Infant Feeding Practices and Subsequent Development of Adipose Tissue

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Abstract

The main aspects of infant feeding that have been studied in humans in association with the subsequent development of adipose tissue include breastfeeding, rapid infancy weight gain, and weaning practices. While observational studies have consistently shown a protective effect of breastfeeding on the development of obesity, these studies may be confounded by unmeasured or unknown factors, as suggested by one study using a sibling design and one study using a randomized breastfeeding promotion intervention design. Observational studies and findings from a limited number of experimental studies suggest that rapid weight gain during infancy may be associated with an increased risk for obesity in childhood and adulthood. The association of weaning practices with later obesity has not been extensively studied, and the preliminary findings are inconsistent. Additional research studies, especially randomized interventions with long-term follow-up, are necessary in order to assess if short nutrition interventions during the critical period of infancy can have long-term benefits on the prevention of obesity.

The association of infant feeding practices with the development of adipose tissue, in particular excessive adipose tissue or obesity, has been extensively examined [1–4]. This review is not meant to be comprehensive, but rather a critical assessment of selected research findings with an emphasis on adipose tissue measurement methods.

Adipose Tissue in Humans: Measurements and Surrogates

One clinically significant aspect of adipose tissue in humans is that its excessive accumulation, as part of obesity, is associated with unfavorable
health and psychosocial consequences during childhood and adulthood, such as type 2 diabetes, hypertension, dyslipidemia, some cancers, fatty liver disease, polycystic ovary syndrome, osteoarthritis, and social stigmatization [5]. Direct measurement of adipose tissue mass in living humans is not possible; therefore, research and clinical assessments rely on indirect or surrogate measurements of body composition. Body composition indicates that the human body can be partitioned into fat mass (adipose tissue) and lean mass. Lean mass can further be partitioned into bone and lean soft tissues.

Underwater weighing is often considered as the in vivo gold standard to measure fat vs. lean mass. Based on Archimedes’ principle, body volume can be derived from bodyweight under water and outside water. Using measurement of lung volume and assumption about the density of fat and lean body mass, the proportion of fat mass can be estimated. The advantage of this method is that it is very precise, but it is not widely available or transportable and it requires the subject’s complete cooperation to stay still underwater and to measure lung volume, making it difficult to use in children.

In children, dual-energy X-ray absorptiometry (DXA) is often considered as the age-appropriate gold standard for measurement of body composition. Using X-ray properties of differential absorption by calcium, fat, and water (the main component of lean tissue), DXA provides images that can be analyzed to estimate the mass of bone, fat, and lean soft tissues. The advantages of DXA are that it requires only minimal cooperation from the subject and is rapid and reproducible. Its disadvantages are that it cannot easily be transportable to the field for epidemiological studies and that it leads to a small exposure to X-rays. Additionally, there are no undisputable reference data of body composition from DXA available to adjust for the physiological changes during growth and puberty in children and for differences between sexes. Therefore, most studies use an internal reference and compare subjects above and below a specified percentile of fat mass of percent body fat.

A more transportable method of assessment of adipose tissue is the measure of skinfold thickness using a precise caliper and by pinching the skin at specific body locations. The advantages of the method are its low cost and transportability and the existence of reference data [6]. Its disadvantages are that it is very dependent on the observer and therefore requires extensive training and reliability testing to provide reproducible data and that it can be difficult to assess in very obese individuals. Furthermore, skinfold thickness only measures subcutaneous fat and not intra-abdominal or visceral fat, which is thought to be more strongly associated with metabolic complications of obesity.

Several other methods of body composition measurement have been used in children, including total body potassium by whole-body 40K counting, tritium dilution, bioimpedance, and air displacement plethysmography. The limitations of these methods however make them less feasible, less reliable, or less reproducible than the ones listed above.
As can be seen from the above discussion, the direct measurement of adiposity in the clinical setting or epidemiological research setting can be challenging, and surrogates of adiposity based on simple measurement of weight and height are therefore useful in these settings. The most widely used surrogate for measurement of adipose tissue is body mass index (BMI) as defined by the weight in kg divided by the height in meters squared (kg/m²). BMI is closely correlated with adiposity and performs well at classifying subjects as obese, including children, using DXA as a reference method [7]. BMI is relatively independent of stature, very reproducible, easy to measure with minimal training, and has good reference data to adjust for the physiological differences between ages and sexes [8]. The disadvantage of BMI is that it measures body mass relative to height and not body composition or adipose tissue. Therefore, very muscular individuals can sometimes be misclassified as obese (BMI above the 95th percentile of the reference population for children or 30 for adults), but in the general population of children, this is unusual, and most children classified as obese using BMI truly have excessive adipose tissue [7].

