Adequate nutrition in the first 2 years of life is essential for both short- and long-term health. Malnutrition in the early years of life increases the risk of later chronic diseases. There is a wealth of studies available within this area of research, and this chapter specifically looks at growth and body composition as outcome measures in countries where obesity and related diseases in later life is a large public health problem. For this short review, we have included 10 publications on the topic of early nutrition and its effect on growth, body composition, and later obesity. We think these 10 included publications, published during the period of July 1, 2016 to June 30, 2017, are of special interest and all present findings can shape future research on this topic. We have chosen to focus on 3 key areas in this review; (i) human milk composition, including studies on breast milk minerals, hormones, and free amino acids (FAA) concentrations (4 studies), (ii) protein intake and later growth, including studies on how protein intake in early childhood is associated with body mass index (BMI; 4 studies), and lastly (iii) early infant feeding and later overweight and obesity, including studies on infant breastfeeding and circadian feeding pattern and the association with later overweight and obesity (2 studies).
Key articles reviewed for this chapter

Human Milk Composition

Associations between human breast milk hormones and adipocytokines and infant growth and body composition in the first 6 months of life
Fields DA, George B, Williams M, Whitaker K, Allison DB, Teague A, Demerath EW
Pediatr Obes Pediatr Obes 2017;12(suppl 1):78–85

Higher leptin but not human milk macronutrient concentration distinguishes normal-weight from obese mothers at 1-month postpartum
PLoS One 2016;11:e0168568

Free amino acids in human milk and associations with maternal anthropometry and infant growth

Minerals and trace elements in human breast milk are associated with Guatemalan infant anthropometric outcomes within the first 6 months
Li C, Solomons NW, Scott ME, Koski KG
J Nutr 2016;146:2067–2074

Protein Intake and Later Growth

Protein intake and dietary glycemic load of 4-year-olds and association with adiposity and serum insulin at 7 years of age: sex-nutrient and nutrient-nutrient interactions
Durão C, Oliveira A, Santos AC, Severo M, Guerra A, Barros H, Lopes C
Int J Obes (Lond) 2017;41:533–541

Dietary intake of protein in early childhood is associated with growth trajectories between 1 and 9 years of age
Braun KV, Erler NS, Kiefte-de Jong JC, Jaddoe VW, van den Hooven EH, Franco OH, Voortman T
J Nutr 2016;146:2361–2367

The association of trajectories of protein intake and age-specific protein intakes from 2 to 22 years with BMI in early adulthood
Wright M, Sotres-Alvarez D, Mendez MA, Adair L
Br J Nutr 2017;117:750–758

Early life protein intake: food sources, correlates, and tracking across the first 5 years of life
J Acad Nutr Diet 2017;117:1188–1197
Human Milk Composition

Associations between human breast milk hormones and adipocytokines and infant growth and body composition in the first 6 months of life

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Pediatr Obes 2017;12(suppl 1):78–85

Background: The concentration of hormones in human breast milk (HBM) and the association with infant growth and body composition needs investigation.

Objectives: In this study, the relationship between the HBM content of insulin, glucose, leptin, interleukin-6 and tumor necrosis factor-α and the maternal BMI, lactation stage (month 1 vs. 6), offspring sex and body composition was explored.

Methods: HBM was collected from 37 exclusively breastfeeding mothers at 1 and 6 months of lactation and analyzed for concentration of various hormones. The maternal BMI ranged from 19 to 47. The infants (16 girls, 21 boys) had body composition measured using dual-energy X-ray absorptiometry.

Results: There was an effect modification by infant sex and maternal BMI on the insulin levels in HBM ($p = 0.032$) such that insulin was 229% higher in obese mothers nursing female infants than in normal-weight mothers nursing female infants and 179% higher than obese mothers nursing male infants.
For leptin, a positive association with BMI category was observed \((p < 0.0001)\), such that overweight and obese mothers had 96.5 and 315.1% higher leptin levels than normal-weight mothers, respectively. Leptin decreased 33.7% from 1 to 6 months, controlling for maternal BMI category and sex \((p = 0.0004)\). Furthermore, the month 1 leptin concentrations were inversely associated with infant length \((p = 0.026)\), percent body fat \((p = 0.022)\), total fat mass \((p = 0.023)\), and trunk fat mass \((p = 0.011)\) at 6 months. No associations or modifications were observed for glucose, tumor necrosis factor-\(\alpha\) or interleukin-6.

**Conclusion:** These data indicate that HBM is modified by maternal adiposity, infant sex, and stage of lactation regarding the concentration of insulin and leptin and that these might influence infant growth and body composition.

Comments on this manuscript will be together with comments on the next manuscript.

