Early Nutrition as a Major Determinant of ‘Immune Health’: Implications for Allergy, Obesity and Other Noncommunicable Diseases

Susan L. Prescott

Early-life nutritional exposures are significant determinants of the development and future health of all organ systems. Modern humans show many hallmarks of animals living in captivity, prone to obesity and inflammation. The low-grade inflammation that characterizes virtually all noncommunicable diseases suggests a central role of the immune system in the risk and pathogenesis of these conditions. Indeed, there is increasing evidence that our propensity for inflammation in adulthood [higher baseline C-reactive protein (CRP)] is determined by early-life conditions, including nutrition, poverty, breastfeeding, pollutants and more hygienic environmental conditions. This increases the risk of heart disease, diabetes and all-cause mortality. This appears to be the result of a complex interplay between immune and metabolic pathways through adipokines [such as leptin – a member of the interleukin (IL)-6 family] which, in addition to effects on appetite and energy homeostasis, also promote inflammation through innate and T-cell activation. In particular, the dramatic rise in infant immune diseases, most notably allergy, indicates the specific vulnerability of the immune system to early environmental changes.

Dietary changes are also at the center of the emerging epigenetic paradigms that underpin the rise in many modern inflammatory and metabolic diseases. There is growing evidence that exposures in pregnancy and the early postnatal period can modify gene expression and disease susceptibility. Although modern dietary changes are complex and involve changing patterns of many nutrients, there is also interest in the developmental effects of specific nutrients. Oligosaccharides (soluble fiber), antioxidants, polyunsaturated fatty acids, folate and other vitamins have documented effects on immune function as well as metabolism. Some have also been implicated in modified risk of both
obesity and allergic disease in observational studies. Intervention studies are largely limited to trials with polyunsaturated fatty acids and oligosaccharides, showing preliminary but yet unconfirmed benefits in disease prevention.

As well as progressively ‘cleaner’ environments, nutritional changes may also be influencing gut biodiversity. The high-fat, low-fiber ‘western’ diet also adversely changes the gut microbiome, with recognized implications for immune development and increased risk of allergic disease. There are also associated effects on gut barrier function, increasing systemic antigenic load and low-grade endotoxemia – as driving factors for insulin resistance, obesity and diabetes. This is associated with increased CRP and higher levels of circulating IL-1, tumor necrosis factor, IL-6 and adiponectin as evidenced by increased low-grade systemic inflammation. This provides new perspectives on how modern dietary patterns may be increasing the risk of both immune and metabolic diseases. This is a major factor contributing to the more proinflammatory conditions of the modern lifestyle. These effects begin in uterine life and may offer important opportunities for noninvasive prevention strategies using nutritional measures.

Understanding how environmental influences disrupt the finely balanced development of immune and metabolic programming is of critical importance. Diet-sensitive pathways are likely to be crucial in these processes. While epigenetic mechanisms provide a strong explanation of how nutritional exposures can affect the fetal gene expression and subsequent disease risk, other diet-induced tissue compositional changes may also contribute directly to altered immune and metabolic function – including diet-induced changes in the microbiome. A better understanding of nutritional programming of immune health, nutritional epigenetics and the biological processes sensitive to nutritional exposures in early life may lead to dietary strategies that provide more tolerogenic conditions during early immune programming, and reduce the burden of many inflammatory diseases – not just allergy.

**Suggested Reading**


The Future of Infant and Young Children’s Food: Food Supply, Manufacturing and Human Health Challenges in the 21st Century

Carina Venter and Kate Maslin

Infant food and weaning practices are highly debated with lots of unanswered questions. Sales of commercial infant foods are increasing and one can question their effect on long-term health, particularly for allergic disease.

There are certain issues with eating more commercially available foods, such as a reduced microbial load and nutritional content of these foods. It is interesting to note that sales of commercial baby food mirror the increase in hospital admissions due to food anaphylaxis in the UK. This picture is not as simple when looking at the prevalence of all allergic diseases, as a steady rise have not been seen in developed countries in the past few years. However, it may be worth to take these possible concerns into account.

Infant foods and the weaning diet (also referred to as introduction of solid foods) have been at the forefront of dialogues in the scientific world and media over the past few decades. Answers to questions such as the most appropriate age of introduction of solids or allergenic foods, should breastfeeding continue alongside solid food introduction, what are the crucial times for introduction of different textures, and should organic or nonorganic foods be used have been sought.

Central to all of these points is the use of homemade versus commercially available infant foods. The UK has seen an increase in baby food sales from GBP 303 million in 1995 to GBP 872 million in 2013 [1]. This is reflected in particular by the increase in sales of organic baby food. Worryingly, an increase in consumption of commercial infant foods indicates lower rates of consumption for home-cooked foods and may even affect the diversity of foods introduced during the weaning period. A recent study indicated that commercial infant food in the UK is inferior to home-cooked food in terms of nutrient content [2].
Such a striking change in food intake in early life leads experts to question whether this may have possible health effects, particularly the development of allergic disease. It is thought that gut microbiota have an effect on the development of allergic disease and that certain foods and nutrients may also play a role in the prevention of allergic disease, e.g. fish/fish oil, vitamins A, E, C and D, selenium and zinc. Recent studies also indicate that a home-prepared [3] and diverse diet leads to less allergic disease [3–5].

In the future, the introduction of food to infants will have to focus on:
(1) Parental cooking skills to provide, freshly cooked, homemade food
(2) The possible bacterial content of commercial (sterilized vs. pasteurized) versus homemade foods
(3) The particular nutrient content of commercial baby foods and diversity of the infant diet.

