Advances in Our Understanding of the Biology of Human Milk and Its Effects on the Offspring¹,²

Lene Schack-Nielsen and Kim F. Michaelsen*

Department of Human Nutrition, Faculty of Life Science, University of Copenhagen, DK-1958, Frederiksberg C, Denmark

Abstract

There is an intense interest in the effects of breast-feeding on the offspring and in understanding the mechanisms behind these effects. More than 50 papers are published monthly on topics such as the influence of breast-feeding on aspects of growth, immune-related effects, mental development, and noncommunicable diseases. Most breast-feeding data are observational; confounding can be difficult to rule out because some maternal factors are associated with both breast-feeding and infant outcomes (e.g., obesity and mental development). The most important short-term immunological benefit of breast-feeding is the protection against infectious diseases. There is also some evidence of lower prevalence of inflammatory bowel diseases, childhood cancers, and type I diabetes in breast-fed infants, suggesting that breast-feeding influences the development of the infant’s own immune system. One of the most consistent findings of breast-feeding is a positive effect on later intelligence tests with a few test points advantage for breast-fed infants. In the last few years, several systematic reviews and meta-analyses have examined the effect of breast-feeding on noncommunicable diseases. There seems to be a small protective effect against later overweight and obesity. Blood pressure and blood cholesterol seem to be slightly lower in breast-fed infants; however, the few studies examining breast-feeding and the risk of coronary heart disease in later life did not find an association. Recent data have suggested that breast-feeding can program the insulin-like growth factor-I axis, as 3 studies found that breast-fed infants are taller as adults. J. Nutr. 137: 503S–510S, 2007.

The biology of human milk and its effects on offspring is a topic that has generated considerable research. This article focuses on aspects of growth, immune-related effects, mental development, and some noncommunicable diseases.

There are some methodological problems involved with the study of breast-feeding. It is unethical to randomize individual healthy term infants to be breast-fed or to receive an alternative feeding. In the published literature, there is evidence available from 2 different types of intervention studies. The first was a U.K. study of hospitalized preterm infants born 1982–1985, who were randomized to receive either donated banked breast milk, enriched preterm formula, or standard formula (1). The second study was a cluster randomized trial of hospitals in Belarus, randomized to either breast-feeding promotion through the Baby-Friendly Hospital Initiative (BFHI)³ or standard care. BFHI is a joint initiative of WHO and the United Nations Children’s Fund consisting of 10 steps to promote breast-feeding including education of health personnel. The hospitals forming the control group continued with the existing infant-feeding practices. All singleton full-term infants with a birth weight of at least 2.5 kg born at the included hospitals were enrolled in the study (2).

The remaining data on breast-feeding are observational, for which confounding is a potential problem. In industrialized countries, mothers who choose to breast-feed typically have higher socioeconomic status and are better educated than mothers who choose to formula feed. In developing countries and countries in transition, the opposite pattern is often evident. It is important

¹ Published as a supplement to The Journal of Nutrition; Presented at the conference “Advances in Meeting the Nutritional Needs of Infants Worldwide,” held in San Francisco, CA, April 5, 2006. The conference was sponsored by the International Formula Council (IFC), Atlanta, GA. The contents are the sole responsibility of the authors. The papers comprising this supplement were developed independently, and the conclusions drawn do not represent the official views of IFC. The mention of trade names, commercial products, or organizations does not imply endorsement by IFC. Guest Editor was Catherine Klein, Life Sciences Research Office, Bethesda, MD. Guest Editor disclosure: C. J. Klein is an employee of the Life Sciences Research Office, which is under contract to the International Formula Council to assist authors in preparing manuscripts for publication. Hence, the receipt of compensation from the supplement sponsor for services performed as guest editor is considered a potential conflict of interest. There are no other or pending financial interests with the sponsor, members of the sponsor’s trade organization, or their products.

² Author disclosure: K.F.M. has been a speaker at scientific meetings sponsored by infant formula companies.