Most studies using a life course approach to obesity epidemiology that examined the association between infant feeding and the subsequent development of adipose tissue are based on BMI or a BMI-based classification of obesity, because the large sample size necessary to demonstrate these relatively small effect sizes makes it difficult to use more direct measures of adiposity. Some studies, however, have used such methods and will be highlighted in this review. Because the risk for negative health outcomes associated with adipose tissue, at least in adults, is not linear, but rather increases rapidly above a threshold close to the definition of obesity [9], a dichotomous outcome of obese vs. non-obese is generally considered as more clinically relevant and preferred as opposed to a continuous measurement of adiposity.

**Breastfeeding and Later Obesity**

Many observational studies have tested the hypothesis that breastfed infants are at lower risk to become obese than are formula-fed infants. While some early studies were inconsistent [10], most recent studies have consistently shown a negative association between breastfeeding or breastfeeding duration and the risk for later obesity. In one of the most convincing studies, Gillman et al. [11] demonstrated a ‘dose-response’ effect, in that the longer the children were breastfed, the lower the risk for obesity in adolescence. Interestingly, in a study of more than 4,000 British children aged 9–10 years, Toschke et al. [12] showed no significant association between the duration of breastfeeding and the risk for overweight or obesity as defined using BMI after adjustment for important confounding factors. However, in this same study, they demonstrated a lower risk for having fat mass above the 90th percentile, as measured by DXA, among the children who were breastfed longer.
These results suggest that breastfeeding may be protective against excessive adipose tissue accumulation, even without association with weight status measured by BMI. In a meta-analysis of 28 observational studies published before 2005, Owen et al. [4] found a combined decreased risk for obesity of 13% (95% CI: 11–15%) in formerly breastfed versus formula-fed children and adults, but also described evidence for a publication bias, i.e. a higher chance of positive vs. inconclusive studies to be published.

As consistent as these observational studies might be and as careful as the researchers can be to adjust for confounding factors associated with breastfeeding and obesity later in life, the major limitation of these observational studies is the possibility of unmeasured or unknown confounding factors. In fact, it is difficult to imagine that, even at the same level of education and income, a mother who chooses to breastfeed is not different from a mother who does not choose to breastfeed in her health behaviors and the health behavior of her children in ways that affect the risk for obesity through mechanisms other than breastfeeding. In order to address this inherent limitation of observational studies, Nelson et al. [13] studied pairs of siblings discordant in their breastfeeding history and showed that after taking into account the sibling status, the association between breastfeeding and obesity demonstrated without taking this family relationship into account was no longer present. Another sibling study, however, confirmed an association between breastfeeding and obesity, after taking sibling status into consideration [14].

The best way to demonstrate a causal protective effect of breastfeeding on obesity would be a randomized trial of breastfeeding versus formula feeding. This would not only be difficult to conduct, but unethical, considering all the known benefits of breastfeeding unrelated to obesity. However, it is ethical and feasible to randomize hospitals to optimal vs. usual breastfeeding promotion and support, so that the difference in breastfeeding rate and related outcomes are not linked to confounding factors but due to the randomization to the intervention in ways that strongly suggest causality. Using such a design, Kramer et al. [15] did not show a protective effect of breastfeeding on BMI status at age 6 years, suggesting that the association described in observational studies might be due to unmeasured or unknown confounding factors rather than a true causal effect. However, it is possible that a protective effect of breastfeeding only manifests at a later age or that a more direct measurement of adiposity would provide different results.

**Infancy Growth Rate and Later Obesity**

Several studies published in the 1970s suggest that a more rapid rate of weight gain in infancy could be associated with a higher risk for obesity later in life, perhaps through a ‘programming’ or ‘imprinting’ effect [16, 17]. In a large US cohort study, we demonstrated a positive association between the
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rate of weight gain in the first 4 months of life and obesity at age 7 years, regardless of birthweight [18]. These findings were confirmed in a subsample followed up to young adulthood where rapid weight gain in the first 4 months of life (change in weight for age of 1 standard deviation or more) was associated with obesity, defined using BMI, as well as overweight and over-fat status, defined using a combination of BMI with skinfold thickness measurements [19]. In that study, the population attributable risk for rapid infancy weight gain was estimated at about 30% for obesity 20 years later. Using DXA, Cameron et al. [20] confirmed an association of rapid infancy weight gain with adiposity at age 9 years. Similar results were reported by Ong et al. [21] in 10-year-old girls also using DXA to measure adiposity. In a meta-analysis based on subject level data from 9 studies, Druet et al. [22] reported a combined 93% increased risk for childhood obesity and a combined 22% increased risk for adult obesity for each one standard deviation increase in weight-for-age in the first year of life.

