Breast feeding and future health

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Purpose of review

This review discusses the long-term health effects of breast feeding, based on the most relevant publications from the second half of 2004 and 2005.

Recent findings

The positive effect of breast feeding on later cognitive function continues to be the most consistent and important effect. Also, breast feeding is likely to protect against some immune-related diseases later in life, such as type 1 diabetes, coeliac disease, inflammatory bowel diseases and perhaps cancer. The evidence for an effect on allergic disease continues to be inconclusive. Furthermore, breast feeding seems to be associated with a lower blood pressure and serum cholesterol, but there is no clear association with cardiovascular disease or death. Most new studies and meta-analyses show a protective effect against later obesity, but this seems to be small. A new hypothesis suggests that breast feeding programmes the insulin-like growth factor axis and results in higher growth velocity later in childhood.

Summary

Evidence is increasing that breast feeding, beyond its well-established beneficial effects during the breast-feeding period, also confers long-term benefits. These effects are not strong at the individual level, but are likely to be of importance at the population level. Since the majority of the studies are observational, however, it is difficult to prove causality.

Keywords

bone density, breast feeding, cancer, cardiovascular disease and risk factors, cognitive development, growth, immune-related diseases, insulin-like growth factor-I (IGF-I), obesity

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Abbreviations

BMI	body mass index
DHA	docosahexaenoic acid
IGF	insulin-like growth factor
LCPUFA	long chain polyunsaturated fatty acids

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Introduction

During the last few decades, evidence for positive health effects of breast feeding during the breast-feeding period has been increasing. The clearest benefit is protection against infectious diseases, which is most pronounced in populations from low-income countries with a high prevalence of infectious diseases, but is also evident in industrialized countries. It has also become clear, however, that there are long-term effects on development and risk of later diseases, suggesting that breast feeding can to some degree programme future health, although it is difficult to establish causality, as most of the studies are observational.

From mid-2004 to late 2005, more than 1100 publications on human milk and lactation became available, and over 120 of these focused on long-term effects. These figures are based on bibliographies published by the International Society for Research in Human Milk and Lactation (ISRHML) every 2 months, which, with a 2-month delay, are available free of charge on the home page of the society (www.isrhml.org). The aim of this review is to highlight and comment on the most important of these publications from the last half of 2004 and 2005. Emphasis is on epidemiological studies, meta-analysis and systematic reviews. A few references from before that period have been included where it was necessary to set the scene.

Cardiovascular risk factors and disease

There are an extensive number of studies on how breast feeding is associated with risk factors for cardiovascular disease, and based on these a large number of comprehensive meta-analyses have been conducted. Only a few studies have focused on disease endpoints and mortality.

Blood lipids have attracted attention because breast-fed infants have higher levels of blood cholesterol, since there is cholesterol in human milk and not in infant formula. This difference, however, does not seem to persist into later life, since a meta-analysis found that the adult cholesterol level was in fact slightly lower (0.18 mmol/l) among those who were breast fed compared with those who were bottle fed [1]. Breast feeding also seems to be associated with a small reduction in systolic blood pressure in later life, as shown in two quite similar meta-analyses from 2003 [2] and 2005 [3]. The reported effect estimates were decreases of 1.10 and 1.4 mmHg respectively, and were both independent of age at blood pressure measurement. Both studies showed

indication of publication bias, however, since large studies reported smaller differences than smaller studies. This means that conclusions on public health effects should be drawn cautiously. A study by Lucas and co-workers in which preterm infants were randomized to receive either breast milk (banked donor milk) or infants formula and were followed up in adolescence confirmed the beneficial effects of breast milk intake on blood pressure and lipid profile [4,5]. In addition to these beneficial effects, a recent study [6] showed that longer duration of breast feeding was associated with an increase in arterial stiffness in children, which has previously been shown in young adults [7]. The long-term effect of this is not known.