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**Higher leptin but not human milk macronutrient concentration distinguishes normal-weight from obese mothers at 1-month postpartum**

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*PLoS One 2016;11:e0168568*

**Background:** It has been shown that the weight gain during the first month of life of exclusively breastfed infants born to obese mothers is less compared to infants of normal-weight mothers. Our hypothesis is that human milk composition and volume may differ between obese and normal-weight mothers.

**Objectives:** To investigate the difference in human milk from exclusively breastfeeding obese and normal-weight mothers regarding milk leptin and macronutrient concentrations and volume at 1 month postpartum. The maternal and infant characteristics for the 2 groups were compared as a secondary aim.

**Methods:** In this cross-sectional observational study, 50 obese mothers and 50 normal-weight mothers were matched regarding age, parity, ethnic origin, and educational level. All mothers exclusively breastfed their infants for at least 1 month. Human milk samples were collected at an early lactation stage (1 month postpartum) and the volume was assessed. Physical examinations of the mother and infant were conducted at 1 month postpartum.

**Results:** Human milk from obese, exclusively breastfeeding mothers showed a higher leptin concentration compared to normal-weight, exclusively breastfeeding mothers \((4.8 \pm 2.7 \text{ vs. } 2.5 \pm 1.5 \text{ ng/mL}, p < 0.001)\). No difference was observed regarding the concentration of protein, lipid, and carbohydrate and milk volume between obese and normal-weight mothers. Likewise, the infant weight gain during for the first month of life was the same for the 2 groups.

**Conclusion:** The breast milk of obese and normal-weight mothers differed regarding the leptin concentration with higher concentrations in the milk of obese mothers. However, there was
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The composition of human breast milk is complex and changes according to lactation stages and varies between mothers [1, 2]. The impact of maternal factors on the human milk composition has attained considerable interest, especially the impact of maternal adiposity due to the growing number of overweight and obese mothers in many parts of the world. In the 2 studies by Fields et al. [3] and De Luca et al. [4], the influence of maternal BMI on leptin concentrations at 1 month postpartum and growth were investigated and adds interesting knowledge to this topic. Both studies found that leptin concentration in breast milk was positively associated with maternal BMI. In the study by Fields et al. [3], insulin was also measured and an interesting interaction between maternal BMI and infant sex was observed, indicating differential sex-based composition of breast milk. A modifying effect on breast milk composition has also been reported for macronutrients and volume [5, 6], which support that a sex-dimorphism in breast milk could be present. A limitation of the present study is the small sample size, and future studies based on larger sample size are warranted to further investigate this remarkable potential sex differences and the mechanism behind.

De Luca et al. [4] did not find a lower weight gain in infants born to obese mothers during the first month of life compared to infants born to normal-weight mothers. The hypothesis suggested by De Luca et al. [4] regarding an association between leptin in breast milk and weight gain during the first month was thus not supported. In the study by De Luca et al. [4], there was no follow-up with later growth measurements, but in the study by Fields et al. [3] growth and body composition up to 6 months of age were determined. Here breast milk leptin concentrations at 1 month postpartum were inversely associated with length and adiposity measures at 6 months postpartum and tended to be negatively associated with weight gain. These are new interesting findings, and existing studies show conflicting results [7, 8]. Studies looking at the role of leptin and other low-abundant proteins in human breast milk in relation to both maternal factors and infant outcomes, such as growth and body composition, are emerging and warranted. Breastfeeding is still advisable for all women, and as pre-pregnancy obesity is a growing public health concern, this area of research is of immediate importance.

Free amino acids in human milk and associations with maternal anthropometry and infant growth

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**Background:** The concentrations of free amino acids (FAA); glutamic acid and glutamine, are high in breast milk, and studies with infant formula have suggested that FAA, especially glutamic acid, can affect appetite and thus downregulate dietary intake.
**Objectives:** The objective of this study was to investigate: (i) the association between glutamic acid or glutamine concentrations in breast milk and current size or early infant growth in fully breastfed Danish infants (using growth as a proxy for breast milk intake) and (ii) how maternal anthropometry was associated with these FFA concentrations in breast milk.

**Methods:** From a subgroup of 78 mother-infant pairs, of which 50 infants were fully breastfeed, from the Odense Child Cohort, breast milk samples, infant feeding practice data and infant weight and length were collected at 4 months postpartum. The FAA was analyzed by reverse-phase high-performance liquid chromatography.

**Results:** There was no correlation between the 2 FAA and infant weight or BMI. Infant length at 4 months of age was, however, positively associated with glutamine ($p = 0.013$), but the correlation was attenuated when controlled for birth length ($p = 0.089$). There was a large variation in the concentration of the FAA between mothers. Glutamic acid was positively correlated with mother’s prepregnancy weight and height ($p \leq 0.028$), but not BMI.

