# General introduction

## INTRODUCTION

In 2012 our research group started the Sophia Pluto Study, investigating growth, detailed body composition and feeding patterns in healthy, term-born infants during the first two years of life, with a focus on finding determinants of adiposity programming in early life. This thesis describes the results of six new studies embedded in the Sophia Pluto Study.

This introduction describes the current knowledge concerning the influence of infant growth on adult health and the potential factors that might influence infant body composition. In addition, the objectives of the studies presented in this thesis are described.

### Infant weight gain influencing adult health

Accelerated weight gain during early life has been associated with an increased risk for adult diseases (1-4). In the PROGRAM-study, initiated in 2002, our research group showed that rapid gain in weight-for-length during the first months of life was associated with higher body fat percentage, increased serum levels of total cholesterol, triglycerides, low density lipoprotein cholesterol (LDL) and higher systolic and diastolic blood pressure in early adulthood (5). These findings suggested the presence of a critical window for adiposity programming in the first postnatal months and indicated that accelerated weight-for-length standard deviation score (SDS) should be avoided to reduce the risk for obesity, type 2 diabetes and cardiovascular diseases in later life (5-7). Others also showed that the first postnatal months are important for adiposity programming (8).

In 2019, ~13% of the Dutch children between age 4 and 17 years was overweight. At age 2 years already ~8% of the infants had moderate or severe overweight (9). Obesity during childhood is associated with short-term morbidity, such as asthma and psychological problems. It has also been associated with an increased risk for adolescent and adult obesity (10-13), as most adolescents with obesity will have excessive adiposity during adulthood. This in turn puts them at risk for later cardiovascular diseases and cancer (13).

Over the last years, progress has been made in unraveling the genetics and epigenetics of obesity (14), but only a low proportion of the heritability of obesity has now been explained (15). The established loci, the position of genes on a chromosome, involved in obesity development explain only a small part of the variance and can only poorly predict obesity (16). It can, therefore, not be clinically used as a predictive tool (15). Since obesity has a multifactorial etiology (13), single treatment strategies are not likely to be effective for all obesity patients.

In addition, obesity later in life requires lifelong treatment (13). Treatment options range from nutritional diet with increased physical activity to drugs and surgery (14), but the

success rate is generally very low in obtaining and maintaining a healthy weight. It is, therefore, crucial to elucidate which factors influence adiposity programming in early life as this will help to develop prevention strategies for childhood obesity in the future.

**Infant body composition**

There is increasing evidence that excessive weight gain in early life increases the risk of more fat mass in childhood and in later life. It is important to specify weight gain in terms of gain in fat mass and fat-free mass in early life. Most studies, however, have mainly focused on longitudinal anthropometric outcomes like weight-for-length SDS, BMI and skinfold measurements as proxy for adiposity during infancy (17). As the first 1000 days, from conception until age 2 years, are an important period for the development of the body and brain of the infant (18, 19), it is crucial to obtain longitudinal values of fat mass and fat-free mass during the first 2 years of life. Nowadays, there are various tools to measure detailed body composition in infants.

*Methods for measuring infant body composition*

For many years weight and the ponderal index after birth, calculated based on birth weight and birth length, were used as a proxy for body composition. These measures, however, do not reflect actual body composition (20). Techniques to determine body composition by the multi-component model for quantifying fat, water, mineral and protein or by magnetic resonance imaging (MRI) have been applied in infancy and childhood (21-23). These methods can accurately determine body composition, but are very expensive and cannot be used routinely in large studies.