This will have to be provided with the backdrop of current dwindling world resources, focusing specifically on the availability and sustainable production of fish and meat, better food distribution and less food waste at home.

**References**


Food allergy is a common disease [1]. In recent years, recommendations for the prevention of food allergy have been shifted from avoidance strategies to active oral tolerance induction. Due to evidence from observational studies, it has been suggested that sensitization occurs via the skin especially in children with atopic dermatitis due to skin barrier defects, whereas early oral introduction of the allergenic food(s) will promote tolerance [2]. The current evidence does not justify recommendations about either withholding or encouraging exposure to potentially allergenic food(s) after 4 months once weaning has commenced, irrespective of atopic heredity [3]. However, intervention studies are currently conducted to prove this hypothesis generated by observational studies.

References

Food allergy is defined as an aberrant immunologic response towards an ingested food [1]. It can be mediated via IgE and non-IgE mechanisms. The prevalence of food allergy has increased worldwide, initially in the highly developed societies with the so-called western life style (USA, UK, Canada, Australia and Western Europe), followed by Asia and Latin America [2]. With an estimated prevalence of 8% in US children, food allergy has become a serious public health problem. Currently, there is no cure for food allergy; dietary avoidance and management of accidental reactions remain the cornerstone of therapy [1].

Food allergy is thought to result from failure to develop or a breach in oral tolerance. Oral tolerance is defined as a state of selective systemic unresponsiveness to the ingested food antigens [3]. It is mediated by the gut-associated lymphoid tissue and is thought to depend on the generation antigen-specific T-regulatory cells (Tregs). In some models, T-cell anergy and deletion is also associated with oral tolerance. Dietary factors (vitamins A and D) and microbial factors (Clostridium spp. and Bacteroides fragilis polysaccharide A) promote the generation of induced Tregs. In contrast, bacterial adjuvants such as Staphylococcus aureus enterotoxin B and exposure to food allergens via an impaired skin barrier, e.g. in atopic dermatitis or filaggrin gene mutations, promote allergic sensitization.

Therapies for food allergy aim at restoring oral tolerance [4]. At this time, there is no conclusive evidence that permanent oral tolerance can be induced. The most advanced diverse strategies for food immunotherapy are presented in figure 1; here, we focus on the strategies for the treatment of IgE-mediated food allergy involving food proteins administered via oral (OIT), sublingual (SLIT) or epicutaneous immunotherapy (EPIT), i.e. via skin patch, hypoallergenic formulas and pre-/probiotics.

Extensively heated (baked) milk and egg diets have been already adopted into clinical practice and benefit the majority of milk- and
egg-allergic children by accelerating development of tolerance to unheated milk/egg [5].

OIT utilizes the pathways underlying oral tolerance. The aim of food allergy therapy is to first achieve desensitization and then to reestablish permanent oral tolerance. Desensitization is a state of temporary antigen hyporesponsiveness that depends on the regular ingestion of the food. The immunologic mechanism of desensitization is not known, but it is associated with decreased reactivity of mast cells (measured with skin prick test reactivity) and basophils, increased food-specific serum and salivary IgG4 and IgA antibodies, and initially increased but eventually decreased serum food-specific IgE antibodies. Similarly, the mechanism of permanent tolerance is not known, but it presumably involves generation of Tregs followed by anergy and/or deletion of effector T cells. To date, no development of permanent tolerance (or even long-term desensitization) due to OIT as opposed to natural acquisition has been conclusively demonstrated. Milk OIT is more efficacious for desensitization than SLIT alone, but was associated with more systemic side effects. Large clinical trials are currently underway for peanut and milk allergy EPIT. EPIT is applied by the patient at home, rotating the application site, and is generally better tolerated and more convenient than OIT.

OIT, SLIT and EPIT with native foods remain in the sphere of clinical research with encouraging data suggesting that they may induce desensitization in a large proportion of treated subjects and potentially

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**Fig. 1.** Diverse approaches to food allergy therapy tested in clinical trials. Reprinted with permission from Albin and Nowak-Węgrzyn [6].

![Diagram showing diverse approaches to food allergy therapy tested in clinical trials.](image-url)
permanent tolerance following an adequately long period of treatment. Synbiotics appear to have the most beneficial role in the prevention of food allergy; *Lactobacillus rhamnosus* GG may promote the development of tolerance to milk in allergic infants.

**References**

Interrupting Intergenerational Cycles of Maternal Obesity

Matthew W. Gillman

Factors operating in the preconception and prenatal periods, such as maternal obesity, excessive gestational weight gain and gestational diabetes, predict a substantial fraction of childhood obesity as well as lifelong adverse health consequences in the mother. These periods may lend themselves to successful intervention to reduce such risk factors because

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**Fig. 1.** Intergenerational vicious cycles of maternal obesity. CVD = Cardiovascular diseases; GWG = gestational weight gain; GDM = gestational diabetes mellitus.
parents may be especially willing to change behavior if it confers health advantages to their children. If effective interventions started before or during pregnancy can be maintained after birth, they have the potential to lower the risk of both maternal obesity in the next pregnancy and obesity in the growing child, thus helping to interrupt maternal and child inter-generational vicious cycles of obesity, diabetes and related cardiometabolic health consequences (fig. 1). While this paradigm is appealing, challenges include determining the magnitude, causality and modifiability of these risk factors, and quantifying any adverse consequences of intervention.
Patterns of health, illness and disease are influenced at different stages of the life course by a combination of genetic, epigenetic and environmental factors. Substantial research has demonstrated that during early development, responses to a range of stimuli are likely to ‘program’ the risk of metabolic and other noncommunicable disorders (NCDs), as articulated by the ‘developmental origins of health and disease’ or ‘DOHaD’ concept. Subsequent environmental exposures during infancy, childhood and adult life may modify or condition this later risk of disease. In middle and later life, social, psychological, physical and occupational factors in the environment can accentuate the risk of ill health and disease.

