General discussion

GENERAL DISCUSSION

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

We addressed the use of a vacuum cushion during Dual Energy X-ray Absorptiometry (DXA) scans for obtaining accurate measurements of body composition in order to construct longitudinal values of body composition. We investigated the influence of a rapid increase in fat mass in early life on body composition during the first 2 years of life. In addition, we explored the influence of human milk macronutrients, infant appetite, leukocyte telomere length and appetite regulating hormones on body composition development during the first 2 years of life.

In this chapter, the results of the studies are discussed in light of current literature. In addition, the clinical implications of our findings and the directions for future research are addressed.

Body composition assessment in early life

Chapter 2 describes the reliability of the use of a vacuum cushion during Dual Energy X-ray Absorptiometry (DXA) scans to prevent movement artifacts in infants between age 6 months and 2 years. It also describes the comparability between body composition measurements by air-displacement plethysmography (ADP) up to age 6 months and DXA measurements from age 6 months. In addition, this chapter presents longitudinal sex-specific reference values for body composition until age 2 years.

We show that the use of a vacuum cushion during DXA measurements limited movement artifacts and resulted in reliable measurements of fat mass percentage (FM%) up to the age of 2 years. The measurements of FM% by ADP and DXA with vacuum cushion were comparable at the transition point of both measurement techniques at age 6 months, whereas the measurements of ADP and DXA without vacuum cushion were not. These findings allowed us to use a vacuum cushion during DXA scans in order to construct for the first time longitudinal body composition charts from 1 month until 2 years, which are important for clinical and research use. Our reference charts show that FM% increased until age 6 months and declined from 6 months to 2 years. Girls had higher FM% compared to boys.

DXA measurements are difficult to perform in young infants due to movement artifacts, resulting in high percentages of unsuccessful measurements (1, 2). For the first time we show that the use of a vacuum cushion resulted in a high number of successful DXA measurements by limiting movement artifacts. The use of a vacuum cushion also resulted in reliable FM% measurements. A recent review of body composition measurements from birth until age 5 years stated that swaddling of children older than age 6 months during DXA scan was ineffective at preventing movement (3) and that it is important to avoid infants and children to be separated from their parent during body composition measurements, because it may

cause distress (3). Our approach of measuring FM% by ADP until 6 months, with the infant being able to see its parent during a short duration of the measurement, followed by DXA with vacuum cushion from age 6 months, with the parent being close to the infant, proved to be effective in preventing distress and movement during DXA.

FM% measurements by ADP and DXA with vacuum cushion were comparable at the transition point at age 6 months, with Bland-Altman plot showing no potential bias. These results are in contrast to FM% measurements of ADP and DXA without vacuum cushion, which showed potential bias. Measurements of body composition by DXA without vacuum cushion at this young age are, therefore, not suitable. Two earlier studies compared FM% by ADP and DXA (4, 5), but showed conflicting results, probably due to the small group of infants. In addition, both studies did not use a vacuum cushion during DXA scan. One study showed higher FM% measured by ADP compared to DXA (5), while another study showed higher FM% by DXA without cushion compared to ADP (4).

Our abovementioned findings allowed us to use a vacuum cushion during DXA scans to prevent movement artifacts and to subsequently construct longitudinal body composition charts from age 1 month until 2 years for the first time. These longitudinal charts are particularly important for clinical and research use. Earlier studies were based on anthropometric outcomes, for example weight-for-length SDS and BMI (6), but we have previously shown that infants with a similar weight and weight-for-length SDS may have a different FM% (7). Until now, assessment of longitudinal body composition from infancy into childhood was challenging as the various methodologies have barriers and limitations (8-10). A very recent study compared body composition by ADP, DXA and quantitative nuclear magnetic resonance and computed the 4C model in infants and children until age 6 years with completed study visits at the age range of 14 days until 74 months (8). In infants, ADP was the best method for assessment of individual FM, whereas DXA was best in estimating individual and group FM in children (8). Bland-Altman plots in infants revealed bias in all methods compared with the 4C model, with DXA having the lowest agreement in infants. That study, however, did not use a vacuum cushion during DXA scan. The use of a vacuum cushion resolves this low agreement between measurements.