In The Boyd Orr Cohort [8], it was shown that the degree of atherosclerosis at age 65 years, determined as ultrasound-measured intima-media thickness, was lower in breast-fed compared with bottle-fed participants. Adjusting for blood pressure, cholesterol and insulin resistance made little difference to the effect estimates, suggesting that these factors were not on the causal pathway. No dose–response association between duration of breast feeding and intima-media thickness was seen, however [8]. Furthermore, a previous paper from the same cohort [9], but based on a larger number of participants (since it was not restricted to those participating in a clinical examination), showed that breast feeding was not associated with cardiovascular or ischaemic heart disease. In the Caerphilly Study, however, which only included men aged 45–59 years at inclusion in 1978–1983, breast feeding was associated with a 54% increased risk of coronary heart disease incidence and a 73% increased risk of coronary heart disease mortality [10•]. The estimates were stable to adjustment for potential confounders, including social class in childhood and adulthood. In contrast, it was found in the Nurses' Health Study, which included women aged 30–55 years at inclusion in 1976, that being breast fed was associated with an 8% reduced risk of coronary heart disease (fatal and non-fatal) [11•]. A major limitation of both of these studies is the use of information on breast feeding collected decades after the breast-feeding periods. Furthermore, none of the studies provided evidence for a dose–response association between duration of breast feeding and cardiovascular disease.

In conclusion, these results on risk factors and disease endpoints do not point to any major effects of breast feeding on cardiovascular disease.

Type 2 diabetes and insulin resistance

A systematic review of breast feeding and type 2 diabetes mellitus was published recently, but only as an abstract [12]. Breast feeding appeared to be associated with a decreased risk of type 2 diabetes in adulthood, and with a lesser degree of insulin resistance in childhood and adult life. In studies of infants, breast feeding was also associated with lower blood glucose and insulin levels, and it was hypothesized that this short-term effect of breast feeding programmed a long-term protective effect against type 2 diabetes.

A recent publication from the Newcastle Thousand Families Study [13] found an inverse relationship between breast feeding and insulin resistance for men, but not for women. On the other hand, a large study of school children from Denmark and Estonia did not show any difference in insulin resistance between exclusively breast fed children and those who had never been breast fed, and there was also no dose–response association between duration of exclusive breast feeding and insulin resistance [14]. In conclusion, there are still only a few studies on breast feeding and type 2 diabetes, and no convincing association has been demonstrated.

Interestingly, a recent publication from the Nurses' Health Study [15] showed that longer duration of breast feeding is consistently associated with a decreased risk for later development of type 2 diabetes in the mothers. The protective effect of breast feeding persisted after adjustment for a number of relevant co-variates known to be risk factors for type 2 diabetes, including current body mass index (BMI) [15].

Obesity

The large number of epidemiological studies analysing the effects of breast feeding on obesity later in life have been summarized in four systematic reviews or meta-analyses published during the last 2 years. Many studies are included in several of these reviews, but as they have used different inclusion criteria and methodology, the results differ somewhat. A major problem is that the studies have used different definitions of breast feeding, and some studies only distinguish between 'never' and 'ever' breast fed. Furthermore, the numbers of potential confounders included in the analysis of the individual studies are very different, with some of the studies not controlling for any confounders. An important confounder is maternal obesity, since obese mothers breast feed for a shorter period, as shown in a recent study from a large cohort in Denmark [16] and summarized in a review [17].

In a systematic review by Arenz *et al.* [18], nine studies with more than 69 000 participants were included. The adjusted odds ratio for being obese was 0.78 if the infant was ever breast-fed, and in four of the studies included there was a dose–response effect. These authors found no indication of publication bias. In the meta-analysis by Harder *et al.* [19], 17 studies met the inclusion criteria, and they found a significant dose–response effect, with a

4% decrease in risk of being overweight for each month of breast feeding. Owen *et al.* [20•] included 28 studies with almost 300 000 subjects, and found that breast feeding was associated with a reduced risk of obesity with an odds ratio of 0.87, but they also found that the effect was smaller (odds ratio 0.93) in the studies controlling for the three major potential confounders, namely parental obesity, maternal smoking and social class. As the effect was larger in smaller studies, a publication bias was likely. In a subsequent analysis including a further 10 previously unpublished studies with BMI as a continuous variable as the outcome, no effect of breast feeding was seen after adjustment for relevant confounders [21].

