemiddelde

huidplooidikte en buikomvang lagen echter hoger dan het populatiegemiddelde. Meer groei voor de geboorte was geassocieerd met een groter gewicht, een grotere lengte en een hogere BMI op jongvolwassen leeftijd, maar niet met een andere vetmassa of vetverdeling. Meer groei kort na de geboorte daarentegen leidde tot zowel een hogere BMI als tot een groter percentage lichaamsvet en een grotere buikomvang op 19-jarige leeftijd, gecorrigeerd voor het effect van geboortegewicht.

### **Hoofdstuk 9. Discussie**

In dit hoofdstuk worden de belangrijkste bevindingen uit dit proefschrift in een breder wetenschappelijk kader geplaatst.

Wij bevestigen in dit proefschrift niet de eerder gevonden associatie tussen een laag geboortegewicht en een verhoogde kans op het metabool syndroom op volwassen leeftijd. Hiervoor zijn verschillende verklaringen denkbaar. Daarnaast verminderen onze bevindingen over de verschillende associaties van geboortegewicht met de afzonderlijke componenten van het metabool syndroom de reeds in twijfel getrokken toegevoegde waarde van het concept metabool syndroom nog iets meer.

De resultaten met betrekking tot de associatie tussen verminderde prenatale groei en een verhoogde kans op een laagnormale nierfunctie op volwassen leeftijd komen overeen met de bestaande literatuur over onderzoek in andere populaties.

Bij het onderzoek van veel te vroeg geboren en vinden wij evenmin een negatief of U-vormig verband tussen geboortegewicht en de kans op een hoger gewicht of ongunstiger lichaamssamenstelling op jongvolwassen leeftijd. Dit kan betekenen dat dit verband, gevonden in andere studies, pas ontstaat in het derde trimester van de zwangerschap, of door methodologische verschillen tussen deze studies en de POPS-19 studie, bijvoorbeeld in populatie of in analysemethode.

Het is moeilijk om de resultaten van de POPS-19 studie te generaliseren naar de huidige generatie van veel te vroeg geboren kinderen. Dit wordt vooral veroorzaakt door een groot verschil in behandelmogelijkheden tussen toen en nu. Hierdoor overleven meer kinderen en daarmee een ander soort kinderen de zeer vroege geboorte. Dit kan een weerslag hebben op de mate waarin vroege invloeden doorwerken in het volwassen leven.

Om openstaande vragen over het metabool syndroom, *de timing van de early origins of adult disease* en de effecten van vroege invloeden in de huidige generatie veel te vroeg geboren te beantwoorden, is verder onderzoek nodig. De methodologische artikelen in

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dit proefschrift leveren een bijdrage aan dit toekomstig onderzoek door handreikingen te bieden voor het maken van een interpreteerbaar regressiemodel en het efficiënt opzetten van reproduceerbaarheidsonderzoek, ook voor getransformeerde uitkomstmaten.

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## Curriculum Vitae

Anne Margriet Euser werd geboren op 8 april 1981 te Leiden. In 1999 behaalde zij haar VWO diploma aan het Andreas College te Katwijk aan Zee (cum laude), waarna zij geneeskunde studeerde aan de Universiteit Leiden en in 2004 haar doctoraal examen behaalde (cum laude). Tijdens haar tweede studiejaar werd zij geselecteerd voor het excellente studenttraject van het LUMC en sindsdien heeft zij actief geparticipeerd in het wetenschappelijk onderzoek binnen de POPS-19 studie vanuit de afdelingen kindergeneeskunde (prof. dr J.M. Wit) en klinische epidemiologie (Prof. dr F.R. Rosendaal, dr F.W. Dekker), alwaar zij ook haar afstudeerstage uitvoerde. Zowel de medisch inhoudelijke als de methodologische aspecten van het onderzoek wekten haar interesse. Na een klinische stage in Targu Mures in Roemenië, doorliep zij haar co-schappen en behaalde in januari 2006 haar artsexamen (cum laude). Vervolgens heeft zij enige tijd onderzoek verricht naar de 'early *origins hypothesis*' in de algemene populatie in Trondheim in Noorwegen. Na terugkeer werkte zij een jaar als arts-assistent niet in opleiding (agnio) op de afdeling kindergeneeskunde van het Rijnland Ziekenhuis te Leiderdorp. Sinds medio 2007 werkte zij aan de voltooiing van dit proefschrift, gedurende welke periode zij tevens de opleiding tot epidemioloog B heeft gevolgd. Momenteel is zij werkzaam als agnio klinische genetica in het Leids Universitair Medisch Centrum.



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