³ Abbreviations: ALL, acute lymphoblastic leukemia; ALSPAC, Avon Longitudinal Study of Parents and Children; BFHI, Baby-Friendly Hospital Initiative; DHA, docosahexaenoic acid; IGF, insulin-like growth factor; LC, long-chain; OR, odds ratio; sIgA, secretory IgA; Th, helper T cells.

0022-3166/07 $8.00 © 2007 American Society for Nutrition.
to control for other confounding factors that are also associated with the outcomes (e.g., obesity and mental development). Another methodological consideration is the definition of breast-feeding, which varies across studies. Some studies compare infants who were never breast-fed with those who received any breast-feeding, and some compare infants exclusively fed breast milk with those partially fed breast milk. Still other studies focus on the duration of breast-feeding. Another factor to consider is that the alternative to breast-feeding, in most cases infant formula, has improved over the last decades, which should be taken into consideration when interpreting the results from older cohorts.

**Effect of breast milk on linear growth**

Dewey et al. (3) conducted a pooled analysis of studies comparing growth of infants who were exclusively breast-fed for 4 mo or longer, consistent with WHO recommendations at that time, and continued with some breast-feeding up to 12 mo. The length-for-age of breast-fed infants tended to be shorter (−0.29 Z-score) than the National Center for Health Statistics standard, which was based on a population with a low prevalence of breast-feeding. In a later review several studies showed that breast-fed infants had a slower linear growth compared with formula-fed infants, whereas the remaining studies showed no consistent pattern (4).

Nevertheless, at least 3 studies indicate that breast-fed infants are taller as adults. In the Boyd-Orr cohort study of 2995 adults born in the United Kingdom between 1920 and 1930, men and women who had been breast-fed were 2.5 cm taller (P = 0.002) and 1.0 cm taller (P = 0.12), respectively, than those who were not (5). The difference was more pronounced for leg than for trunk length, suggesting that leg length may be especially influenced by type of feeding (5). Similarly, using multiple regression analysis of data from the U.K. national birth cohort of 2879 participants born in 1946 (77% of whom were breast-fed), Wadsworth et al. (6) determined that leg length at 43 y of age was 0.13 standard deviation greater for adults who had been breast-fed. Consistent with these results, Victora et al. (7) found a borderline direct association between total duration of breast-feeding and adult height (P = 0.06) among 2135 Brazilians born in 1982. However, no association was seen for duration of breast-feeding and leg length. In older studies, the alternative to breast-feeding was not optimal, so poor nutrition could be a contributing factor to differences in the growth observed between or among cohorts.

**Insulin-like growth factor-I hypothesis.** Insulin-like growth factor (IGF)-I is an important modulator of growth hormone activity in linear growth. Recent research is exploring the question of whether breast-feeding might possibly “program” linear growth by altering the IGF axis.

Recent studies provide data that IGF-1 is lower in breast-fed infants compared with formula-fed infants at 3 mo of age (8), at 4 to 8 mo of age (9), and at 6 mo (10). It is thus possible that the higher protein content in formula compared with breast milk has a stimulating effect on IGF-1. Lower IGF-1 concentration is consistent with data for slower growth velocity of breast-fed infants compared with infants fed formula. Despite this lag in growth, there is some evidence that children and adults who were breast-fed as infants tend to be taller and to have higher IGF-1 concentrations than those who were not.

The Avon Longitudinal Study of Parents and Children (ALSPAC) cohort in the United Kingdom demonstrated a significant association between IGF-1 levels measured at 7 to 8 y of life and the history of breast-feeding. Compared with children who had never been breast-fed (~142 μg/L), children who had been partially breast-fed (+6.1 μg/L) or exclusively breast-fed for at least 2 mo (+13.8 μg/L) had significantly (P = 0.04) higher IGF-1 concentrations (11). This led the authors to suggest that programming of the IGF axis could underlie some of the associations observed with breast-feeding and adult noncommunicable disease. Evidence that IGF-1 concentrations are negatively associated with birth weight when current height is controlled for (12) and that IGF-1 is higher in preterm than term infants, from 2 through 12 mo but not at birth (13), provides additional support to the weak but fascinating hypothesis that the IGF-1 axis can either be programmed in early life and cause increased linear growth after infancy or it can be programmed by a high linear growth rate.