**Figure 1.** PEA POD by Cosmed. derived from the brochure on www.cosmed.com.

*Body composition by air-displacement plethysmography*

Body composition in infants can nowadays be assessed by air-displacement plethysmography (PEA POD, Infant Body Composition System, COSMED, Italy). ADP assesses fat mass (FM), fat mass percentage (FM%), fat-free mass and fat-free mass percentage by direct measurements of body mass and body volume, based on the whole-body densitometry principle (24). Body mass is measured on the integrated scale of the PEA POD and body volume is measured inside the closed test chamber by applying pertinent gas laws that relate pressure changes to volumes of air. Details of the principle and operating procedure of the PEA POD have been described (25, 26). Studies have shown that ADP is a valid, non-invasive and fast technique for measuring body composition in infants from birth until the upper limit of ap-

proximately 8 kg (27-29). Another ADP system, BOD POD, is available from approximately 2-3 years onward (30), but there are no ADP systems for children between age 6 months (± 8 kg) and 2 years, which complicates obtaining longitudinal body composition by ADP during the important first 2 years of life.

**Figure 2.** DXA https://www.acertys.com/nl/producten/ge-lunar-prodigy

*Body composition by dual-energy X-ray Absorptiometry*

Dual-energy X-ray absorptiometry (DXA) is an alternative measurement technique for body composition in infants (29, 31-33). DXA has good reproducibility in infants in case of a successful scan (31), but successful measurements are extremely difficult to obtain of infants, especially between the age of 1 and 2 years, due to movement artifacts (34-36). Also, it has been reported that DXA might overestimate FM (35). Reference values for body composition measured by DXA scan only exist from age 4 years onwards (37).

**Figure 3.** DXA with vacuum cushion. Photo depicted with permission from parents.

As abovementioned, obtaining successful measurements of infant body composition by DXA scan is limited due to movement artifacts. The use of a vacuum cushion might be a solution in preventing movement during DXA scan, which might improve the chance of obtaining successful measurements. It was unknown if this would indeed be the case. An evaluation of the use of a vacuum cushion was, therefore, required.

In addition, it was unknown whether measurements of body composition by ADP and DXA, either with or without a vacuum cushion, would be comparable at the transition point at age 6 months. This is essential for using longitudinal measurements of body composition during infancy by ADP and DXA.

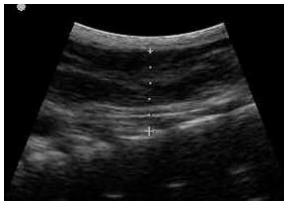

**Figure 4.** Visceral fat mass thickness by ultrasound.

*Abdominal subcutaneous and visceral fat mass by ultrasound*

Not only the total amount of fat mass, but also the location of fat mass is important. Particularly increased abdominal visceral FM has been associated with an unfavorable metabolic health profile during childhood and later on (38, 39).

Ultrasound is a non-invasive method to estimate abdominal fat mass. Ultrasound measurements of subcutaneous and

visceral fat mass thickness are reliable and reproducible estimates of abdominal subcutaneous fat mass and intra-abdominal (visceral) fat mass (40, 41).

*Body composition – potential influencing factors*

Several factors might influence the development of infant body composition (Figure 5), which are explained point-by-point below.

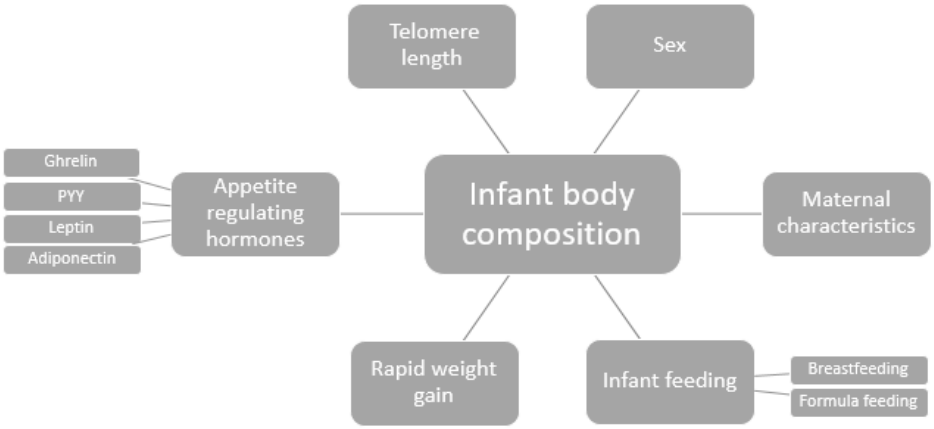


**Figure 5.** Potential influencing factors of infant body composition development.

*Boys and girls*

Sex differences in body composition development during the first 2 years of life might be present due to different sex hormone levels in boys and girls in early life. It was already known that girls have higher fat mass and lower fat-free mass compared to boys after birth and we previously described higher fat mass in girls at age 6 months (27, 42-44), but the fat mass development until age 2 years was unknown.