**Conclusion:** The hypothesis that a high content of glutamic acid and glutamine in breast milk can downregulate milk intake to a degree affecting early growth could not be confirmed in this study. Maternal factors associated with the concentrations of these FAA in milk and the potential influence on the infant should be investigated further.

**Comments**

In this study by Larnkjær et al. [9], the hypothesis that high breast milk glutamic acid and glutamine concentrations downregulate milk intake to a degree that affects infant growth could not be confirmed. However, this study did not measure breast milk intake, but used infant growth as a proxy measure of intake, and furthermore the sample size was small ($n = 78$). No other study has yet investigated the association between milk glutamic acid and glutamine concentrations and infant breast milk intake, which is needed to either reject or accept the hypothesis. The data available in this area of research has been taken from formula-fed infants given hydrolyzed formula that has a high concentration of FAA and nitrogen. These studies have shown a lower intake of the hydrolyzed formula and a growth pattern closer to the pattern of breastfed infants [10, 11]. Furthermore, an intervention study found that adding free glutamic acid to infant formula resulted in a significant reduction in formula intake compared to ordinary formula [12]. This current study by Larnkjær et al. [9] also investigated maternal determinants of breast milk FAA concentrations and found that maternal weight and height were positively associated with the concentration of free glutamic acid in breast milk. An increase in maternal weight of 1 kg corresponded to an increase of 5.6 μmol/L glutamic acid concentration. This has not previously been investigated by others, suggesting the need for further research in maternal determinants of milk FAA concentrations.
Minerals and trace elements in human breast milk are associated with Guatemalan infant anthropometric outcomes within the first 6 months

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Background: Infants are relying on breast milk as the only source of nutrients in the first few months of life, but it is not known how breast milk mineral and trace elements are associated with infant growth.

Objectives: To investigate the concentration of Guatemalan mothers’ breast milk mineral and trace element concentrations at three lactation stages to estimate the total daily infant intakes and to determine whether infant intakes were associated with early infant growth.

Methods: In this cross-sectional study, breast milk samples were collected from Mam-Mayan mothers during transitional (5–17 days, n = 56), early (18–46 days, n = 75), and established lactation (4–6 months, n = 103) via full manual expression. Infant z-scores for weight (WAZ), length (LAZ), and head circumference (HCAZ) were measured from exclusively or predominantly breast-fed infants. Inductively coupled plasma-mass spectrometry was used to analyze calcium, potassium, magnesium, sodium, copper, iron, manganese, rubidium, selenium, strontium, and zinc concentrations. Daily breast milk mineral intakes were based on estimations. Principal component analyses identified clusters of minerals; principal components (PCs) were used in multiple linear regression analyses for anthropometric outcomes.

Results: Guatemalan infants had a high rate of growth faltering in this study, with 45% stunting at 4–6 months of age. Estimated infant intakes of calcium, magnesium, potassium, sodium, and selenium were below the Institute of Medicine Adequate Intake for males and females at all 3 stages of lactation. In early lactation, PC1 (calcium, magnesium, potassium, rubidium, and strontium intakes) was positively associated with infant WAZ, LAZ, and HCAZ. In established lactation, the same PC with sodium added was positively associated with all 3 anthropometric outcomes; a second PC (PC2: zinc, copper, and selenium intakes) was associated with WAZ and LAZ but not HCAZ.

Conclusion: A higher intake of breast milk minerals and trace elements of Guatemalan infants could be beneficial for infant growth during early infancy.

Comments: The investigation of breast milk micronutrient composition has started to emerge in the scientific literature, especially because reliable quantification methods have evolved over the past few years [13]. However limited studies are available in this area of research. For instance, few high-quality studies are available on how maternal micronutrient deficiencies influence breast milk micronutrient composition. More importantly for breast milk minerals, the adequate concentration of micronutrients in human milk for healthy growth and development are unknown. Furthermore, very limited evidence is available on how breast milk micronutrient composition is associated with infant growth. This study by Li et al. [14] contributes to the knowledge regarding how breast milk mineral and trace element concentrations are associated with infant growth in a population in Guatemala where infant growth faltering is common, and where maternal height is one of the lowest in the world [15]. However, there are several limitations to the results and conclusions by Li et al. [14]. In this study, breast milk intakes were not measured but based on estimates. This is a limitation as...
breast milk intake often varies substantially among exclusively breastfed infants [16], and it is therefore not possible to distinguish if the observed association with growth reported by Li et al. [14] is driven by infant breast milk intakes or by breast milk mineral concentrations. Another general limitation is that, it is not possible to determine if the breast milk mineral concentrations reported in this study are too low or inadequate for healthy growth and development, as it is not yet known what the adequate micronutrient concentrations in breast milk are. Concluding on any inadequacy of breast milk micronutrient concentrations should thus be done with caution, especially if neither maternal nor infant status are investigated. This study by Li et al. [14] highlights the need for further research on breast milk micronutrient composition in resource-poor settings where growth faltering is experienced in early infancy during the period of exclusive breastfeeding and the need for establishing reference values in populations with adequate nutritional status.