**Immune-related effects of breast milk**

Human milk contains numerous immune-related compounds, and there is a comprehensive literature on the potential immune effects of human milk (14). Several immune-related compounds are listed in Table 1. Live white blood cells in milk, once consumed, could exert an effect in the infant as well. In animal studies, it appears that some white blood cells in milk are absorbed into the bloodstream of the offspring. It is unknown if this occurs in humans. Several of these components of milk offer passive protection in the upper respiratory system and the gastrointestinal tract, preventing adherence of pathogens to the mucosa, and thereby protect the infant against invasive infections. There are data suggesting that breast milk stimulates the child’s own immune system as well. Evidence from developing countries demonstrates that breast-feeding or not breast-feeding can be a matter of life or death for the at-risk infant. The relative risk of death from acute respiratory infection and diarrhea among non-breast-fed children in developing countries has been explored in 2 studies (15,16). Compared with breast-fed infants [odds ratio (OR) of mortality of 1], non-breast-fed infants younger than 2 mo of age have 6 times the OR of mortality from acute respiratory infection and diarrhea; the OR remains at least 1.5 times greater than that in breast-fed infants up to 2 y of life. In addition to the protective effect of human milk, the alternative to breast-feeding in developing countries is often not optimal from both nutritional and hygienic perspectives.

In industrialized countries with a considerably lower incidence of infectious disease, there are also many studies showing that breast-feeding protects against acute infections. The

### Table 1 Antibodies and other defense agents in human milk

<table>
<thead>
<tr>
<th>Category</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>sIgA</strong></td>
<td>Leukocytes</td>
</tr>
<tr>
<td></td>
<td>– B lymphocytes</td>
</tr>
<tr>
<td></td>
<td>– Macrophages</td>
</tr>
<tr>
<td></td>
<td>– Neutrophil</td>
</tr>
<tr>
<td></td>
<td>– T lymphocytes <strong>1</strong></td>
</tr>
<tr>
<td>Oligosaccharides</td>
<td></td>
</tr>
<tr>
<td>Bifidus factor</td>
<td>Lysozyme</td>
</tr>
<tr>
<td></td>
<td>Lactoferrin</td>
</tr>
<tr>
<td>Interferon-<strong>γ</strong></td>
<td></td>
</tr>
<tr>
<td>Nucleotides <strong>1</strong></td>
<td></td>
</tr>
<tr>
<td>Cytokines <strong>1</strong></td>
<td></td>
</tr>
</tbody>
</table>

**1** Factors that potentially may impart an imprint on the child’s own immune system.
protection seems to be strongest against diarrheal disease (2,17) and otitis media (18), but there are also studies showing an effect against respiratory tract infections (19).

Several lines of evidence support the hypothesis that the child’s own immune system is influenced by breast milk. The thymus plays an important role in the maturation of the immune system. Ultrasound measures of thymus size in healthy Danish infants at 4 mo of age revealed that the thymus of breast-fed infants is twice the size of that in formula-fed infants (20). It is not known how breast-feeding influences thymic growth or how alterations in thymic size might affect long-term health. The levels of immune response after some vaccinations also differ significantly between breast-fed infants and other infants, with breast-fed infants exhibiting better response (21). Furthermore, tuberculin reactivity is transmitted by breast milk, although the details of the transfer are not yet known (22). Secretory IgA (sIgA) concentration in urine is also higher in breast-fed infants compared with formula-fed infants (23). Evidence supporting a role for breast milk’s ability to bolster the child’s immune system is derived from data following kidney transplant from a maternal donor; rejection rates and 1-y graft function are better if the recipient had been breast-fed (24).

Some of the effects of breast-feeding on the child’s risk of acquiring infectious diseases seem to continue after breast-feeding is terminated. Protection against Haemophilus influenzae type B may last for 10 y (25,26), against respiratory tract infections for 7 y (27), against otitis media for 3 y (28), and against diarrhea for 2 y, accompanied by a reduced rate of hospital admission (17).