Although it has been proposed that the associations between fetal or infant growth and later adult disease represent the pleiotropic effects of genes transmitted from mother to child, maternally mediated environmental modulation of gene expression in offspring and gene-environment interactions appear to be more important than purely heritable genetic risks. There is also growing evidence that epigenetic mechanisms (DNA methylation, histone modification and noncoding RNAs) are responsible for tissue-specific gene expression during growth and development, and that these mechanisms underlie the processes of developmental plasticity. We have shown that epigenetic gene promoter methylation at birth is associated with the child’s later adiposity and measures of bone health [1, 2] and that peroxisomal proliferator-activated receptor-γ coactivator-1α promoter methylation in blood at 5–7 years of age is stable across childhood and associated with adiposity from 9 to 14 years [3]. Our recent studies have shown that genetic differences alone best explain 25% of the neonatal methylome variation, with the remaining 75% explained by the interaction of genetic differences with the prenatal environment [4].

Figure 1 shows the conceptual framework for ongoing research. The risk of NCDs increases across the life course as a result of declining plasticity and accumulative effects of inadequate responses to new challenges (triangles). The greatest increase occurs in adult life, but the
trajectory is set much earlier, being influenced by factors such as the mother’s diet and body composition before and during pregnancy, and fetal, infant and childhood nutrition. In early life, timely interventions can have a large effect on disease risk later (middle right: Early – arrow), while later intervention can remain impactful for vulnerable groups (top right: Late – arrow). Intervention in childhood and adolescence increases the biological capital and may have an important impact on the next generation.

Experimental evidence is accruing that endocrine or nutritional interventions during early postnatal life can reverse epigenetic and phenotypic changes induced, for example, by an unbalanced maternal diet during pregnancy. Elucidation of these epigenetic processes may permit perinatal identification of individuals at risk of later NCDs and facilitate a new generation of early intervention strategies to reduce such risk.

References


Endocrine and Metabolic Biomarkers Predicting Early Childhood Obesity Risk

Piotr Socha, Christian Hellmuth, Dariusz Gruszfeld, Hans Demmelmaier, Peter Rzehak, Veit Grote, Martina Weber, Joaquin Escribano, Ricardo Closa-Monasterolo, Elena Dain, Jean-Paul Langhendries, Enrica Riva, Elvira Verduci and Berthold Koletzko for the European Childhood Obesity Trial Study Group

There is an increasing body of evidence that genome and metabolic regulation can be modified by prenatal or early postnatal external factors, such as nutritional environment. Maternal diet and nutritional status during pregnancy, as well as the early diet of the offspring during suckling, weaning and early childhood, play an important role in later health. The benefit of breastfeeding with regard to decreasing disease risk in later life was documented in numerous studies, and obesity and its complications also seem to be prevented by breastfeeding [1]. There are a number of observational trials which have shown the protective effect of breastfeeding on obesity risk [2]. There are several factors which could be involved in the so-called programming effect of obesity risk in infancy – high protein intake with formula feeding is claimed to play the major role. The high-protein programming hypothesis was tested in the EU Childhood Obesity Project (CHOP) [3], where infants randomized to formula with a higher protein concentration for the 1st year (which promoted faster weight and length gain) had greater BMI at 2 years compared to infants fed a low-protein formula and breastfed. Data from the follow-up at 6 years of age confirmed the programming effect of nutritional intervention in the 1st year of life [4]. The most sensitive window for a programming effect is still uncertain and usually is expected within the first weeks of life [5]; in addition, weight gain in infancy and after the 2nd year of life has been demonstrated to have an impact on later obesity [6]. Systematic reviews support the hypothesis that faster weight gain in infancy increases the long-term risk of obesity [6]. A similar association with infant growth can be demonstrated for blood pressure, as reviewed by Ben-Shlomo et al. [7], and for insulin resistance.
Several endocrine markers were studied to explain early dietary influence on later obesity risk. As insulin, leptin and adiponectin have already been proven to be related to obesity and metabolic syndrome, these endocrine markers were extensively studied both in animal models as well as in infants and pregnant women.

We investigated the metabolic mechanisms of obesity programming within CHOP, for which we collected blood and urine samples from infants at the age of 6 months. Our results indicated clearly that the protein content of infant formulae modulates the IGF axis and insulin release, which is associated with a higher BMI at the age of 2 years. A formula reduced in protein content, which is more similar to the protein content of human milk, supports an endocrine and metabolic profile of formula-fed infants that is closer to the response of breastfed infants [8]. Our hypothesis was built on earlier observations that diet and mainly protein intake modulate blood concentrations of insulin-like growth factor (IGF)-1 [9]. The IGF axis was shown to regulate early growth, adipose tissue differentiation and early adipogenesis in animals and humans [10–12]. IGF-1 has a strong structural homology to insulin, which is also reflected by the binding motifs of IGF-binding proteins (IGFBPs). Amino acids, in particular the branched-chained amino acids, were proven to stimulate insulin secretion [13].