Protein Intake and Later Growth

Protein intake and dietary glycemic load of 4-year-olds and association with adiposity and serum insulin at 7 years of age: sex-nutrient and nutrient-nutrient interactions

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**Background:** Limited prospective studies have investigated the role of protein intake (PI) and dietary glycemic load (GL) in preschool children on later adiposity.

**Objective:** The aim of this study was to examine the association of PI and GL at 4 years with adiposity and fasting serum insulin (FSI) at 7 years, and to evaluate if sex modified this association. Furthermore, a possible interaction between PI and GL was examined.

**Methods:** For the analyses in this study, the population-based birth cohort, Generation XXI (Porto, Portugal, 2005–2006) including 1999 singleton children was used. A 3-day food diary was used to assess the diet at 4 years of age. Both PI and GL (g/day) were energy-adjusted and converted into sex-specific tertiles (T). World Health Organization (WHO) standards were used to calculate the BMI z-scores at 7 years of age. Body composition was determined by bioelectric impedance and sex-specific z-scores were computed for fat mass index (FMI), waist-to-height ratio (W/Ht), and FSI. Linear regression was used to estimate associations.

**Results:** PI in girls and boys were similar while girls had slightly lower GL than boys. For both girls and boys, PI was positively associated with BMI (T2 vs. T1: β = 0.187; 95% CI 0.015–0.359) and (T3 vs. T1: β = 0.205; 95% CI 0.003–0.406, respectively), while PI was only associated with FSI in boys (T3 vs. T1: β = 0.207; 95% CI 0.011–0.404; P-interaction = 0.026). Similarly GL was associated with BMI only in boys (T3 vs. T1: β = 0.362; 95% CI 0.031–0.693; P-interaction = 0.006). Significant in-
teractions between PI and GL were found on the association with FMI ($p = 0.019$) and W/Ht ($p = 0.039$) in boys only. Boys belonging to the third tertile of both PI and GL at 4 years had higher FMI ($\beta = 0.505; 95\% \text{ CI} 0.085–0.925$) and W/Ht ($\beta = 0.428; 95\% \text{ CI} 0.022–0.834$) 3 years later.

**Conclusion:** This study showed that for preschool children PI was positively associated with later BMI in both sexes, while PI was positively associated with FSI in boys only. Dietary GL was only positively associated with adiposity in boys.

**Comments**

This study is one of few studies evaluating the effect of higher PI on later obesity in preschool-aged children. The study showed, like several other studies with children in different age groups, that high PI was associated with higher BMI years later in both girls and boys [17]. Furthermore, the study focused on sex differences in response to nutrients and showed some interesting results. PI was positively associated with serum insulin and dietary GL to BMI in boys only. In girls, the influence of energy intake was independent of macronutrient distribution, while in contrast, boys were dependent on energy from either protein or carbohydrate. The authors discussed possible mechanism behind this sex differences in response to the same food. They proposed that physiologically females prefer to use fat as a substrate while males have a larger propensity to rely on glucose and protein metabolism. Another interesting topic in this study was the analyses of possible nutrient-nutrient interactions. The study showed that dietary GL interacts with PI in boys. Boys in the highest tertile of both GL and PI at 4 years had higher FMI and waist/height ratio at 7 years of age. Possible mechanisms behind this association to central adiposity were also discussed. High PI may increase levels of branched-chain amino acids, which stimulate secretion of IGF-1 and insulin. Glucose similarly stimulate insulin production, and it is known that males are more sensitive to insulin and thereby develop central adiposity. However, the authors underline that more studies are needed to further understand the sex-nutrient and nutrient-nutrient interactions.

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**Dietary intake of protein in early childhood is associated with growth trajectories between 1 and 9 years of age**

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**Background:** High protein intake in infancy may lead to a higher BMI in childhood. However, it is not known whether different sources of protein have the same relation to later BMI.

**Objective:** Associations between intake of total protein, different protein sources, and single amino acids in early childhood and later height, weight, and BMI up to the age of 9 years were analyzed.

**Methods:** The children analyzed ($n = 3,564$) participated in multi-ethnic population-based prospective cohort study, the Generation R, in Rotterdam, The Netherlands. A food-frequency questionnaire was used to assess intakes of total protein, animal protein, vegetable protein, and individual amino acids (including methionine, arginine, lysine, threonine, valine, leucine, isoleucine, phenylalanine, tryptophan, histidine, cysteine, tyrosine, alanine, asparagine, glutamine, glycine,
proline, and serine) at 1 year. At the approximate ages of 14, 18, 24, 30, 36, and 45 months and at 6 and 9 years, height and weight were measured and BMI calculated.