It is difficult to exclude the possibility that residual confounding factors could explain some of the positive findings of these studies, even if many of the studies controlled for parental BMI, maternal smoking and social status. The available studies make it plausible that there is a protective effect of breast feeding against obesity, at least in some settings at certain ages. It could be that breast feeding is only influencing the upper tail of the BMI distribution, and that the effect is greater in populations with a high prevalence of obesity. The effect is not likely to be strong at the individual level, but could be important at the population level.

Asthma, allergy, and pulmonary function

The evidence for a protective effect of breast feeding with regard to asthma and other allergic diseases is inconclusive, with some studies even showing that breast feeding increases the risk. Several recent large studies on possible protection against atopic dermatitis have also shown divergent results. In a large study from the Danish National Birth Cohort [22], there was no overall effect of breast feeding, but when stratified according to family history, exclusive breast feeding for at least 4 months was associated with an increased risk (incidence rate ratio 1.29) if there was no family history of allergy. Among those with a family history, there was a tendency that the more members of the family that had an allergic disease, the better the infant was protected against atopic dermatitis. The GINI-study [23] could not support the hypothesis that exclusive breast feeding is a risk factor, but when the data were re-analysed [24], a tendency was found that breast feeding was associated with a decreased risk of atopic dermatitis if both parents had a family history of atopic disease. In a large study from Sweden only looking at the effect of exclusive breast feeding for 4 months or more, compared with shorter exclusive breast feeding, there were no effects of breast feeding on the risk of atopic dermatitis during the first year of life [25], which was also the case among those with a family history of this condition. A study from New Zealand found that duration of breast feeding was associated with an increased risk of atopic dermatitis at 3.5 years of age, adjusted for parental atophy [26]. The effect of breast feeding on the development of various phenotypes of eczema up to 4 years was examined in a Swedish population [27], and exclusive breast feeding for 4 months or more reduced the risk of eczema at 4 years (odds ratio 0.78). In the same cohort, it was also shown that exclusive breast feeding for 4 months or more reduced the risk of asthma during the first 4 years of life [28]. There are no obvious explanations for the conflicting results with regard to a protective effect against atopic dermatitis, but the fatty acid composition of breast milk has been suggested to have a role. A small study from Finland [29] found that, in mothers with atopic dermatitis, the breast-milk level of saturated fatty acids was higher and the levels of $n-3$ fatty acids were lower in those whose offspring also developed atopic dermatitis.

Children with asthma, wheezing, or frequent or prolonged respiratory tract infections are more likely to have reduced pulmonary functions in later life. A study by Shaukat *et al.* [30] was the first to look at whether breast feeding is associated with adult pulmonary function. Overall, there was no effect of breast feeding on lung function, but stratifying on current smoking status showed a protective effect of breast feeding on forced expiratory volume in former smokers, although not on lung function measured as forced vital capacity [30]. A major limitation, however, was that information on history of breast feeding was self-reported and not collected until inclusion in the study at age 35–79 years.

Type 1 diabetes

Type 1 diabetes mellitus is an autoimmune disease triggered by environmental factors that develop in genetically susceptible individuals. Breast feeding has been suggested to be protective against pancreatic β-cell destruction [31]. This hypothesis has, however, been challenged by the suggestion that early exposure to cow's milk antigens could be a risk factor for type 1 diabetes, so appropriate mutual adjustment is important. A European multicentre study from 2002 [32] showed that breast feeding of any duration was associated with a 41% reduction in risk of type 1 diabetes.