We were able to combine these earlier findings of the insulin and IGF-1 relationship to protein intake with our CHOP results to formulate the role of endocrine response in metabolic programming of obesity. We found increased plasma levels of essential amino acids, especially branched-chain amino acids, in infants fed a high-protein diet, which was accompanied by increased concentrations of total and free IGF-1, whereas IGFBP-2 was decreased and IGFBP-3 was unaffected by the protein intake. Urinary C-peptide levels representing endogenous insulin secretion were increased, and serum glucose levels were lowered. Breastfed children had generally lower plasma amino acid levels, a less active IGF-1 axis and lower insulin production than formula-fed children. Thus, lowering protein intake with infant formula resulted in a more similar metabolic and endocrine response in formula-fed as compared to breastfed infants, and finally a lower BMI at the age of 2 years. Within CHOP, we also showed the influence of a high-protein diet on kidney size and performed additional statistical analysis to assess the influence of IGF-1 concentrations. Linear regression analyses showed a significant effect of free IGF-1 on kidney volume in models, including significant effects of a high-protein formula and anthropometry. We concluded that IGF-1 partly mediates protein-induced kidney growth in healthy infants. IGF-1 could be involved in a pathway for the programming of the renal system [14].
We also analyzed genetic regulation of IGF-1 secretion and were able to prove that variants of the IGF-1 gene play an important role in regulating serum levels of the IGF-1 axis, but there was no gene-protein interaction. The predominant nutritional regulation of IGF-1 and IGFBP-3 provided further evidence that higher protein intake contributes to metabolic programming of growth [15].

We have also tracked the endocrine markers in our cohort and will be able to provide information on changes in IGF-1 in relation to anthropometric parameters with advancing age. An interesting study was conducted in Belarus, where an intervention study succeeded in improving the duration and exclusivity of breastfeeding, which did not prevent overweight or obesity, nor did it affect IGF-1 levels at 11.5 years of age [16]. However, they did study IGF-1 in infancy.

Leptin was also investigated in infants whose obesity was assessed in later life. Savino et al. [17] found that breastfed infants had significantly higher serum leptin levels than formula-fed ones, and children who were formula fed in infancy had a significantly higher BMI at follow-up than those who were breastfed. Still, as this is an observational trial, it is difficult to make conclusions and to explain this finding mechanistically. Volberg et al. [18] published an interesting paper showing leptin and adiponectin trajectories from birth to 9 years of age. Leptin was positively related to child body size at all ages, but adiponectin had inverse and weaker associations with BMI at 2, 5 and 9 years. The authors concluded that there are developmental differences in leptin and adiponectin over the childhood period. Leptin closely reflects child body size; however, factors affecting adiponectin and long-term consequences of its changes over infancy need to be further explored. Interestingly, leptin during pregnancy can also significantly affect birth weight. This effect was shown by Misra et al. [19] only in overweight/obese women in whom an increase in the rate of change in maternal serum leptin in the second half of pregnancy was significantly associated with a decrease in infant birth weight adjusted for gestational age at delivery. They found that this effect was distinct from that of maternal weight.

References


The infant's metabolic response adapts to environmental and particularly dietary exposure and appears to affect growth, body composition and later disease risks [1]. Compared to feeding conventional infant formula, breastfeeding was shown to induce different metabolic and endocrine responses, and it has been associated with differences in growth, body composition and disease risk throughout childhood and in adult life. Breastfed children show a lower prevalence of overweight and obesity at school age. The underlying programming mechanisms remain to be explored. Recent publications point to epigenetic modifications of genes affecting different proteins and hormones, like leptin, insulin-like growth factor (IGF)-1 and insulin.

Whatever the primary mechanism, changes will be induced in the metabolome of people fed different diets in infancy, since metabolites (molecules <1,500 Da) are the downstream products of both genetic and epigenetic determinants as well as environmental factors, including diet. Metabolomics is able to enhance the understanding of metabolic regulation in response to environmental influences. The 'programming effects' of infant formula with different contents of protein are reflected in the metabolome and in metabolic pathways. Martin et al. [2] found formula-fed babies to differ from breastfed infants in markers of protein processing and of lipid and energy metabolism.

In a large, double-blind, randomized, clinical trial, we studied the effect of infant and follow-on formula with conventionally high or reduced protein contents on infant metabolism. In this trial, the high-protein formula led to higher BMI than low-protein formula at 2 years of age and at school age [3]. At the age of 6 months, children with higher protein intake, compared to those randomized to reduced protein intake as well as to a reference group of breastfed infants, showed significantly increased plasma concentrations of nondispensable amino acids, including the
Fig. 1. The relation between BCAA (a Ile, b Leu and c Val) and their corresponding short-chain acylcarnitine indicates a concentration-dependent saturation of BCAA catabolism in infants. Modified from Kirchberg et al. [4].
branched-chain amino acids (BCAA) Ile, Leu and Val, as well as increased levels of the oxidation products of BCAA, short-chain acylcarnitines [4]. Regression models revealed that with increasing BCAA levels, short-chain acylcarnitines only increased until a break point was reached (fig. 1).

After this point, the corresponding acylcarnitines did not longer increase with increasing BCAA concentration. Thus, BCAA seemed to escape their degradation after reaching a certain plasma BCAA level, which indicates a saturation of BCAA catabolism in infants. This could potentially be of major biological importance in infants fed protein contents that exceed the catabolic capacity for BCAA, and where a markedly increased risk of adverse effects mediated through BCAA may result.