The Th1/Th2 hypothesis

Infants are born with an immature immune system dominated by helper T cells (Th) of subtype-2. Breast-feeding may accelerate the maturation of the immune system by stimulating development of Th subtype-1 cells, thereby achieving a Th1-dominated Th1/Th2 ratio sooner than does formula feeding (29). Th cells are classified by their cytokine profile, with, for example, Th1 cells secreting more IL-2 and INF-γ, and Th2 cells secreting more IL-4, IL-10, and IL-13.

The types of fat in the mother’s diet might alter the ability of breast milk to influence Th1-cell maturation in the infant. In a study by Lauritzen et al. (30), postpartum mothers were randomized to consume either 4.5 g fish oil or olive oil for the first 4 mo of lactation. Ex vivo LPS-stimulated production of INF-γ and IL-10 in whole-blood cultures from infants were measured at 2.5 y of age. The ratio of the INF-γ/IL-10 cytokine profile (i.e., reflecting Th1/Th2 cell subtypes) was higher for the fish oil group (0.27 vs. 0.07, \( P = 0.02 \)). These results suggest that a higher content of (n-3) PUFA in breast milk accelerates maturation of the infant immune system. Because measures were obtained after breast-feeding had been terminated and when erythrocyte (n-3) PUFA levels in infants did not differ between groups, the findings suggest a sustained effect of breast-feeding on Th1/Th2 maturation.

Effects on atopic disease

Studies of the effect of breast-feeding on atopic manifestations (eczema, asthma, and rhinoconjunctivitis) are not definitive. Some studies show that breast-feeding does not provide any significant protection, but many others do demonstrate an effect. A multidisciplinary review of the early literature (1966–2001) (31) concluded that breast-feeding seems to protect against the development of atopic disease. The protection appears to be strongest in families with a history of atopic disease. Two additional reviews suggest that breast-feeding offers a protective effect against asthma (32,33).

The findings remain inconclusive for effects of breast-feeding on atopic dermatitis. Three reviews concluded there was a protective effect of different sizes (32,34,35). However, 2 studies showed greater risk (36,37). To better interpret these data, research is needed to understand the influence of genetics and whether there are sensitizing substances in milk.

Breast-feeding and immune-related diseases

Klement et al. (39) conducted a systematic review and meta-analysis to explore the relationship between breast-feeding and inflammatory bowel disease. Of the 17 studies included, 4 studies of Crohn’s disease and 4 studies of ulcerative colitis were judged to be of high quality. The overall and high-quality subset data indicated that breast-feeding might offer a protective effect against both Crohn’s disease and ulcerative colitis.

Several studies suggest there may be a decreased risk of type 1 diabetes in breast-fed infants (40,41). For example, the large EURODIAB study (42) indicated that breast-fed infants had a 25% reduced risk for diabetes [OR 0.75 (95% CI: 0.58, 0.96)] and a 41% lower risk in models adjusted for early growth and standard deviation scores for height and body mass index [OR 0.59 (95% CI: 0.35, 0.97)]. Although some have proposed an alternate hypothesis, that early exposure to cow’s milk might provoke the onset of type 1 diabetes, neither introduction of cow’s milk nor of infant formula before 3 mo of age in the EURODIAB study displayed a significant relationship to the risk of diabetes. Among children who developed type 1 diabetes, height and weight standard deviation scores were significantly increased from 1 mo after birth, indicating that early rapid growth increased the risk of diabetes or was a marker of infants at risk. The effects of early growth and breast-feeding seemed to be independent.