We conclude that the use of a vacuum cushion to prevent movements during DXA scan provides reliable measurements of body composition that are comparable to ADP measurements, allowing the construction of longitudinal body composition charts. Our longitudinal measurements show that FM% increases until age 6 months and decreases thereafter until age 2 years and that girls have higher FM% compared to boys.

Fat mass in early life and later body composition

In Chapter 3, associations between gain in FM% SDS in the first and second 6 months of life with body composition at age 2 years were assessed. In addition, we investigated whether a

rapid increase in FM% in the first 6 months of life was associated with higher trajectories of body fat mass during the first 2 years of life.

We show that only the change in FM% in the first 6 months of life, and not in the 6 months thereafter, was associated with more adiposity at age 2 years. Infants with a rapid increase in FM% in these first 6 months had higher trajectories of FM% and FM index during the first 2 years of life.

The first 2 years of life are important for infant and adiposity development (11, 12). Accelerated weight gain, defined as a change in weight-for-age SDS of >0.67 between two time points (13, 14), has been associated with overweight and obesity in childhood and adulthood (15). Accelerated weight gain from birth to 2 years has been associated with more fat and more central fat distribution at the age of 5 years (14), and with an increase in visceral fat, abdominal subcutaneous fat and total adiposity in adulthood, at a mean age of 46.5 years (16).

Our research group previously reported that particularly rapid catch-up in weight in the first months of life, instead of the first 2 years, resulted in a higher FM%, more central adiposity and reduced insulin sensitivity in young adults (17). Others also reported a contribution of rapid weight gain during the first months to the risk of adiposity in infants (18, 19), not only in infants with low birthweight or born small-for-gestational age (20-22). The first 6 months of life are, therefore, considered a critical window for adiposity programming (17, 23).

For the first time we now show the associations of a rapid increase in FM%, instead of weight-for-age SDS, during the first year of life with later FM trajectories. FM measurements were used as we previously found differences in FM% in neonates with a similar weight (7). The change in FM% in the first 6 months of life, and not the 6 months thereafter, positively associated with adiposity at age 2 years. In addition, we found that infants with a rapid increase in FM% during the first 6 months of life had higher trajectories of FM% and FM index during the first 2 years of life, resulting in a higher FM% and FM index at age 2 years.

Our findings convincingly show that there is a critical window for adiposity programming during the first 6 months of life. This knowledge is important for future research and particularly for the development of primary health care guidelines to prevent adiposity programming in the first months after birth.

Our study shows that the change in FM% during the first 6 months of life associates with more adiposity at the age of 2 years and that infants with a rapid increase in FM% during this period have higher trajectories of FM% until the age of 2 years. Our results support a critical window for adiposity programming in early life.

Human milk macronutrients, body composition and infant appetite

Chapter 4 describes longitudinal human hind milk macronutrient composition collected at infant's age of 1 and 3 months and associations with infant body composition until age 2 years and appetite during early life, in exclusively breastfed infants.

In 133 exclusively breastfed infants we show that human milk protein and energy content decreased between age 1 and 3 months, while fat and carbohydrate content tended to decrease. Human milk macronutrient composition was remarkably different between mothers, particularly in fat content. Higher milk fat and energy at age 3 months were associated with higher FM% at 6 months and higher gain in FM% between age 1 and 6 months. Furthermore, infants receiving higher caloric human milk satiated earlier and finished feeding faster. Human milk composition studies are very difficult to compare due to large variations in sampling and measurements. A review from 2018 by Eriksen et al, highlighted the importance of using standardized sampling and measurements to obtain high quality studies with comparable results (24). We instructed the mothers to collect human milk samples according to our study protocol and analyzed all samples by one human milk analyzer (Miris, Uppsala, Sweden), according to a standardized protocol. One investigator handled all samples (KdF) in order to limit measurement variations, which strengthened our results.