*Maternal characteristics*

Maternal pre-pregnancy body mass index (BMI) and gestational weight gain are determinants of fetal growth, infant birth weight and fat mass percentage at birth (45-47). Associations between these maternal factors and body composition in infants and children were not found during the postnatal period until age 6 months (48, 49), but independent relationships of maternal early pregnancy BMI with childhood BMI and adiposity have been found at age 6 years (50). However, little is known about the effect of maternal pre-pregnancy BMI and gestational weight gain on early infant body composition trajectories.

*Infant feeding*

Breastfeeding and formula feeding are two types of infant feeding. Breastfeeding is considered the gold standard infant feeding, as it can result in health benefits for mother and child (51). Breastfeeding lowers the risk for adiposity during childhood (52-56) and is a protective factor against several infections (51), asthma development (57), eczema and allergic rhinitis (58) by supporting the development of the immune system and microbiota (59). For mothers, breastfeeding lowers the risk of breast cancer (51).

Breastfeeding is, however, not always possible, for example due to maternal disease and/or use of medication or is not desired by parents. In such cases, formula feeding is another option. Differences between breastfeeding and formula feeding exist in macronutrient composition and bioactive factors (60). In addition, there are also different formula feeding options, in brand and compound (61). Formula feeding has been associated with altered body composition in infancy compared to breastfeeding, as shown in small cohorts and short-term follow-up periods (60).

Human milk is composed of macronutrients, micronutrients and bioactive factors (62). Different techniques exist for analyzing macronutrient composition, with infrared human milk analyzers (HMA) being a method to estimate this composition. These methods are mainly used for optimizing feeding for preterm infants. It is, however, unknown to what extent human milk macronutrients might be involved in early adiposity programming, since studies investigating human milk macronutrients in association with (changes in) body composition in early life are very limited.

*Rapid weight gain in early life*

Accelerated gain in weight-for-age SDS during the first postnatal months has been associated with an increased risk for overweight and obesity in childhood and adulthood (63-67), unfavorable metabolic health profiles in young adults (6, 7, 68) and cardiovascular diseases in later life (4, 69). In addition, associations between early weight gain and childhood obesity have been described (55, 70, 71).

We have previously shown that newborns with similar weight and weight-for-length SDS might have different fat mass (72). Until now, data on associations between gain in fat mass, instead of gain in weight, and body composition trajectories in early life do not exist.

Longitudinal reference values for FM% until the age of 2 years are also lacking due to the different measurement techniques at different ages. Obtaining these longitudinal measurements is of great importance as this period in early life is important for infant development (18, 19). In addition, it is important to compare body composition during the first 6 months of life, a critical window for adiposity programming, with the period from 6 months to 2 years. These data are of interest since two studies showed that fat mass accretion until age 6 months associated with higher fat mass index at age 4 years and that fat mass accretion

until age 8 months associated with overweight/obesity at age 6-11 years in a small group of children (73, 74).

*Appetite regulating hormones*

Appetite regulating hormones (ARH) are involved in the regulation of food intake through specific brain centers. The hypothalamus plays a key role in controlling glucose and energy homeostasis and food intake (75, 76). Active ghrelin, a stimulating hormone, increases food intake, while other hormones like leptin and PYY decrease food intake and increase metabolic rate and adiponectin increases the uptake of fatty acids and carbohydrates (76, 77). Furthermore, the (active) ghrelin/PYY ratio is a marker of orexigenic drive (78, 79).