The topic of breast-feeding and childhood cancers is being explored by the UK Childhood Cancer Research Group and others. Past analyses included 3500 children with cancer and 6964 controls, of whom 62 and 64%, respectively, were reported to have ever been breast-fed (43). Breast-feeding was only weakly associated with a protective effect for leukemia (OR 0.89, \( P = 0.06 \)) and for all cancers (OR 0.92, \( P = 0.05 \)). In a review by Kwan et al. (44), the effect of breast-feeding on the risk of childhood leukemia was further examined using meta-analysis of 14 case-control studies. Findings of a significant negative association hinted that either short-term or long-term (more than 6 mo) breast-feeding might impart protection against childhood acute lymphoblastic leukemia (ALL) and acute myeloblastic leukemia. However, a more recent report by Kwan et al. (45) investigating breast-feeding patterns in the Northern California Childhood Leukemia Study provided no evidence that breast-feeding compared with never-breast-feeding affects the occurrence of ALL at ages 1–14 y. Martin et al. (46) conducted a systematic review with meta-analysis of 26 studies...
(1966 to 2004) that published an OR. A 9% (95% CI: 2%, 16%) reduction was suggested for ALL. Single-study-driven results of a 24% (95% CI: 3%, 40%) reduction for Hodgkin's disease and a 41% (95% CI: 22%, 56%) reduction for neuroblastoma were reported for individuals who had been breast-fed. Despite the estimates apparently being robust, a variety of potential confounders such as socioeconomic and reproductive factors or early exposure to infectious disease, noncausal explanations are possible (46).

**Effect of breast milk on mental development**

A meta-analysis of 11 studies by Anderson et al. (47), which is still a cornerstone in the research on breast-feeding and mental development, found that breast-feeding conferred a benefit of 5.3 (95% CI: 4.5, 6.1) points in cognitive function between 6 mo and 16 y of age compared with formula-feeding and a significant benefit of 3.2 (95% CI: 2.4, 4.0) points after adjusting for relevant covariant factors such as maternal intelligence. The benefit attributed to breast-feeding was most pronounced in children of low–birth weight (5.2 points compared with 2.7 points for those of normal birth weight). In the same analysis, there were also data supporting a dose-response effect of breast-feeding on cognitive function (47). The longer the infant was breast-fed, the better the scores in cognitive function (Table 2).

Jain et al. (48) critically examined 40 studies (1929–2001) of breast-feeding and intelligence but identified only 2 studies of full-term infants that met the reviewers’ criteria for excellence of study design and control of confounding variables. Of these studies 1 showed no significant advantage in the type of feeding at 6 mo of age and resulting intelligence at 2, 4, 7, or 11–13 y of age for 375 children, after adjusting for sociodemographic, environmental, and biomedical factors. The other study, in which the type of feeding was recorded for 200 infants at birth and biweekly thereafter for 2 y, measured a 4.6-point higher mean intelligence at 3 y of age for those children who were breast-fed after controlling for several relevant variables (49).

A cohort of 9125 individuals in Denmark born between 1959–1961 were studied, whose early feeding was recorded at 12 mo of age (50). Of these, 2280 men were examined for intelligence and maternal attention and caring, may contribute to the development later on.

Additional information on the relation between breast-feeding and mental development has been contributed by studies of populations in which the mother’s socioeconomic status is inversely correlated with breast-feeding (51). Data from a nonverbal intelligence test at 8.5 y of age in the Cebu Longitudinal Health and Nutrition survey in the Philippines indicated that there were 1.6- and 9.8-point advantages in cognitive abilities for breast-feeding compared with no breast-feeding in normal-weight and low-weight infants, respectively.

To limit familial confounding variables, comparisons of breast-feeding and intelligence were made in 2734 sibling pairs from data obtained in the National Longitudinal Study of Adolescent Health (52). Intelligence was measured by the Peabody Picture Vocabulary Test during adolescence. Those having ever been breast-fed scored 1.7 and 2.4 points higher in intelligence, within and between families, respectively. The duration of breast-feeding also affected intelligence, resulting in scores raised by 0.2 points/month of breast-feeding, both within and between families.