Human milk protein and energy content decreased, and fat and carbohydrate content tended to decrease over time, in line with literature (25-29). In addition, there was a wide variation in human milk macronutrient composition between mothers, particularly in fat content. We show for the first time that higher milk fat and energy at 3 months associate with higher FM% at 6 months and higher gain in FM% between age 1 and 6 months, in a large group of exclusively breastfed infants. Studies investigating human milk macronutrients in association with longitudinally measured FM% were very scarce (24). These studies comprised only small groups of infants (30, 31) or used skinfold measurements in the newborn, at 3 and 12 months to estimate adiposity (32).

In breastfed infants, it is difficult to determine the exact amount of daily milk intake (33) and thus the daily macronutrient intake. For the first time we show that infants receiving human milk with higher fat and energy content satiated earlier and finished feeding faster, which could be an important self-regulatory mechanism. This mechanism could prevent the intake of excessive macronutrients and subsequent abnormal adiposity programming. The difference in caloric value of human milk between mothers might also explain why some infants drink for a longer time than others. This is an important finding for parents, caretakers, researchers and health care professionals.

Our study shows that human milk fat and energy content at age 3 months associate with FM% at age 6 months and with the gain in FM% from age 1 to 6 months, the critical window for adiposity programming. Exclusively breastfed infants receiving higher caloric human milk satiate earlier and finish feeding faster.

Telomere length and body composition

Chapter 5 describes the results of longitudinal measures of leukocyte telomere length (LTL) during the first two years of life and the associations with potential stressors of LTL and body composition until age 2 years.

Our findings show that LTL shortened considerably (8.5%) between age 3 months and 2 years. More shortening in LTL from 3 months to 2 years was associated with a higher FM%, FM index and visceral FM at age 2 years. LTL shortening during the first 2 years of life tended to associate with the gain in FM% from 3 to 6 months.

Not only the change in LTL from age 3 months to 2 years was investigated, but we also compared our data to a previously published study by our research group with LTL measurements at age 21 years. These subjects met the same inclusion criteria of healthy, term-born infants of the Sophia Pluto Cohort and LTL measurements were performed at the same laboratory using the same quantitative PCR-based technique (34). LTL decreased significantly more during the first 2 years of life compared to the period from age 2 years to 21 years.

LTL is one of the markers of biological aging since shortening occurs over time (35, 36). Shortening in LTL is influenced by factors such as inflammation, stress, radiation and obesity (37). Furthermore, shorter LTL has been linked to an increased risk of cardiovascular diseases in later life (36).

Until now, only one other study has investigated LTL longitudinally during infancy (38), which also presents an impressive decline in LTL during the first 2 years of life. This study, however, started measuring LTL at an older age (mean age of 8.6 months) and did not investigate LTL in association with body composition. It is challenging to obtain longitudinal blood samples of healthy infants in early life, which could explain the lack of longitudinal studies. We were able to collect 2 samples during infancy, at age 3 months and 2 years. These samples were collected by toe prick to limit the discomfort, resulting in parents giving permission for these blood collections.

Several methods exist for measuring telomere length (39), but it remains impossible to compare LTL between different cell types, such as blood cells, buccal cells and fibroblasts. We used the quantitative PCR-based technique to measure LTL (35, 40). This technique has the advantage that smaller DNA amounts are sufficient (39) and is therefore suitable for studying infant DNA.

Obesity has been associated with shorter LTL in adults (37, 41-43) and in children at the age of 8 years (44). It is for the first time that we present associations between LTL and body composition measurements during the first 2 years of life, which is an important window for infant development (11, 12). Our first LTL measurements took place at infant's age of 3 months, within the critical window for adiposity programming in the first 6 months after birth.