Data on ARH trajectories during early life are very limited. ARH have been associated with later growth and adiposity, but most studies used cord blood (80-85) instead of blood samples obtained during early infancy and specifically during the first 6 postnatal months. Investigating ARH and their trajectories in early life is of interest as they might play a role in adiposity programming.

Three studies compared ARH levels between breastfed and formula fed infants and reported different ARH levels in early life between both groups (86-88), but associations of ARH with human milk macronutrients, infant appetite and body composition have not been reported.

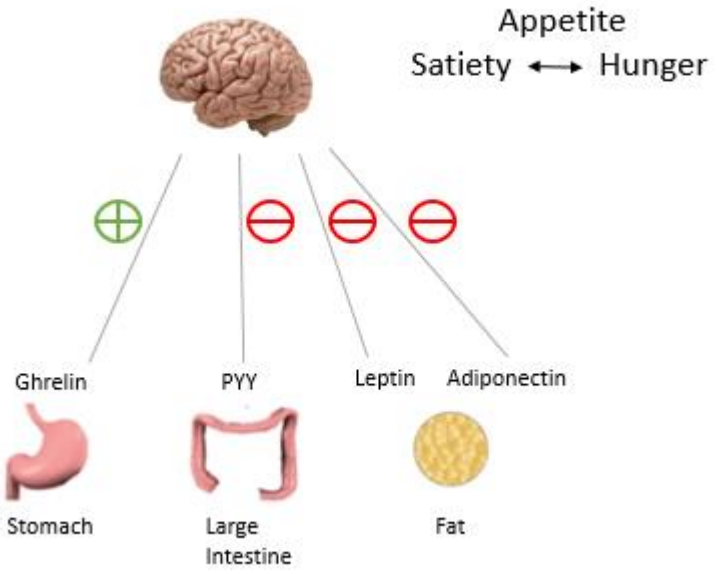


**Figure 6.** Appetite regulating hormones (partly adapted from www.sigmanutrition.com).

*Leukocyte telomere length*

Telomeres are non-coding repetitive DNA sequences located at the end of chromosomes, protecting DNA in maintaining stability (89). Leukocyte telomere length (LTL) is a marker of biological aging as shortening occurs over time, because DNA polymerase is not able to fully replicate the end of chromosomes. When telomeres are reduced to a critical length, cells enter a state of arrest (90). By using a quantitative PCR technique, telomere length can be measured in leukocytes (90, 91). Shorter LTL has been associated with adiposity and a higher risk of cardiovascular diseases (92, 93). Until now, only one study has investigated longitudinal LTL during the first two years of life (94), which is an important period for infant development (18). Their first LTL measurement, however, was at a mean age of 8.6 months, thus not during the critical window for adiposity programming until age 6 months. It is important to specifically investigate LTL during this period in early life in association with changes in body composition until the age of 2 years.

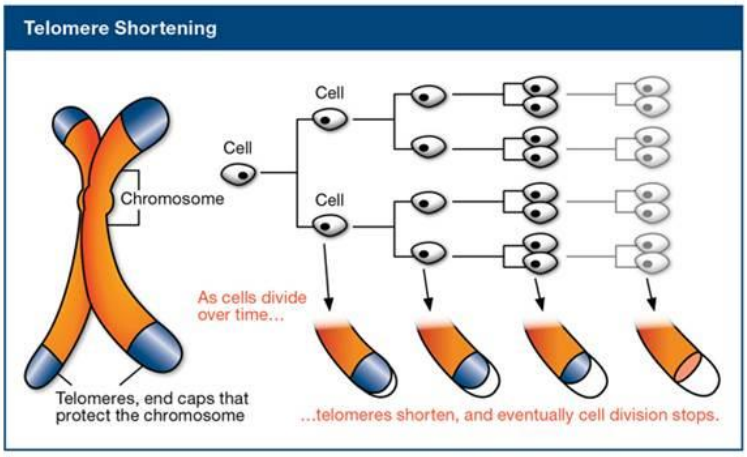


**Figure 7.** Telomere shortening (adapted from http://www.wholehealthinsider.com/newsletter/2012/a-genetic-solution-to-slowing-aging-and-preventing-disease/ and thesis Lin Smeets: Silver-Russell Syndrome & Small for Gestational Age – long-term health perspectives.)