The elevation in BCAA in the study group fed conventional, protein-rich formula contributes to increased insulin levels, as we have shown previously [5], and it seems to affect β-oxidation of fatty acids. The ratios of long-chain acylcarnitines to free carnitine decreased in infants who received the high-protein formula, which indicates a lower initial step of the β-oxidation. Thus, high protein and BCAA intakes may inhibit fat oxidation and thereby enhance body fat deposition and the risk of adiposity.

Protein supply also affects the metabolism of other amino acids in infants. Aromatic amino acids, which are known to promote IGF-1 secretion, were also elevated in the plasma of infants fed conventional formula with higher protein contents, possibly due to a competitive cellular uptake mechanism with BCAA. Other metabolites that responded to a high protein supply to infants, such as several single species of nonesterified fatty acids, organic acids, acylcarnitines and phospholipids, have been previously reported as metabolomic markers for obesity risk. The underlying mechanisms and pathways require further exploration.

References

In some developed and emerging countries, more than 50% of young women are now overweight (BMI 25–30) or obese (BMI ≥30). If overweight/obese mothers are breastfeeding, gain weight of their infants is faster during the first 12 months than indicated by the 50th percentile of the WHO standards. Rapid weight gain during infancy is associated with higher risk of obesity during childhood and adult life. There is increasing evidence that maternal obesity can result in unfavorable (epigenetic) pre-and postnatal programming of important genes of the offspring. This can have lifelong consequences such as increased risk of noncommunicable diseases. It has also been speculated that rapid early weight gain is associated with changes in the microbiome and increased protein concentration in breast milk.

Many studies indicate that infants of obese- and nonobese mothers who were fed traditional (high-protein) formulas gain weight more rapidly than breastfed infants. Those formulas are still recommended by Codex Alimentarius. An updated meta-analysis (n = 1,150) now indicates that infants from 4 continents who are fed a whey-based low-protein formula (1.8 g/100 kcal) with an essential amino-acid profile close to breast milk grow as indicated by the WHO standard (0–4 months). One study in infants of mothers with BMI <25 (France) shows that continuation of the low-protein formula until 12 months results in anthropometric parameters which are similar to those of breastfed infants. A new experimental low-protein formula (1.61–1.65 g protein/100 kcal) for infants between 3 and 12 months was recently tested in 2 randomized clinical trials, and children were followed until 3 years. Growth and biomarkers were compared with infants who were fed formulas with higher protein concentrations and breastfed reference groups. One trial was in a general US population where growth of infants fed the low-protein formula was not inferior to
the WHO standards and the breastfed reference group. The percentage of infants who were above the 85th percentile of the WHO standards during the intervention period was lower (p < 0.015) in the group fed the low-protein formula than in the group fed the control formula with 2.15 g protein/100 kcal. The second trial (Chile) was in infants of mothers with BMI >25. Infants fed the low-protein formula gained less weight until 12 months (p = 0.015) and 36 months (p = 0.031) than infants fed the control formula with 2.7 g protein/100 kcal, but weight gain was similar to the breastfed reference group. In both trials, biomarkers of protein metabolism (IGF-1 and C-peptide) of the infants fed the low-protein formulas were closer to breastfed infants than the respective biomarkers of the infants fed the high-protein formulas.

Prevention measures of childhood and adult obesity should start during the first 1,000 days of life. Unfavorable fetal programming can be prevented by weight management/lifestyle change programs of young women before and during pregnancy. After birth, promotion of breastfeeding beyond 6 months is most important to prevent excessive weight gain during infancy. Our studies indicate that nonbreastfed infants fed a low-protein formula (1.8 g/100 kcal) until 12 months grow according to the WHO standard. Feeding a new experimental low-protein formula (1.61–1.65 g/100 kcal) between 3 and 12 months of age can help to slow rapid weight gain during infancy in at-risk infants, which might contribute to a reduced obesity risk in childhood and adult life.
Infant Feeding and Opportunities for Obesity Risk Reduction

Jose M. Saavedra

The epidemic of childhood obesity is now recognized to begin during the infant and toddler age. Infant adiposity or increased BMI, as early as 2 weeks through 24 months of age, has been associated with a significantly increased risk of overweight during toddler or preschool-age years. Children who were obese at 9 or 24 months were 3 times more likely to retain an unfavorable obese weight at 4 years compared to nonobese children assessed during their first 2 years of life. Although socioeconomic and racial disparities exist, young children are affected by early overweight and obesity worldwide.

Multiple dietary and parent feeding practices have been associated with weight status in children, even in children as young as infant age. These risk factors are associated with early childhood overweight, accelerated rate of weight gain during infancy, as well as increased weight for length, BMI or measures of adiposity during the first 24 months of life and through the toddler age. Review of these factors suggests the majority is potentially modifiable and could influence a child’s weight status at a very early age. These include diet-related factors such as too early introduction of complementary foods, high intake of sweetened beverages, low intake of fruit and vegetables and excessive protein intake. However, behavior and child rearing-modifiable factors appear to play a role that is as critical as the diet per se. These include breastfeeding, lack of responsive feeding practices by the caregiver (low attention to hunger and satiety cues, use of overly restrictive, controlling, rewarding or pressurized feeding), low total and nocturnal sleep, lack of family meals, TV/screen viewing time and decreased active play.