In conclusion, LTL decreases considerably during the first 2 years of life. More shortening in LTL from age 3 months to 2 years associates with higher FM%, FM index and visceral FM, and tends to associate with the gain in FM% from 3 to 6 months, suggesting that adverse adiposity programming in early life could contribute to more LTL shortening.

Appetite regulating hormones and body composition during the first 6 months

Chapter 6 presents appetite regulating hormone (ARH) levels during the first 6 months of life, a critical window for adiposity programming. We investigated fasting serum levels of ghrelin, peptide YY (PYY) and leptin at age 3 and 6 months and the associations of these hormones with body composition development until age 6 months.

For this study, we investigated three hormones; ghrelin stimulating food intake and PYY and leptin inhibiting appetite and increasing metabolic rate (45, 46). These hormones are involved in the regulation of food intake through specific brain centers (45, 47) and might thus contribute to adiposity programming early in life. However, studies investigating ARH during these first 6 months were very limited. We also determined the ghrelin/PYY ratio, as this ratio is a marker of orexigenic drive rather than both hormones separately (48, 49). Infant blood collection and body composition measurements were performed on the same day, at age of 3 and 6 months.

Our findings show that that ghrelin levels and ghrelin/PYY ratio increased from 3 to 6 months, while PYY and leptin levels decreased. Girls had a higher leptin at 3 months than boys, but other ARH levels were similar between boys and girls. Leptin correlated with FM% at 3 and 6 months and the gain in FM% from 1 to 6 months in exclusively breastfed (BF) and formula fed (FF) infants. In BF infants only, ghrelin and ghrelin/PYY ratio correlated also with the gain in FM% from 1 to 6 months. BF infants had lower ghrelin and higher PYY levels at age 3 months compared to FF infants. ARH levels did not correlate with human milk macronutrients. Regarding appetite, higher PYY levels in FF infants correlated with infants having more difficulty getting full up during a feed, while a higher ghrelin level and ghrelin/PYY ratio tended to correlate with less satiety.

We found that higher ghrelin and leptin, but not PYY, were associated with more FM development during the first 6 months of life, suggesting that they are involved in early adiposity programming. Leptin has been associated with adiposity, but most studies in infants or children used cord blood or neonatal blood spots instead of longitudinal ARH values in the first 6 months of life (50-56). Studies with one leptin measurement either at birth (57), at age 4 months (58) or leptin measurements during the first 6 months in a small group of infants (59) showed associations with body composition, which is in line with our study.

We found differences between ARH levels in BF and FF infants at age 3 months. Only few studies (58, 60), including a previous study of our own research group (61), investigated differences in early ARH levels of BF and FF infants. These differences might contribute to BF and FF infants having different body composition (62, 63).

Exclusively BF infants had lower ghrelin, higher PYY and as a result a lower ghrelin/PYY ratio than FF infants. This suggests that exclusively BF infants have more satiety, which is in line with a study describing that breastfeeding in the first year of life promotes satiety responsiveness in infants between age 18 and 24 months (64).

We now show that, in FF infants, a higher PYY at age 3 months correlated with having more difficulty getting full up during a feed. PYY decreases food intake and the finding of lower PYY levels in FF infants compared to BF infants therefore suggests that FF infants might indeed have less satiety. In addition, PYY correlated with the gain in FM% from 1 to 6 months in FF infants, but not in BF infants, which suggests that early life PYY levels might indeed contribute to the differences in body fat mass development between BF and FF infants.

Our study shows increasing ghrelin and decreasing PYY levels until age 6 months, resulting in an increasing ghrelin/PYY ratio. This suggests an increasing orexigenic drive until the age of 6 months. Ghrelin and leptin, but not PYY, associate with more FM development during the first 6 months, suggesting that they might be involved in early adiposity programming. Appetite regulating hormones at the age of 3 months are different between BF and FF infants, with lower ghrelin and higher PYY levels in BF infants.