As for the association of breastfeeding with later obesity, the association of rapid infancy weight gain with later obesity in observational studies could be explained by unmeasured or unknown confounding factors. To address this limitation and better adjust for family-level confounding factors, we analyzed data from siblings discordant in their infancy weight gain, and found evidence that the association of rapid infancy weight gain with obesity at age 7 years is not due to family level confounding factors [23].

As part of a series of experimental studies of cardiovascular risk factors in children who were born premature and fed different types of infant formula for the first few weeks of life, Singhal et al. [24] showed that the subjects assigned to a formula that led to an improved weight gain during these first few weeks of life showed signs of leptin resistance, an endocrine condition associated with obesity but not with a significantly increased weight status. In another experimental study of subjects born at full term and randomly assigned to a formula with lower or higher protein concentration, Koletzko et al. [25] showed an increased weight gain in the first year of life that was followed by an increased BMI at age 2 years. Taken together, these studies suggest that there might be a causal link between rapid infancy weight gain and later obesity and could lead to new approaches to obesity prevention during short critical periods of life.

Weaning Practices and Later Obesity

The American Academy of Pediatrics recommends feeding exclusively breast milk, or formula for non-breastfed infants, for a minimum of 4, but preferably 6 months [26]. However, the practice of introducing other foods, especially cereals, before 6 and even 3 months is frequent in the US [27], and has been hypothesized to contribute to excessive infancy weight gain and subsequent development of excessive adipose tissue. A recent study of
42-year-old adults showed a decreased risk for overweight or obesity by 10% (95% CI: 2–19%) for each younger month of age at introduction of vegetables, by 7% (95% CI: 0–13%) for meat, and by 8% (95% CI: 2–14%) for firm foods [28]. No statistically significant associations were observed for age at introduction of spoon-feeding or eggs. Burdette et al. [29], however, did not show a statistically significant association between adhering to the American Academy of Pediatrics guidelines on age at introduction of complementary foods and high levels of adiposity measured by DXA in 5-year-old children.

**Conclusions and Research Needs**

Breastfeeding is associated with a lower risk for obesity later in life in many observational studies, but not in the only published randomized study. Rapid infancy weight gain is associated with subsequent obesity in many observational studies, but the limited experimental studies are inconsistent. Evidence for an association of timing of introduction of complementary feeding with later obesity is inconclusive.

Based on this brief review, the following research areas can be identified. Although there is no need for additional observational studies of the association between breastfeeding or rapid infancy weight gain with later obesity, experimental studies for these two exposures with long-term follow-up are critical and should be research priorities. Additional observational studies, meta-analyses, and experimental studies investigating early introduction of complementary food as a risk factor for subsequent development of adipose tissue are necessary. Although measures of obesity based on BMI are adequate, due to some contradictory results, more direct measurements of adiposity are useful when possible in the research setting. The study of the association of infant feeding practices with the subsequent development of adipose tissue may lead to novel approaches to obesity prevention targeting short critical periods with long-term benefits.

**References**

Discussion

Dr. Siega-Riz: I have an observation from one of the studies that we're about ready to publish. That study actually showed that children fed lower nutrient formula ended up having a lower likelihood of developing obesity later in life. It struck me that in fact the breastfed babies lose weight in the first week of life. That's a very normal and natural thing for them to do. So, in fact that's sort of mimicking what is happening, and I think what you are saying is fetal program is contributing to something, but there must be some programming going on in that first week of life that is very critical.

Dr. Stettler: Yes, that was the point of that study that was presented at the Obesity Society Meeting, where they showed a very clear weight loss on the modified formula in the first week of life. They had a control group (obviously not randomized) of breastfed infants who also lost weight. The infants on regular infant formula hardly lost any weight. Those on the experimental formula mimicked more closely what breastfed infants did.