**Results:** Linear mixed models were used for analyses and after adjustment for confounders, a 10-g higher total protein intake/day at 1 year was significantly associated with a 0.03-SD greater height (95% CI 0.00–0.06), a 0.06-SD higher weight (95% CI 0.03–0.09), and a 0.05-SD higher BMI (95% CI 0.03–0.08) up to the age of 9 years. Animal protein intake was more strongly associated with BMI than vegetable protein intake, but dairy and non-dairy animal protein did not differ. Similarly, there were no differences between specific amino acids. There were no significant interactions between protein intake and age or outcome measurements, sex or ethnicity.

**Conclusion:** Higher intake of protein at 1 year of age, especially animal protein, was associated with a greater height, weight, and BMI in childhood up to 9 year of age. The association was not different for dairy and non-dairy animal protein. However, the role of growth hormones and whether protein intake in early childhood affects health later in life need further investigation.

**Comments**
This study is one of several studies based on data from the Generation R study [20]. It is interesting both because of the large sample size followed by longitudinal anthropometric measurements up to the age of 9 years. Furthermore, this study is interesting as it investigates the impact of different protein sources. The basis for this is the detailed analyses of the food intake by using a semi-quantitative FFQ with 211 food items, which estimates intake of total protein, animal protein, and vegetable protein. Furthermore, the intake of animal protein was divided into dairy and non-dairy protein, and the intake of different amino acids were calculated. The FFQ was validated against three 24-h-recalls. The detailed food registration provides an opportunity to investigate which role different proteins and amino acids have for growth and the risk of development of later overweight or obesity.

The study also underlines that the positive association with height, weight, and BMI is stronger for animal protein intake than vegetable protein. Studies have further shown that there is a difference in the effect of dairy and non-dairy animal protein; a high intake of milk, but not meat, increases IGF-1 and insulin in short-term studies with school-aged boys [21, 22]. It was thus surprising that Braun et al. [19] did not find any differences between diary and non-dairy animal protein. The idea suggested by others concerning a special growth stimulating effect of certain amino acids like arginine and lysine was however not confirmed in this study. More studies are needed to understand the effect of different protein sources.

The early protein hypothesis has been examined in multiple cohorts; however, protein intake measured at multiple time-points from early childhood to young adulthood has not been assessed. This study associates the intake across childhood, adolescent, and young adulthood to adult BMI. The association of estimated protein intake at 2, 11, 15, 19, and 22 years were assessed with age- and
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sex-standardized BMI at 22 years (early adulthood). Linear regression models with dietary and anthropometric data from a Filipino birth cohort (1985–2005, n = 2,586) were used to associate protein intake and adult BMI. Latent growth curve analysis was used to identify trajectories of protein intake relative to age-specific recommended daily allowance (intake in g/kg body weight) from 2 to 22 years. This resulted in four mutually exclusive trajectories of protein intake, which were related to early adulthood BMI using linear regression models. Lean mass and fat mass were determined by skinfold measurements, which were secondary outcomes. Regression models adjusted for several socioeconomic, dietary, and anthropometric confounders from early life and adulthood were used. It was found that a higher protein intake relative to needs at age 2 years was positively associated with BMI and lean mass at age 22 years, in females but not males. Protein intakes at ages 11, 15, and 22 years were overall inversely associated with early adulthood BMI, fat, and fat-free mass in both males and females, however, the associations were more consistent in females. Individuals were then classified into four mutually exclusive trajectories: (i) normal consumers, who had a protein intake just above recommendations (referent trajectory, 58% of cohort), (ii) high protein consumers in infancy, with a subsequent protein intake just above recommendations (20%), (iii) usually high consumers who had high intakes before age 19, with very high intake at age 11 (18%), and (iv) always high consumers, who had high protein intake at 2 years of age and thereafter (5%). Compared with the normal consumers “usually high,” consumption was inversely associated with BMI, lean mass, and fat mass at age 22 years whereas “always high” consumption was inversely associated with lean mass in males only. It seemed that protein intake more close to adulthood was a more important contributor to early adult BMI relative to early-childhood protein intake; protein intake trajectory history was differentially associated with adulthood body sizes.

Comments on this manuscript will be together with comments on the next manuscript.

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Early life protein intake: food sources, correlates, and tracking across the first 5 years of life


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Background: A high consumption of protein has been associated with accelerated growth and adiposity in early childhood.

Objective: The aim of this study was to describe dietary intake, food sources, correlates, and tracking of protein intake in young children.