Appetite regulating hormones and body composition during the first 2 years

Chapter 7 describes longitudinal appetite regulating hormone levels during the first 2 years of life. We investigated fasting serum levels of ghrelin, PYY, adiponectin and leptin at age 3 and 6 months and age 2 years and associated these levels with FM parameters measured at age 2 years to determine if ARH levels at 3 and 6 months are predictive for later FM. In addition, we investigated the associations of appetite regulating hormone trajectories until age 6 months and from 6 months to 2 years with trajectories of FM parameters during the same periods.

Our findings in 174 healthy infants show that ghrelin and ghrelin/PYY ratio increased and PYY, adiponectin and leptin decreased during the first 2 years of life. When investigating the potential predictive value of ARH for adiposity development, adiponectin levels at 3 and 6 months and a greater decline in adiponectin during the first 2 years as well as leptin levels at all ages correlated with higher FM% at 2 years. When investigating ARH trajectories, ghrelin and ghrelin/PYY ratio trajectories from 3 to 6 months were associated with the visceral FM trajectory during the same period. The leptin trajectory was associated with the FM% trajectory until age 2 years.

For the first time we show ARH trajectories in association with measured FM parameters. Studies on multiple ARH trajectories in early life were very scarce. Most studies used cord blood (50-54, 65) or newborn blood spots (55, 56) to investigate ARH at birth in association with later body composition. Two studies investigated ARH trajectories at birth or 6 months until childhood, but they did not investigate ARH in multiple blood samples during the first 2 years of life (46, 66).

Ghrelin increases food intake, while PYY reduces intake (45, 47). The ghrelin/PYY ratio is of interest as a marker of orexigenic drive rather than both levels separately (48, 49). Ghrelin and ghrelin/PYY ratio at age 3 and 6 months were, in contrast to our hypothesis, not predictive for FM% at age 2 years. A greater increase in ghrelin and ghrelin/PYY ratio during the

first 6 months of life, however, associated with less increase in visceral FM during the same period in the total group. These findings are in line with literature showing higher ghrelin levels and less visceral adiposity in subjects with Prader-Willi syndrome, characterized by hyperphagia and excessive weight, compared to obese controls (67-69). In addition, a higher ghrelin and ghrelin/PYY ratio at 2 years associated with lower visceral FM at age 2 years in exclusively FF infants, while also a greater increase in ghrelin and ghrelin/PYY ratio from 6 months to 2 years associated with lower visceral FM at 2 years.

Our data show that ghrelin and ghrelin/PYY ratio trajectories during the critical window for adiposity programming could contribute to visceral FM development instead of FM development. This is an important finding, because specifically increased visceral FM has been associated with unfavorable metabolic health during childhood and later on (70, 71).

Higher adiponectin levels at 3 and 6 months were significantly associated with higher FM% at age 2 years. Also a greater decline in adiponectin until age 2 years was associated with a higher FM% at 2 years, which could be explained by the fact that infants with a greater decline had higher levels at age 3 and 6 months. These findings can contribute to the understanding why lower adiponectin levels were found in adults with overweight and obesity (72-74), as we now show that specifically adiponectin during the first 6 months might be involved in the adiposity programming.

Leptin levels mainly reflected current FM%, which is in line with literature (46), but we showed that early leptin levels had also some predictive value for later FM%. In addition, the leptin trajectory during the first two years of life corresponded with the FM% trajectory during the same period.

In conclusion, ghrelin and ghrelin/PYY ratio increase during the first 2 years of life, while PYY, adiponectin and leptin decrease. Ghrelin levels and ghrelin/PYY ratio during the first 6 months of life have no predictive value for later FM%, but might be involved in visceral FM development. Early adiponectin levels might predict FM% at 2 years, suggesting that adiponectin is involved in early adiposity programming. Leptin levels mainly reflect current FM%, but have also some predictive value for later FM%. Our findings can potentially be used for the development of personalized screening tools for obesity prevention in early infancy.