Breastfeeding duration and/or exclusivity have been inversely associated with the rate of weight gain, body weight, adiposity or risk of overweight in children. The mechanisms by which breastfeeding could decrease risk of overweight or obesity remain unclear. Increased protein or energy intake, or both have been documented as potential contributory factors. It is also plausible that breastfed infants develop a feeding style
that allows a stronger self-regulation of intake compared to when they are bottle-fed. The act of bottle-feeding per se may affect a caregiver’s recognition and interpretation of hunger and satiety cues. In addition, a vast array of flavors derived from foods, spices and beverages ingested by the mother may influence the infant’s subsequent preferences.

Analyses of data from the US Feeding Infants and Toddlers Study indicate that infants before 2 years of age develop dietary patterns far from ideal (high in energy, protein, sodium and saturated fat, and low in fiber and potassium), and also show that this pattern, including food group preferences and relative energy contribution of each food group, is practically set by 20–22 months of age. For example, by 18 months of age, and throughout the preschool years, only 7% of total caloric contribution was from fruit and only 5% from vegetables, mimicking the adult diet. Preferences for sweet and salty foods are inborn or easy to induce, while acceptance of bitter-tasting foods (e.g. some fruits and green vegetables) will need to be taught by parents and learned by children. Early taste exposure may have long-lasting effects, and some research suggests this exposure may start in utero and continue during breastfeeding by providing ‘early taste lessons,’ increasing the likelihood of later acceptance. A critical window for acceptance of flavors associated with healthy fruits and vegetables may be during weaning, when all solid foods are new and food ‘neophobia’ (the fear and avoidance of novel foods and flavors) is relatively weak. Parental understanding and management of this window of opportunity to shape dietary patterns may be a critical factor in dealing with the problem.

Parental feeding practices that appear to contribute to the prevalence of overweight in young children can be addressed during the first years of life. Parents and their parenting practices are integral in the process of helping young children accept new flavors and foods, and influential in how children learn to eat. Infants and young toddlers have an innate ability to regulate energy intake, yet individual differences in parents’ feeding practices have been linked to individual differences in children’s self-regulation of energy intake. It is appropriate for responsive feeding practices to begin at birth, as there are some indications that the unlearning of appetite regulation can begin shortly after birth as well-meaning parental feeding practices can override an infant’s inborn mechanism to control energy intake.

Responsive feeding practices can nurture or impede the development of appropriate energy self-regulation, and potentially shape a child’s food preference and ultimate food choices when they begin to make independent food decisions. Feeding environments consistent with responsive feeding include parental warmth, nurturing, acceptance, caring and empathy. Unresponsive parent feeding involves excessive control from the
parent with practices such as undue pressuring the child to finish a bottle or meal, overt excessive restriction of foods, too little control of the child’s eating (uninvolved feeding) or too much control by the child (indulgent feeding). Authoritarian, indulgent and uninvolved parenting practices have been associated with an increased risk of overweight in childhood.

In summary, food preferences and intake patterns emerge prior to 24 months of age and tend to persist through the first few years of life. Diet quality and quantity during the first 2 years of life is paramount in setting the stage for establishing food intake patterns for life. Recognizing these as major windows of opportunity offers health care practitioners and policymakers areas of potential intervention to curb the obesity epidemic.
Can Optimal Complementary Feeding Improve Later Health and Development?

Mary S. Fewtrell

Nutrition and growth during infancy influence later health and development, but most research has focussed on the period of milk feeding, and the possibility that the timing, content or method of complementary feeding (CF) might have similar later effects has received less attention. Such effects are plausible, since the CF period is one of rapid growth and development when infants are susceptible to nutrient deficiencies and excesses, and during which there are marked changes in the diet with exposures to many new foods, tastes and feeding experiences. CF practices could influence later outcome by several potential mechanisms including programming effects but also lasting effects on food preferences, appetite and eating behavior. These mechanisms may not be mutually exclusive and may be difficult to separate in practice.

Research – particularly using randomized trials - in this field is challenging, which may explain why the majority of existing data come from observational studies. Mothers often have strong opinions about CF practices and may not agree to be randomized to alternatives. Furthermore, unlike the situation in early infancy where an infant receives a single food – milk – the CF period is complex, and it is more difficult to design effective and pragmatic interventions when the diet is rapidly diversifying, and behavioral and cultural aspects are becoming more important. Related to this is the problem of distinguishing between effects of specific nutrients, foods or whole diets. These factors may also limit the generalizability of the findings of any intervention.

Other papers in this section focus on taste, psychological and behavioral aspects of CF, and the later impact of infant food patterns. This paper summarizes evidence for effects of the timing, content and mode of feeding on later outcomes, including obesity, development, risk of allergy and celiac disease (CD). Evidence mainly from observational studies suggests an increased risk of later obesity and allergy if solids are introduced
before 15 weeks, with little evidence that timing is influential beyond this age [1, 2]. Current advice to introduce gluten between 4 and 6 months alongside breastfeeding to reduce the risk of CD is also based on observational data [3], and has been challenged by the results of two recent randomized controlled trials, which found no effect of age at introduction of gluten or breastfeeding on the risk of CD [4, 5]. There is little evidence for an effect of timing of introduction of solids on developmental outcome. Few studies have examined later outcomes in relation to specific nutrients or foods during CF, although there is concern that high protein intakes during this period could increase obesity risk; observational data suggest that any increased risk may be associated with dairy protein rather than meat or vegetable protein, perhaps mediated by insulin-like growth factor-1. Limited observational data suggest that mode of feeding – breast versus bottle, spoon versus baby led – could influence later eating behavior and perhaps obesity risk. In summary, whilst it seems plausible and indeed likely that CF practices will influence later outcomes, there is currently limited evidence apart from the suggestion that solids should be introduced after 15 weeks to reduce later obesity or allergy risk. Most data come from observational studies with a high risk of confounding. Further research, where possible using an experimental approach, is required.