**Biological superiority of breast milk or residual confounding?** The difference between formula and breast-milk patterns of essential and nonessential long-chain (LC) PUFA content is a plausible hypothesis for the differences observed in cognitive development. Docosahexaenoic acid (DHA) content of human milk in particular has been singled out for study because it can be incorporated into cell membranes in the central nervous system (53). One study tested whether maternal supplementation with DHA to enhance DHA content in milk would enhance performance of their breast-fed infants (54). Mothers were supplemented with 200 mg DHA or placebo from delivery to 4 mo postpartum. Mother’s milk and infant plasma DHA were significantly higher in the DHA group during the period of supplementation. There was no effect on visual acuity at 4 or 8 mo or on neurodevelopment at 12 mo. Psychomotor indices but not the Mental Development Index was higher at 30 mo in the DHA supplement group ($P < 0.01$), suggesting that greater intake of this (n-3) fatty acid may be beneficial.

Although the data supporting a cause-and-effect relation are strong, it is difficult to rule out confounding. Uncontrolled factors that correlate with both duration of breast-feeding and the offspring's intellectual development, such as maternal intelligence and maternal attention and caring, may contribute to the effects observed. For example, mothers who choose to breast-feed may also be better at stimulating their child's cognitive development later on.

There may also be a cause-and-effect relation of breast-feeding on cognitive development by a mechanism other than that exerted by the composition of the milk. Factors associated with the feeding situation that might affect development include physical and psychological contact during breast-feeding.

### TABLE 2

<table>
<thead>
<tr>
<th>Breast-feeding duration, wk</th>
<th>Studies, n</th>
<th>Mean difference (Breast-fed − Formula-fed)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>4–7</td>
<td>4</td>
<td>2,609</td>
<td>8,413</td>
</tr>
<tr>
<td>8–11</td>
<td>5</td>
<td>3,070</td>
<td>10,198</td>
</tr>
<tr>
<td>12–19</td>
<td>4</td>
<td>2,458</td>
<td>9,569</td>
</tr>
<tr>
<td>20–27</td>
<td>4</td>
<td>1,232</td>
<td>2,767</td>
</tr>
<tr>
<td>≥28</td>
<td>3</td>
<td>2,910</td>
<td>1,840</td>
</tr>
</tbody>
</table>

Source: Adapted from The American Journal of Clinical Nutrition (47).
Behavior of the mother could stimulate cognitive development and reinforce maternal breast-feeding behavior. Some studies (55,56) suggest that maternal hormones triggered by breast-feeding (e.g., oxytocin, prolactin) or perhaps through bonding might influence the behavioral pattern of the mother to exhibit more focus on the infant, more affectionate touch, and less depression, which could foster cognitive development (Fig. 1).

The effects of pregnancy, lactation, and plasma oxytocin concentration on maternal memory and attention were explored by comparing performance to that of nonpregnant women (55). Cognitive performance of mothers improved significantly 6–12 mo after delivery compared with late pregnancy and lactation (at 3 mo), leading the authors to suggest that memory and attention were impaired during the peripartal period, including periods when oxytocin concentration was elevated. Building on those results, Heinrichs et al. (56) administered intranasal oxytocin or placebo to 38 healthy young men 50 min before the study phase (incidental learning) of 3 memory tests. Oxytocin significantly impaired recall performance. In their discussion, the researchers considered the value of this effect of oxytocin on lactating mothers and their relation to their infant. Under these conditions, oxytocin might isolate the mother from distracting stimuli during lactation and focus maternal attention on the interaction between mother and infant.

**Summary of effects on mental development.** Overall, a consistent pattern is observed of a positive association between breast-feeding and higher performance on intelligence tests later in life. Once established, the effect seems stable and persists with age. The effect appears to be dose-responsive, in that intelligence improves with the duration of breast-feeding. The measured effect is most pronounced in preterm infants. Strong supporting evidence is available from studies that control for familial factors and for socioeconomic advantages, as in studies in societies that have a negative association between breast-feeding and social class/education.

The observed effect is not large, just a few points difference on intelligence tests, but the effect is likely to have a considerable impact at the population level contributing to higher educational and occupational achievements, as pointed out by Drane and Logemann (57). Plausible explanations include the LCPUFA content of human milk and stimulation and reinforcement of beneficial maternal behaviors during breast-feeding.