Methods: This study was a secondary analysis of the Melbourne Infant Feeding Activity and Nutrition Trial which consisted of first-time mothers and their child (n = 542). They participated in an 18-month intervention to prevent childhood obesity, and the cohort was followed-up with no intervention when children were aged 3.5 and 5 years. Dietary data were collected using three 24-h dietary recalls at ages 9 and 18 months as well as 3.5 and 5 years. Protein intake, food sources, correlates, and tracking of protein were included in the analysis of the main outcomes.

Statistical analyses performed: The child and maternal correlates of protein intake were identified using linear regression models and tracking of protein intake was examined using Pearson correlations of residualized protein scores between time points.

Results: The mean protein (g/day) intake was 29.7 ± 11.0, 46.3 ± 11.5, 54.2 ± 13.8, and 60.0 ± 14.8 at 9 and 18 months at 3.5 and 5 years, respectively. The mean protein intake at all age groups was
2–3 times greater than age-appropriate Australian recommendations. The primary source of protein at 9 months was breast/formula milk. At later ages, the principal sources were milk/milk products, breads/cereals, and meat/meat products. Significant predictors of high protein intake at different time-points were earlier breastfeeding cessation, earlier introduction of solids, high dairy milk consumption (≥500 mL), and high maternal education ($p < 0.05$). A slight tracking for protein intakes were found at 9 months, 18 months, and 5 years of age ($r = 0.16–0.21; p < 0.01$).

**Conclusion:** This study provides insights into the food sources of young children’s high protein intakes, and confirms that early life protein intake tracks slightly up to the age of 5 years. Furthermore, this study found correlates of protein intake that might be relevant for future interventions. The findings of the present study have the potential to provide information for nutritional intervention studies to target high protein intake as a potential way to mitigate later obesity risk at an early age.

**Comments**

The early protein hypothesis state that high protein intake early in life may increase the risk of obesity later in life. This is being extensively researched and the 2 present studies, each contribute by (i) examining the association between early life protein intake and BMI/adiposity in adulthood and (ii) examining food sources of protein and early determinants of protein intake.

In the first study, Wright et al. [23] did not show strong associations between protein intake and BMI or adiposity. Furthermore, infants with high early life protein intake and subsequent “normal” protein intake were not different from infants with “normal” protein intake throughout infancy, childhood, and adolescent. However, the study reported sex-specific associations with protein intake, which is in line with other studies showing that the associations between protein intake and BMI/adiposity tends to be stronger in girls than in boys [24]. There might be several reasons why the associations between protein intake and BMI was not as strong in this study as indicated in previous studies. First, the present study measured protein intake throughout childhood, adolescent, and early adulthood, something that has not often been done. The use of repeated dietary assessment is important when examining long-term outcomes, and adds value to the results. However, a limitation of the study is that protein intake was not measured as early as other studies, which have shown a strong association between 1 year protein intake and later adiposity [20]. Furthermore, multiple assessments of diet throughout infancy would add valuable knowledge in determining potential critical phases of exposure. A strength of this study is the long follow-up and measurement of BMI and adiposity in adulthood. However, the results did not show clear differences in lean versus fat mass accretion as the association estimates were of the same direction – therefore, future studies need to add more accurate adiposity measurements. Finally, the study cohort was different compared to other cohorts examining early life protein intake and adiposity, as it had a high prevalence of infant undernutrition and the infant diet had a high grain content and was low in animal protein. In addition, the cohort had a low intake of dairy protein (<10% of protein intake) compared to other cohorts (40–80% of protein intake). This is of special interest because dairy protein has been linked to a specific amino acid composition and thus hypothesized to be more pro-obesogenic/growth spurting, especially in infancy/early childhood compared to other protein sources [17]. Thus, it could be speculated that the lack of high dairy protein intake in infancy contributed to the low effect estimates on later adiposity.

Multiple aspects of the early protein hypothesis remain to be investigated and the findings from Wright et al. [23] warrants further investigation, preferably randomized intervention trials. For such trials, it is important to know which components to target for intervention. The study by Campbell et al. [25] provided information on the major
food sources and other determinants of early life protein intake. The authors showed that milk, cereals, and meat were the main contributors of protein intake at age 9 months to 5 years. The protein intake was substantially higher than the recommendations, which gives room for potential interventions. The authors also examined other determinants of high protein intake to identify potential targets for interventions and found that early introduction of solid foods, early cessation of breastfeeding, and high milk consumption was associated with higher protein intake. Protein intake was weakly correlated (Pearson’s correlation in the order of 0.16–0.21) across different timepoints in infancy indicating tracking.