When we first found in an observational study the importance of the first weeks of life [1], I initially doubted that it would be reproduced and that it might have been a chance finding. But now I think there is something going on, and we need to think about it. This is the period when for the first time, human beings have to regulate how much they are eating. This is really the time when they are learning what hunger is, what the cues are, what is happening when they eat (they are less hungry), how much they need to eat, and so forth. It's also a time, as you know, when there is a lot of the wiring in the brain that is happening, so if you think in these terms, it would make sense that the learning experience in this very early stage could have a long-term impact. It has actually been demonstrated in animal models where they could look at the brain and the influence of feeding in this very short period of time [2]. So, I think that that could be a really interesting new approach.

What I didn't mention is that obviously these data have to be seen in the context of risks and benefits. For breastfeeding promotion, there is really very little risk associated with it, and there are a lot of other benefits, so in terms of clinical practice or public health it's easy to recommend breastfeeding, even if the evidence for obesity prevention is not very strong. When it comes to restricting weight gain in infants, it's a different question. There is a lot of evidence that decreasing rate of weight gain can be associated with negative effect on infection, on the brain, and on statural growth. So obviously, those findings are not directly translatable to clinical practice or to public health, but they are interesting when we try to think about programming and early prevention.

Dr. Siega-Riz: In our study, we followed pregnant women all the way through the first year of postpartum, and then we followed the kids up to 3 years of age – very similar to Matt Gillman study. In our population in which 60% of the women are breast-feeding, the thing that seems to be associated with increased waist status at age 3 is introduction of complementary foods before 4 months of age.

Dr. Simmer: In your presentation, you didn't mention air displacement plethysmography or even ultrasound.

Dr. Stettler: I was limited with time and just wanted to show the methods that were included in the studies that I presented. There are several other ways to measure body composition; air displacement plethysmography is one of them; it uses the same principle as underwater weighting, and has similar disadvantages, in that it requires the collaboration of the subject in terms of breathing. Our experience with this method in children and infants is not very good. So that's one another reason why I haven't presented it. The other way that is really popular, but I also don't think is very good, is bioimpedance. It measures how much electricity goes through the body and, based on
that, derives the percent body fat. These two methods are actually OK to show correlations between methods in percent body fat, but when you look at the individual between-method differences, they are pretty large.

**Dr. Harding:** I am glad you raised the issue of risk-benefit because I think we do have to be worried about what we are preventing here. If we go back to the work of Lucas and Singhal, preterm babies randomized to increased nutrition grew faster and had better developmental outcomes [3]. However, cardiovascular risk and obesity were related to weight gain [4], which raises the question of causality. Rapid postnatal weight gain may reflect recovery from a prenatal restriction, and in animal studies it is the prenatal restriction that results in the long-term disease risk, independently of postnatal weight gain. So, are there any human studies where people have looked carefully and sequentially at prenatal growth? You would need to do repeated ultrasound measurements of growth, and then relate that to postnatal growth and to the long-term outcomes.

**Dr. Stettler:** Those are all good points, and I think the one thing that I can add to your comment is that unlike in animals, infants who are born with intrauterine growth retardation are not at higher risk of obesity. They are at higher risk for cardiovascular disease but clearly not obesity, which is not the case in rats. If you restrict fetal growth in rats, they will catch up, and then they will become obese and diabetic. The question whether the rapid weight gain is related to intrauterine growth retardation is the one we try to address when we stratify children by birthweight, and we still see an association between weight gain and obesity in each of the 5 birthweight categories.

**Dr. Harding:** I think we do then run into the problem of birthweight versus fetal growth, and again it doesn’t really address the question of causality.

**Dr. Öhlund:** I have a question regarding obese women. Obese women can breastfeed less well than normal-weight women. How do you think that affects the children?

**Dr. Stettler:** One of the strongest predictors of childhood obesity that I didn’t talk about is maternal obesity, and many things could explain this association. Obese women are more likely to have diabetes during pregnancy, which is a strong risk factor. They are more likely to have bigger babies at birth, which has also been shown to be a risk factor. They are less likely to breastfeed, which could also be a risk factor. And obviously, the genes are transmitted and the environment is common. So there are a lot of reasons for the association between obesity in the mother and obesity in the child. The question is what are the intervention implications? One of the things that are most exciting is to address weight gain during pregnancy, which is strongly associated with obesity in the offspring. When they become pregnant, many women want to try to do everything right for their baby, so it may be a good opportunity, a good timing, for a preventive intervention for themselves and for the baby.