Regardless of official recommendations, CF practices are strongly influenced by social and cultural factors, and vary markedly between and within countries depending on availability, acceptability and affordability of foods. It is therefore likely that, whilst recommendations for different aspects of CF may be developed in the future based on broad principles and taking account of effects on later outcomes, they will need to be tailored for different populations.

References

We begin infancy on a milk diet but soon must learn to eat a variety of foods to support continued growth and health. Fortunately, we are biologically prepared for this dietary transition; infants have preferences for the basic tastes, preferring sweet, salty and umami, and rejecting sour and bitter. Infants are also prepared to learn to prefer foods and flavors that become familiar. Familiarization is a basic type of learning, which is particularly important in early life. With repeated experience, the initial ‘neophobic’ avoidance reaction to a new flavor can be transformed into a flavor preference. Initially, many flavors from foods in the maternal diet are present in amniotic fluid and breast milk, which prepares the infant to prefer flavors in the mothers’ diet.

Familiarization with foods and flavors involves gradually introducing the infant to ‘table’ foods of the adult diet. This typically begins at around 4–6 months; by 24 months, children are consuming diets similar to those of their parents, diets too high in added sugars, fats and salt, and too low in essential nutrients. New foods tend to be rejected, but with repeated exposure, the novel food can become familiar, accepted and preferred. Several other learning processes also contribute to the acquisition of flavor preferences, including associative conditioning of flavors to the social contexts and physiological consequences of eating. Children also learn about food and eating by observing others.

Today, children in the US and many other countries are learning about food and acquiring flavor preferences in obesogenic environments, characterized by the availability of inexpensive, energy-dense palatable foods. In these environments, it is especially challenging for parents to provide infants and young children with the early experience necessary to promote the acquisition of preferences for many of the foods that are part of a healthy diet.

Because parenting practices evolved to address environmental threats to children’s health and safety, feeding practices were to address the threat of food scarcity and insure that children have adequate food.
Feeding practices include: offering large portions, forcing children to clean their plates, offering preferred foods and using food to soothe. These practices are still in use, although too much food has become a major threat to child health. Results of recent primary prevention trials designed to reduce obesity risk in infancy by changing aspects of infant 'lifestyle' (including feeding, sleeping and soothing) are presented.

**Suggested Reading**


The Development of Flavor Perception and Acceptance: The Roles of Nature and Nurture

Catherine A. Forestell

Over the past several decades, we have gained important insights into the unique flavor world in which children live [see ref. 1 for a review]. Flavor, which in everyday language is often used interchangeably with taste, is elicited by a combination of taste and olfactory sensations. According to its precise definition, taste refers to the sensations that occur when chemicals come into contact with taste receptors throughout the oral cavity, allowing us to perceive a small number of primary taste qualities, namely, sweet, salty, bitter, sour and savory, or umami taste. In contrast, olfaction arises from receptors located in the epithelium of the nasal cavity. Unlike the limited number of primary tastes, there are thousands of distinctive odors with separable sensations, which contribute to the rich array of flavors we experience in foods.

Behavioral studies using a variety of techniques suggest that by the last trimester, taste and olfactory receptors are functional and capable of detecting the continually changing flavor profile of the amniotic fluid. In addition to containing chemicals with distinct taste properties, amniotic fluid contains volatile chemicals transmitted from the maternal diet [2]. Given the extensive prenatal development of the taste and smell systems, it is not surprising that the newborn is sensitive and responsive to odor and taste stimuli after birth.

Studies have revealed that newborn infants can distinguish and differentially respond to basic tastes by emitting a combination of consummatory responses and facial expressions that reflect hedonic or distaste reactions [see ref. 3 for a review]. During the first few hours of life, infants express hedonic responses, such as facial relaxation and suckling movements to sweet and savory tastes. Although little is known about the developmental progression of children’s sensitivity to and preferences for umami taste, we know that within days after birth, infants are adept at detecting dilute sweet solutions. Preference for sweet taste remains
heightened throughout childhood and declines to that observed in the adult during late adolescence. In contrast, aversive responses are observed to concentrated bitter (grimaces and tongue protrusions) and sour (lip pursing and eye squinting) tastes at birth. However, by 18 months of age, initial negative responses to sour tastes transform into preferences. In contrast to the other basic tastes, the ability to detect and respond to salt does not appear until 2–6 months of age. Subsequently, preference for salt emerges throughout childhood that is greater than that of adults.

Early experiences ‘fine-tune’ children’s innate sensory responses and contribute to individual differences in perception and acceptance. Beginning before birth, children are exposed to a wide range of odor volatiles in amniotic fluid and breast milk that reflect the mother’s cuisine. These early exposures, one of the first ways children learn about the foods within their culture, enhance acceptance and preference for similarly flavored foods at weaning [2]. In contrast, children who are formula fed are exposed to a monotonous flavor profile and may be less accepting of flavors and foods that differ from the flavor profile of their formula.