**Breast-feeding, obesity, and cardiovascular disease**

**Breast-feeding and obesity.** Breast-fed infants are leaner at the age of 12 mo (4), and recently there has been a marked increase in the number of studies examining breast-feeding and later obesity.

Obesity in the reproductive period may inhibit lactation performance. Data from 810 Caucasian rural U.S. women who chose to breast-feed at delivery indicated that being overweight or obese before pregnancy had an adjusted OR of 2.54 ($P < 0.05$) and 3.65 ($P < 0.01$), respectively, for failing to successfully breast-feed at hospital discharge and 2 d after delivery (58). Of those who continued breast-feeding, the relative risk of discontinuing exclusive breast-feeding and early termination of any breast-feeding was significantly higher for these women compared with women of normal weight. Maternal obesity should therefore be considered as a confounder in regard to the association between breast-feeding and childhood obesity.

Arenz et al. (59) conducted a systematic review and meta-analysis of studies that examined the relation between breast-feeding and obesity in childhood (measured at 1 to 18 y of age) and adjusted for at least 3 of several defined relevant confounders. Nine studies with >69,000 participants met their inclusion criteria. Overall, the adjusted OR was 0.78 (95% CI: 0.71, 0.85) for a significant effect of breast-feeding on reducing the risk of obesity in childhood.

In another meta-analysis of 28 studies that provided OR estimates for obesity (measured at up to 33 y of age) among breast-fed subjects compared with formula-fed subjects, the protective effect of breast-feeding was replicated [OR 0.87 (95% CI: 0.85, 0.89)] (60). The protective effect of breast-feeding was particularly strong in the smallest studies, indicating publication bias. Furthermore, the association was markedly reduced in the 6 studies that provided estimates adjusted for the 3 most important confounders (parental obesity, maternal smoking, and social class) [adjusted OR 0.93 (95% CI: 0.88, 0.99)] (60). Moreover, in a subsequent meta-analysis that included unpublished studies and also adjusted for relevant confounders, no association was found between breast-feeding and mean body mass index later in life (61). Owen et al. (61) therefore concluded that the difference in obesity observed between breast-feeding and formula-feeding is small and is likely to be strongly influenced by publication bias and confounding factors.

Four studies examined by Arenz et al. (59) reported a dose-dependent inverse effect of breast-feeding duration on the prevalence of obesity in childhood. To investigate this further, Harder et al. (62) conducted a meta-analysis focusing specifically on the duration of breast-feeding and risk of overweight later in life (ages up to 33 y). From the 17 studies meeting their inclusion criteria, they determined that the duration of breast-feeding was inversely associated with the risk of overweight. For each month of breast-feeding the OR was 0.96 (95% CI: 0.94, 0.98), a 4% decline in risk of overweight, and was 0.68 (95% CI: 0.50, 0.91) at >9 mo of breast-feeding, a 32% decline in risk of overweight. This analysis was, however, based on estimates from nonadjusted analyses.

A better understanding of confounding factors (e.g., maternal body size, weight gain in pregnancy, smoking status) is needed for future investigations of the protective role of any breast-feeding or duration of breast-feeding in relation to obesity (63). If breast-feeding does influence weight status later in life, several factors could be investigated for potential involvement, such as...
differences in protein intake, potential bioactive factors in human milk, differences in satiety regulation in breast-fed infants, and the level of parental interest and care. Some exploratory work has been undertaken on the relation of breast-feeding and hormones that affect food intake and energy balance, but the results are inconclusive. Three studies measured higher blood leptin in formula-fed infants compared with breast-fed infants at 4 d and 6 mo of age (64–66), whereas others reported higher leptin (and lower ghrelin) concentration in breast-fed infants who were less than 4 mo of age (9,67).

Overall, studies from countries with a high prevalence of obesity indicate that breast-feeding may provide some protection against the development of childhood obesity. The effect is not large at the individual level but may be relevant at the population level. Understanding the mechanism for this effect might be useful for both prevention and treatment of obesity.