The present study by Campbell et al. [25] is in line with other findings showing that the intake of dairy and meat products in early life contribute to the majority of the protein intake. Among European populations, dairy consumption contributed the most protein at 6 months, decreasing with age until meat and dairy intake contributed almost equally at 24 months of age [26]. Based on these results targeting these foods, by reducing intake, and thereby lowering protein intake could be suggested as a potential intervention in early childhood. However, good sources of protein are also good sources of other key nutrients such as several vitamins and calcium, as also highlighted by Campbell et al. [25] Thus, potential future interventions regarding diet with reduced protein content should still have sufficient amount of other essential nutrients. Furthermore, careful examination of protein intake based on population-specific intake is necessary as different protein sources might vary in relevance between populations as seen in the Wright et al. [23] and Campbell et al. [25] studies.

One further aspect that is intriguing from the studies of Wright et al. [23], Durão et al. [18] and Braun et al. [19] is at what age the association between protein intake and BMI/body composition switches. While all three studies show associations between high protein intake and adiposity at age 1, 2, and 4 years of age, the study by Wright et al. [23] also show opposite associations at age 11. In adulthood, a higher protein intake has been linked to increased satiety, increased thermogenesis, maintenance or accretion of fat-free mass, and may thus be beneficial for weight loss and weight maintenance [27]. Thus, it seems that there is an age-dependent effect of protein on body composition. At what point this switch happens and what the biological mechanisms behind it is, is still largely unknown, but could have something to do with prepubertal changes in sex and growth hormones and insulin sensitivity. However, this warrants further study.
Infant feeding and growth trajectory patterns in childhood and body composition in young adulthood

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**Background:** Growth patterns of breastfed and formula-fed infants differ, with formula-fed infants growing more rapidly than breastfed infants into childhood and adulthood.

**Objective:** The objectives of this study were to: (i) identify growth patterns and (ii) investigate early nutritional programming potential on growth patterns at 6 years and on body composition at 20 years.

**Methods:** Data from the West Australian Pregnancy Cohort (Raine) Study and three European cohort studies (European Childhood Obesity Trial, Norwegian Human Milk Study, and Prevention of Coeliac Disease) were combined, harmonized, and pooled to include information on breastfeeding, anthropometry, and body composition. From zero to 6 years, semi-annual anthropometric measurements were available and BMI was calculated. Latent growth mixture modeling was applied to identify growth patterns among the 6,708 individual growth trajectories. The association of full breastfeeding for <3 months compared with ≥3 months with the identified trajectory classes was assessed by logistic regression. Differences in body composition at 20 years (only in the Raine study; based on skinfolds and dual-energy X-ray absorptiometry) among the identified trajectory classes were tested by analysis of variance.

**Results:** Three BMI trajectory patterns were identified and labeled as follows; class 1: persistent, accelerating, rapid growth (5%); class 2: early, non-persistent, rapid growth (40%); and class 3: normative growth (55%). Full breastfeeding for <3 months was associated with being in rapid-growth class 1 (OR 2.66; 95% CI 1.48–4.79) and class 2 (OR 1.96; 95% CI 1.51–2.55) rather than the normative-growth class 3 after adjustment for covariates. For each additional month of full breastfeeding, there was a reduced risk of being in the rapid growth classes, class 1 and 2 of 17 and 6%, respectively. Both classes showed significant associations with body composition at 20 years (p < 0.0001). Children who had a higher probability of being in one of the 2 rapid-trajectory class had higher BMI, skinfolds, and fat mass index at 20 years compared to the normative growth class.

**Conclusion:** Full breastfeeding for <3 months compared with ≥3 months may be associated with rapid growth in early childhood and body composition in young adulthood. Rapid growth patterns in early childhood could be a mediating link between infant feeding and long-term obesity risk.
Using growth trajectory pattern analysis, and combining four large cohorts with more than 6,000 participants, the authors were able to distinguish three quite different and interesting growth patterns. The largest group class 3 (normative growth, 55% of the children) had a BMI z-score (BAZ) pattern very close to the WHO growth standards from birth to 6 years. Forty percent of the children had an early non-persistent rapid growth (class 2). The rapid growth started in early infancy and had a mean BAZ of about +1 at 2 years of age. From 2 to 6 years of age, there was a steady decline in BAZ reaching a BAZ of about +0.5 at 6 years of age. The smallest group (5%, persisting, accelerating, rapid growth) had an extreme pattern. BMI only started to increase from the age of about one year and then accelerated steadily until 6 years when it reached about +3 BAZ. A strength of the study is that the Raine cohort was followed to 20 years and it was thus possible to examine the long-term effect of these three distinct growth trajectories on body composition in young adults. As Rzehak et al. [28] underline in their concluding sentence, the results are based on observational data and does not allow conclusions about casual effects of breastfeeding as neither reverse causation nor residual confounding can be ruled out.