## HYPOTHESES

We hypothesized that a rapid increase in fat mass percentage in the first 6 postnatal months leads to a higher fat mass percentage at the age of 2 years. We also hypothesized that infant feeding, milk macronutrient composition, leukocyte telomere length and appetite regulating hormones associate with adiposity development in the first two years of life.

### The Sophia Pluto Study birth cohort

The Sophia Pluto Study was initiated in 2012 to prospectively identify determinants of adiposity programming in early life in healthy, term-born infants during the first 2 years of life. The in- and exclusion criteria are described in Appendix A.

### Aims of the studies

This thesis presents the results of 6 studies in healthy, term-born infants participating in the Sophia Pluto Study.

1. *Longitudinal body composition assessment in early life*
   To evaluate the reliability of using a vacuum cushion during dual-energy X-ray absorptiometry (DXA) to prevent movement artifacts and to compare fat mass (FM) measured by DXA with FM measured by air-displacement plethysmography (ADP).
   To construct sex-specific longitudinal body composition values and charts from age 1 month until 2 years.
2. *Rapid increase in fat mass in early life and later body composition*
   To investigate in which postnatal months a change in FM% is associated with FM% at age 2 years
   To investigate whether a rapid increase in FM% in the first months of life is associated with higher trajectories of body fat mass during the first 2 years of life.
3. *Human milk macronutrients, body composition and appetite*
   To investigate human milk macronutrients at age 1 and 3 months in association with body composition and appetite until age 2 years in healthy, term-born infants.
4. *Leukocyte telomere length and body composition*
   To obtain longitudinal LTL measurements and determine the shortening of LTL during the first 2 years of life in healthy, term-born infants and to associate LTL shortening with potential stressors and body composition.
5. *Appetite regulating hormones and body composition until age 6 months*
   To investigate longitudinal serum ghrelin (acylated), PYY, ghrelin/PYY ratio and leptin levels until age 6 months and their associations with body fat mass, infant feeding, human milk macronutrient composition and infant appetite until age 6 months.
6. *Appetite regulating hormones and body composition until age 2 years*
   To investigate longitudinal appetite regulating hormone levels from age 3 months to 2 years in association with FM parameters at age 2 years and their predictive value for FM development until age 2 years.
   To investigate associations of appetite regulating hormone trajectories until 6 months and from 6 months to 2 years with trajectories of FM parameters in the same periods.

## APPENDIX A

### The Sophia Pluto Study cohort

The Sophia Pluto Study birth cohort was initiated based on the outcomes of the PROGRAM study, to prospectively identify determinants of adult disease in early life.

### Subjects

Healthy infants are included in the Sophia Pluto Study. The inclusion into this study is still ongoing and the total number will be 1250 infants.

### Inclusion criteria

- Gestational age of 37 weeks or more
- Age < 28 days
- Uncomplicated neonatal period without signs of severe asphyxia (defined as an Apgar score below three after five minutes), sepsis or long-term complication of respiratory ventilation

### Exclusion criteria

- Known congenital or postnatal disease that could interfere with body composition development
- Confirmed intra-uterine infection
- Maternal use of corticosteroids or significant maternal medical condition that could interfere with infant's body composition development (e.g. diabetes)

### Study design

The Sophia Pluto Study is a prospective, observational follow-up study of a birth cohort. The infants were included before age 28 days and visited the outpatient clinic at age 1, 3, 6, 9 months and 1 year, 18 months and 2 years. During the visits, anthropometrics, body composition and various other parameters were measured and blood samples were collected. Until and including age 6 months, FM% was measured by air-displacement plethysmography (PEA POD) and from 6 months onward by DXA-scan. Abdominal subcutaneous and visceral fat mass were measured by abdominal ultrasound.

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