Breast-feeding and cardiovascular disease. Two reviews of studies measuring blood pressure and its association to the type of early feeding found evidence supporting an approximately −1 mm Hg difference in systolic blood pressure between individuals who had been breast-fed compared with those who had been formula-fed (68,69). However, the effect was found to be substantially less among those studies with 1000 or more participants, −0.16 mm Hg (68) and −0.6 mm Hg (69). Hence, based on data from smaller studies, early claims that breast-feeding influences the development of the infant's own related diseases such as inflammatory bowel diseases, childhood cancers, and type I diabetes seem to be slightly lower in individuals who were breast-fed as infants. However, studies examining morbidity and mortality from cardiovascular disease did not find a protective effect. Recent data have suggested that breast-feeding can program the IGF-1 axis. Serum IGF-1 is lower in breast-fed infants, and a few studies suggest that breast-fed infants have higher levels of IGF-1 later in life and are taller as adults.

There is an intense interest in the effects of breast-feeding on the offspring and in understanding the mechanisms behind these effects. More than 50 articles on this topic are published monthly. The International Society of Research in Human Milk and Lactation compiles a bibliography of relevant titles with abstracts every 2 mo, which are available on its website (www.ISRHML.org).

Question and answer session

[Q1]: Could you describe more about the underlying mechanisms by which the IGF axis could be programmed?

[Dr. Michaelsen]: I can only speculate because we do not know. There may be a sensitive window for IGF-1 programming at certain ages. There are a few studies suggesting that the birth weight influences the IGF-1 levels later in life. Controlling for present height, which in most studies is highly correlated with the IGF-1 levels, these studies found a negative association with birth weight, suggesting that those of smaller birth weight will adjust their IGF-1 levels upward later on, most likely to catch up. This is relevant to all the discussion we have about catch-up growth, growth velocity during the first year of life, and what the rate of growth in the early period means in the long term. There may be both positive and negative health effects later on. If breast-feeding gives lower IGF-1 levels, then the infancy period may be a period when the IGF axis can be programmed to result in higher levels later on. I have no hypothesis yet for what the mechanism would be through which such programming might occur.

[Q2]: The data on IGF-1 seem to be from developed countries; is that true? It would seem that maybe an evolutionary mechanism was in place to make small growth the default; then if conditions were right, the individual could grow bigger. It would be interesting to do some studies in developing countries where there is adversity after birth to determine whether or not the IGF axis is the second programming signal. If the hypothesis is wrong, then the second default would also be to maintain the lower growth rate and smaller size.

[Dr. Michaelsen]: Yes. It would be interesting to conduct more measures of IGF-1 in developing countries. Because IGF-1 concentration closely follows linear growth, it would be interesting to measure IGF-1 in concert with interventions for stunting and determine, in the short term, whether the intervention had an effect on IGF-1. By examining IGF-1 in large cohorts, you would also be able to ascertain if there is a programming in populations with poor growth and poor nutrition.

[Q3]: Are there much data looking at school performance (e.g., attention, learning, and memory) of children in relation to their breast-feeding history?

[Dr. Michaelsen]: There are some studies looking at breast-feeding and school performance, but I do not recall them specifically. I focused primarily on the reports of meta-analysis of studies with intelligence measures [e.g., Anderson et al. (47)].

[Q4]: I am not familiar with the data Dr. Heird presented earlier, that we haven’t been effective in increasing exclusive breast-feeding. Globally that may be true. But certainly for Latin America, we have been very successful, and data have been published from Demographic and Health Surveys showing that, with really strong policies and programs, the duration of
exclusive breast-feeding has increased. Unfortunately we also have evidence from Peru, with the last national survey, that this trend is easily reversed when national policy and programs are weakened. So we can be very effective, I think, programmatically. The challenge is getting the resources to really be able to do that.

[Dr. Michaelsen]: Yes, I fully agree.

Literature Cited


42. EURODIAB Substudy 2 Study Group. Rapid early growth is associated with increased risk of childhood type 1 diabetes in various European populations. Diabetes Care. 2002;25:1755–60.