At weaning, children continue to learn from varied chemosensory experiences. Children who are repeatedly exposed to a wide array of healthful foods learn to like these foods and are more accepting of novel foods [4], whereas those who are routinely fed sweet- and salty-tasting foods learn to prefer these foods more than those who are not exposed [5]. In combination, these findings suggest that mothers who consume an array of healthy foods themselves throughout pregnancy and lactation, and feed their children these foods at weaning, will promote healthful eating habits leading to long-term health benefits for their children.

References
Guidelines for healthy infant feeding during the transition from a milk-based to a family food-based diet provide advice on breastfeeding, complementary feeding and feeding behavior. Dietary patterns can assess adherence to the guidelines. Very few studies have derived dietary patterns during infancy. The Avon Longitudinal Study of Parents and Children (ALSPAC) has used two different methods of deriving dietary patterns: one by comparison to an index based on international infant feeding guidelines and the other using principal component analysis (PCA), a data-driven method. The scores derived have been related to later childhood outcomes. The ALSPAC cohort was recruited during pregnancy in 1991/1992 in an area of southwest England; the parents and offspring have been followed over 8 years [1]. Parent-completed questionnaires assessed infancy diet at 6 and 15 months of age and the social background of the family. The children were weighed and measured at age 7 years and IQ assessed at age 8 years. Food frequency questionnaires completed by parents about the child were collected at 3 and 7 years of age and used to obtain childhood dietary patterns. A complementary feeding utility index was calculated in relation to 14 feeding recommendations [2]. High scores on the index were due to longer breastfeeding, and feeding more fruit and vegetables and less ready-prepared baby foods. High scores on the index showed better adherence to the feeding guidelines and were associated with a more favorable social background. The index scores were positively related to childhood IQ at age 8 years and ‘healthy’ dietary patterns at age 3 and 7 years [3]. Adjustment for social background attenuated but did not abolish the associations. Four dietary patterns were derived from PCA at each age [4]. Three patterns occurred at both ages: ‘HM traditional’ characterized by home-made meat, vegetables and desserts; ‘discretionary’ characterized by biscuits (cookies), sweets, crisps (potato chips), fizzy drinks (soda) and tea, and ‘RM baby food’
infants mainly fed commercial ready-made baby foods. A ‘breastfeeding’ pattern was the fourth pattern at 6 months, with fruit and vegetables also included. At 15 months, a pattern including cheese, fish, nuts, legumes, raw fruit and vegetables was labelled ‘HM contemporary’. The ‘discretionary’ and ‘RM baby food’ patterns at both ages were negatively associated with IQ while the ‘breastfeeding’ and ‘HM contemporary’ patterns were positively associated with IQ [5]. These results suggest that infant diet is likely to influence cognitive development in children and may set a trend for later eating patterns. Comparison of relationships between breastfeeding duration and childhood IQ in two cohorts with different confounding structures (ALSPAC and a Brazilian cohort from Pelotas) confirmed that breastfeeding has an important influence on cognitive development [6]. The infant dietary patterns showed that differences in many other foods and behaviors are associated with breastfeeding; longer breastfeeding occurred in conjunction with the consumption of other recommended foods, such as fruits and vegetables. Infant dietary patterns were associated with childhood dietary patterns and so may be important in setting children on the path to healthy eating.

References

Nature and Nurture in Early Feeding Behavior

Lucy Cooke

Obesity has reached epidemic proportions and research into prevention is increasingly focusing on the earliest stages of life. Eating behaviors characterized by a large appetite have been linked to a higher risk of obesity, and obese individuals tend to eat faster, fill up less easily and to value food more highly than those of a normal weight. Variation in appetite can be seen in infants and are associated with growth trajectories. Research has shown that both weight and appetitive traits are heritable in adults and children, but the dramatic rise in obesity in recent decades is also attributable to a changing food environment. However, the fact that it is the individuals with the highest BMIs who are gaining most weight points to gene-environment interactions. The behavioral susceptibility model suggests that those with more avid appetites are more likely to overeat in environments where palatable food is plentiful.

Studies of appetite in infants are scarce, and the observation that genetic effects on weight are expressed before children reach school age led to the establishment of Gemini – the Health and Development in Twins – Study, comprising over 2,400 UK families with twins. The aim was to investigate genetic and environmental determinants of weight trajectories in early childhood with a focus on appetite and the home environment.

Gemini families have been supplying data at regular intervals, starting when the twins were 8 months old. Analyses of the data on infant appetite and weight have provided a number of important findings. Firstly, a prospective study found that appetite in infancy drives weight gain more strongly than weight drives appetite, although the two processes do coexist [1]. A further study using a subsample of twins discordant for appetite ruled out the possibility of familial confounding, suggesting a causal role for appetite in weight [2]. An investigation of the relative contribution of genes and environment to four appetitive traits resulted in heritability estimates that were moderate to high (53–84%) with the remaining variance explained by environmental factors [3]. Finally, multivariate analyses
indicated that roughly one third of the genes related to weight are also related to appetite and vice versa [4]. These results support the behavioral susceptibility hypothesis that those who are genetically predisposed to a larger appetite will eat more when there is an abundant food supply.

The strong genetic component to appetite does not mean that modification is impossible of course. Environmental factors affecting appetite in infancy are understudied, although research with older children emphasizes the importance of parental feeding practices in changing or maintaining children’s eating behavior. Potential strategies for minimizing the likelihood of over- or underconsumption in at-risk individuals are suggested.

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