It is still discussed if breastfeeding has an effect on the risk of later overweight and obesity. In the Lancet series on breastfeeding from 2016 [29], it was concluded that the evidence was suggestive for a protective effect on breastfeeding. This conclusion was based on a review by Horta et al. [30], which found a risk reduction of 13% based on results from 23 high quality studies. However, in the PROBIT intervention study with a cluster randomized design there was no effect of breastfeeding on later overweight and obesity up to 16 years of age [31]. Apart from residual confounding, reverse causation could also play a role, that is, the weight gain of the infant influences the time when either infant formula or complementary foods are introduced.
Circadian Feeding Pattern and Later Overweight

Predominantly nighttime feeding and weight outcomes in infants

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This manuscript is also discussed in Chapter 2, pages 15–38.

Background: The influence of circadian feeding patterns on weight outcomes has been shown in animal and human studies but not in young children. Adults who consume more energy in the evening tend to be overweight or obese, but this has not been examined in infants. Both food and light are important signals influencing biological rhythms.

Objective: The aim of this study was to examine the association of infant circadian feeding patterns at 12 months of age with subsequent growth from 12 to 24 months and weight status at 24 months.

Methods: Mothers from a Singaporean birth cohort (n = 349) reported the food given to their infants and the feeding time at 12 months of age. Predominantly daytime (pDT; 07.00–18.59; n = 282) and predominantly nighttime (pNT; 19.00–06.59; n = 67) feeding infants were defined by whether daytime energy intake was >50 or <50% of total energy intake as assessed with the use of a 24-h dietary recall. These hours were chosen as they are close to sunrise and sunset in Singapore. BMI-for-age z scores (BAZ) were calculated using the WHO Child Growth Standards 2006 to determine changes in BAZ from 12 to 24 months of age and weight status at 24 months of age. Multivariable linear and logistic regression analyses were performed.

Results: Total 24-h energy intake was not different between pNT- and pDT-feeding infants (815 ± 229 compared with 764 ± 222 kcal, respectively; p = 0.090). The pNT-feeding infants had a lower percentage of energy from protein compared with the pDT-feeding infants (12.7 ± 2.8 vs. 14.8 ± 3.2%; p < 0.001). Compared with pDT feeding, pNT feeding was associated with a higher BAZ gain from 12 to 24 months of age (adjusted β = 0.38; 95% CI 0.11–0.65; p = 0.006) and increased risk of overweight at 24 months of age (adjusted OR 2.78; 95% CI 1.11–6.97; p = 0.029) after adjusting for maternal age, education, ethnicity, monthly household income, parity, infant BAZ at 12 months of age, feeding mode in the first 6 months of life, and total daily energy intake.

Conclusion: These results suggest that the role of the daily distribution of energy consumption in weight regulation may begin in infancy. A pNT feeding pattern of infants was associated with adiposity gain and risk of overweight in early childhood. The inclusion of advice on the appropriate feeding time may be considered when implementing strategies to combat childhood obesity.
The effects on growth of many aspects of infant feeding have been examined in detail, for example, breastfeeding versus formula feeding, composition of breast milk, time of introducing complementary foods, and macronutrient intake, and several of these recent studies are included in this chapter and in our chapter in the Nutrition and Growth Yearbook 2017 [1]. This study is interesting because it is the first to examine if circadian infant feeding pattern can influence growth and risk of obesity. Adults who eat at nighttime have a higher risk of overweight, but most studies have been observational and the mechanisms behind such an effect have not yet been identified [32]. In this study by Cheng et al. [33], the infants who were nighttime feeders (19% of the infants) consumed 63% of their energy between 7 p.m. and 7 a.m., while for the daytime feeders it was only 33%. The largest difference in infant intakes between the 2 groups was from 7 to 10 p.m. A higher proportion of the nighttime feeders were breastfed, both at 6 and 12 months of age, but this was controlled in the analysis of the effect on BMI gain and risk of becoming overweight.

Short sleep duration during infancy has been associated with an increased risk of later overweight [34]. It is possible that there is an interaction between sleep duration and circadian feeding pattern. In the present study, the total sleep duration attenuated the risk of becoming overweight, but the effect was small and sleep duration was only recorded in 41% of the infants.

The mechanisms behind the effect of circadian feeding pattern on BMI seen in this study are unknown and it is not clear to what degree the feeding pattern is driven by the parents or by the infant. Future studies should include measurements of appetite and growth-related hormones, measurements of body composition, and a detailed registration of sleep and food intake. Furthermore, intervention studies could explore the effect of circadian feeding pattern on hormones and other relevant metabolic parameters. Before the mechanisms behind the interesting association found in this study are understood, we will not know if advice on appropriate feeding time will have an effect on growth, later overweight, and obesity.

References