Two case–control studies of Czech [33] and Yugoslavian (Serbian) [34] children gave divergent results. The first showed a protective effect of breast feeding, that was not affected by age at introduction of formula or other supplementary feeding, on the risk of type 1 diabetes [33]. In the study from Yugoslavia, however, the protective effect of breast feeding was only seen in univariate analyses, and disappeared after adjusting for age at introduction of supplementary milk. Furthermore, the effect of age at introduction of supplementary milk also disappeared after adjustment for a variety of factors associated with type 1 diabetes [34]. Despite this last study,

many studies from previous years have quite consistently shown lower risk of type 1 diabetes in breast-fed infants, but the mechanism is still not clear.

Of interest in relation to the possible role of cow's milk in the aetiology of type 1 diabetes is a recent intervention pilot study [35] that randomized infants genetically disposed for type 1 diabetes to either a hydrolysed casein formula or a conventional cow's milk-based formula after exclusive breast feeding had stopped. At a mean age at follow-up at 4.7 years, the children who had received hydrolysed formula showed decreased emergence of β-cell autoimmunity [35].

Other immune-related diseases

Coeliac disease is considered to be an autoimmune disease, and breast feeding has been shown in a meta-analysis of six case–control studies to have a protective effect that, with the exception of one small study, was dose-dependent [36•]. The meta-analysis further showed that breast feeding at the time of introduction of gluten was protective against coeliac disease (odds ratio 0.48) compared with infants who were not breast fed during this period. As the authors state, however, it is not clear from the included studies whether breast feeding delays the onset of symptoms or provides a permanent protection against the disease.

The immuno-modulatory properties of breast milk have also been suggested to have a protective effect against inflammatory bowel disease. In a meta-analysis from 2004 [37] including 17 studies, exclusive breast feeding of any duration was associated with a reduced risk of Crohn's disease (odds ratio 0.67) and ulcerative colitis (odds ratio 0.56). It was, however, not clearly described in all the studies whether exclusive breast feeding was compared with non-exclusive breast feeding or exclusive bottle feeding. The significant protective effects of breast feeding persisted when only the four studies judged to be of high quality were included in the meta-analysis. The results from a population-based case–control study [38] that was judged using the criteria of Klement *et al*. [37] to be of high quality did, however, show that breast feeding was associated with an increased risk of Crohn's disease (odds ratio 2.1). On the other hand, breast feeding was not related to ulcerative colitis.

A paper from The Newcastle Thousand Families Cohort Study [39] showed that increased duration of breast feeding was associated with a reduced risk of *Helicobacter pylori* infection at age 50 years, although only for men. *Helicobacter pylori* infection is the major cause of peptic ulceration and an important risk factor for gastric carcinoma.

Additionally, it has been shown in the Nurses' Health Study [40] that increasing duration of breast feeding is associated with a decreasing risk of rheumatoid arthritis in the mother. Compared with parous women who had not breast fed, women who had been breast feeding for at least 24 months had a 50% reduced risk of developing rheumatoid arthritis [40].

Cancer

Breast milk has been suggested to have a protective effect on risk of cancer by stimulating or modulating the immune system and promoting its maturation. In 2005, two systematic reviews on breast feeding and risk of cancer in childhood [41•] and adulthood [42•] were published. The first included 26 studies, and suggested that having ever been breast-fed was associated with a significant reduced risk of 9% for acute lymphoblastic leukaemia, 24% for Hodgkin's disease, and 41% for neuroblastoma. The last two estimates were, however, driven by single studies. Based on the effect size and number of annual cancer cases in the UK, the authors argued that the public health effect of an increasing prevalence of breast feeding is expected to be limited. Also, another review with more restricted inclusion criteria [43] came to a weaker conclusion regarding the association between breast feeding and leukaemia, since a protective effect was only seen in two of the four studies judged to be of sufficient quality. Furthermore, a recent case–control study from California including 311 cases [44] did not find any association between breast feeding and risk of acute lymphoblastic leukaemia. The meta-analysis on breast feeding and adult cancer included only three studies with all cancers as endpoints, and in this analysis no associations were seen [42•]. A meta-regression analysis including 11 studies suggested that breast feeding had a protective effect against pre-menopausal breast cancer, but not post-menopausal cancer, in female offspring [42•]. A major limitation of the majority of the included studies is that information on breast feeding was collected retrospectively, and in some instances not until adulthood.