**Dr. Klish:** Just a couple of comments about both growth and the measurement of adiposity. In the first week of life, weight loss is usually due to a loss of total body water, but this can happen simultaneously with an increasing lean body mass. So, measurements in that first week depend on how growth is being assessed. I also have a concern about DXA becoming the gold standard of adiposity. When we studied all these methods in the 1980s, the standard error of the estimate for DXA was somewhere in the range of 2 kg of fat. At a young age, the standard error for BMI is about the same. BMI very poorly correlates between adiposity and lean body mass in the normal range, but it correlates better above a score of 30. I think the same thing is true of DXA. You probably pointed out why when you showed the halo effect of DXA. We know from the few studies of total body analysis of the human body that only about half of the adipose tissue in an adult human is in the subcutaneous space. The rest is deep within the body, as marbling of muscle, perinephric fat, omental fat,
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things of that nature. So, we have to always be very careful as to how we interpret DXA.

Dr. Stettler: I agree, DXA has its limitations, I think it’s becoming the gold standard for practical reasons because there is really no better practical alternative. The funny thing about DXA is that reports give a very precise number for fat mass, at the 10th of a gram level, so many people think that DXA is precise to the 10th of the gram. This is really misleading, and one has to remember not to take into account those last digits, because the method is not that precise. Also, I am not too concerned when people use BMI, especially if they are using it as a dichotomous variable, because the vast majority of kids who are above the 95th percentile for BMI really are obese, they have too much fat around.

Dr. Chittal: If we have weight loss in full-term babies, acceptable weight loss, why are we so keen on feeding preterm IUGR babies very aggressively in the first week, aren’t we programming for a future obesity by doing so?

Dr. Stettler: It’s a good question. The situation is very different between full-term infants, preterm infants and infants with intrauterine growth retardation. For most preemies, we are not able to even keep them on their growth curves, they all lose weight or gain insufficient weight. So, I don’t think overfeeding them is a concern; it’s really trying to keep them at the expected level of weight gain, and this has been shown to be associated with neurodevelopmental benefit. It’s a question of priority, do you want to have a preterm baby who has a better neurocognitive development and maybe has an increased risk of obesity, or the opposite? But I am not even sure about the risk of obesity in these situations, because excessive weight gain is not an option, we are just trying to get them to grow at a healthy rate. It is really when the baby is in the excess weight gain range that we are concerned about obesity, not in the normal weight gain or in the low weight gain range.

Dr. Lack: I wondered whether there are any data relating to protein intake, on the quality of protein, vegetable versus animal and, say, soy feeds versus cow’s milk-based feeds, and in older children vegetarian versus normal diets.

Dr. Stettler: I am sure there are. I really don’t know much about that topic. Berthold Koletzko in Germany looked at protein in detail, I think; infant formula manufacturers have also looked at that.

Dr. Klassen: We actually have performed some studies where we could show results going in the same direction as Berthold Koletzko’s study.

Dr. Stettler: He was asking about the quality of the protein, so is there a difference for example between soy protein and cow’s milk protein?

Dr. Klassen: To my knowledge, what has been studied is infant formula based on cow’s milk protein. A low-protein, high-quality infant formula at the lowest limit of current legislation (1.8 g per 100 kcal) can basically be achieved by using a whey-predominant formula since this will allow to supply sufficient amounts of the limiting amino acids. Randomized controlled studies have been performed demonstrating that these formulas result in appropriate growth of the child and also an appropriate amino acid profile. I am not aware of any data for soy, so for the early period of life it’s only cow’s milk protein I am afraid.

Dr. Van Goudoever: I have a remark and a question. The goal for premature infants from a feeding perspective is not to let them drop through the standard curves basically. So it’s not too much about weight gain, it’s more about preventing weight loss, severe weight loss. My question is related to the measurement of fat on ultrasound because in my opinion it’s not only the total amount of fat mass but also the position where it is. What are your ideas about using ultrasound to measure peritoneal fat?

Dr. Stettler: This would be really wonderful, I haven’t seen good reference data, and I think that’s the limitation. You may be aware that this is happening now, and
this would be a great alternative. Intra-abdominal fat so far has been measured with CT scan and MRI that have made it difficult. We need data on ultrasounds and good reference in kids, which is actually really difficult to have now considering that most countries have an obesity problem, but if there is a good reference database, that may be a good way to address it.

Dr. Haschke: Dr. Yajnik has published MRI data from India and UK on distribution of visceral fat versus subcutaneous fat of newborns. Indian newborns have lower birth-weight but already more visceral fat.

Dr. Stettler: This is where ultrasound is going to be very helpful. What I said about intrauterine growth retardation in human not being at risk for obesity is true, but it is a risk for those who do become obese to have a more central fat distribution. This is where the metabolic aspects are becoming more important.

References