GENERAL CONCLUSIONS, CLINICAL IMPLICATIONS AND FUTURE RESEARCH DIRECTIONS

General conclusions

Based on our findings presented in this thesis, we can conclude that there is a critical window for adiposity programming during the first 6 months of life. We found multiple determinants involved in early adiposity programming, such as rapid gain in fat mass during the first months, fat and energy content of human hind milk and satiety. In addition, early appetite

regulating hormone trajectories are involved in early life body composition development. Lastly, the shortening of leukocyte telomere length is also associated with body composition development.

Our findings show that an accelerated increase in weight and particularly in fat mass in the first 6 months should be avoided. For that reason, it is very important to closely monitor infants during the first months after birth. Our findings can potentially be used for the development of personalized screening tools in order to prevent obesity development at an early age. It is very important to prevent obesity in early life, as it is extremely difficult to effectively treat obesity once it has developed (75).

Clinical implications of this thesis

Our detailed body composition charts, using a combination of ADP and DXA with vacuum cushion, in healthy term-born infants from birth until age 2 years are of great importance for clinical and research use. The use of a vacuum cushion contributes to obtaining successful FM% measurements by DXA and allowed us to show the longitudinal changes in FM% during the first 2 years of life. Our body composition data can be used as reference values for our center, but the raw data cannot be just copied one to one if different DXA machines, vacuum cushions or software are being used. Each center should validate their own vacuum cushion and DXA machine.

Our findings show that the first 6 months of life are a critical window for adiposity programming, hence an optimal time for obesity prevention in early life. These findings point out that health care professionals and researchers should closely monitor infants in early life and should be aware of risk factors for developing obesity. If it is not possible to measure fat mass, it is necessary to monitor a proxy for fat mass in early infancy such as gain in weight-for-length and to prevent crossing of SD lines on the weight-for-length SDS charts.

Early appetite hormone levels are involved in adiposity programming in the first months after birth. Adiponectin levels at age 3 and 6 months might predict FM development. These hormones can potentially be used for the development of personalized screening tools for obesity prevention during early infancy. Leptin levels closely reflect FM and have some predictive value for later FM development. Early ghrelin levels and ghrelin/PYY ratio have some predictive value for the gain in FM% in the first 6 months of life, but not for later FM%, while both are involved in visceral FM development.

Human milk macronutrient levels showed wide variations between mothers. Exclusively breastfed infants receiving higher caloric human milk satiated earlier and finished feeding faster. These findings could explain the differences in duration of feeding time between infants. Therefore, presumed that infants have a healthy growth pattern, the duration of drinking could not always be considered a consequence or determinant of underlying problems, because we found that infants receiving higher caloric human milk finished their feeding earlier. This could be a mechanism to protect them from excess adiposity programming

by preventing an abnormally high intake of macronutrients, knowing that higher human milk fat and energy content at 3 months were associated with higher FM% at age 6 months and with more gain in FM% during the first 6 months of life.

Future research directions

Longer-term follow-up of body composition development in healthy term-born infants is warranted, particularly in infants with a rapid increase in fat mass during the first months of life in order to investigate whether they will also have more adiposity and specifically visceral fat mass after the age of 2 years. This could be important for targeted prevention strategies. Future research should also focus on elucidating the differences between hind milk and fore milk samples and their correlations with body composition and appetite. Furthermore, the effects of exclusive breastfeeding versus formula feeding during early life on later body composition need more investigation. The daily food intake, appetite regulating hormone levels and body composition later in life could be different between subjects who received exclusive breastfeeding versus formula feeding during infancy.

More research is required to investigate which additional factors might influence LTL during the first 2 years of life.

Potential effects of early adiposity programming on later cognitive functioning and behavior are presently unknown and need more investigation.

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