In 2002, a meta-analysis showed that breast feeding was associated with a decreased risk of breast cancer for the mother [45]. This was confirmed in a recent American study [46] which, by differentiating subclasses of breast cancer types, was further able to show that the mechanism involved was probably not hormonal, since the risk reduction was not specific for tumours expressing oestrogen or progesterone receptors.

Bone density

The approximately 200 mg of calcium that breast-fed infants ingest per day is thought to provide optimal skeleton development in infancy. Most infant formulas provide higher amounts of calcium due to concerns that other components of the formula may cause inadequate mineral absorption. In 2000, a study was published

showing greater bone density at 8 years in term infants fed human milk for at least 3 months [47], but this conclusion was not supported by a study of healthy 4-year-old American children published in 2005 [48]. In this latter study, no differences in bone mineral content or bone mineral density were seen among children breast fed for at least 4 months compared with those who had received formula [48]. Furthermore, since no studies as yet have explored whether breast feeding has any effect on risk of fracture, any suggestion that breast feeding has a protective effect against osteoporosis must be regarded as speculative.

Because of the considerable calcium content in breast milk, it has been discussed whether this could have an adverse long-term effect on the mother's bone mineral density. A recent review, however [49], concluded that although a consistent loss of bone mineral density is seen during lactation, this effect seems to be reversible, and bone mineral density seems to be restored 6–18 months after weaning. Additionally, there does not seem to be an increased risk of fracture associated with a longer duration of breast feeding [49].

Linear growth

Adult stature and thereby growth is significantly related to a number of health outcomes. The best documented are a positive association with the risk of endocrine cancers such as prostate and mammary cancer, and a negative association with the risk of cardiovascular disease. It is therefore of interest how breast feeding influence linear growth. Several studies have found that breast-fed infants are shorter at the age of 12 months compared with formula-fed infants [50], but this effect does not seem to persist, as found recently in an interesting analysis of data from the Boyd–Orr cohort showing that infants breast-fed in the 1920s and 1930s were taller in childhood and adulthood compared with bottle-fed infants [51]. In a follow-up of the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort at age 7–8 years, Martin *et al.* [52••] found a trend toward higher serum insulin-like growth factor-I (IGF-I) levels in exclusively breast-fed infants, intermediate levels in partially breast-fed infants and lowest levels in those who had never been breast-fed. Based on this finding, these authors suggested the fascinating hypothesis that the IGF axis is programmed during infancy. IGF-I is low in breast-fed infants during the breast-feeding period, and this may result in a re-setting of the pituitary, due to less feedback, resulting in higher IGF-I levels and thereby growth velocity later in childhood. If this is true, they speculate that the association between breast feeding and adult disease could be explained, at least in part, by an effect of breast feeding on the IGF axis. The hypothesis that the difference in IGF-I levels between breast-fed and formula-fed infants is caused by differences in protein intake and quality was supported by an intervention study in 8-year-old boys, which showed that a high intake of skimmed cow's milk stimulated IGF-I levels [53].

Cognitive development

Many studies have found a positive association between breast feeding and cognitive development. The meta-analysis by Anderson *et al.* [54] from 1999 is still a milestone. It included studies of children between 6 months and 15 years, and reported an overall effect of 3.2 IQ points after controlling for potential confounders. The effect was stronger in preterm infants. There was also a significant dose–response relationship with the duration of breast feeding, and the effects seemed to be independent of the age at which outcome was measured. More recently, a short review [55] of the area including studies published up until 2004 confirmed the findings of Anderson *et al.* [54]. From 2004 onwards there have been more studies strongly supporting the hypothesis that breast feeding has a positive effect on cognitive development.

One of the most relevant objections to the evidence that breast feeding has a positive effect on cognitive development is that residual confounding cannot be excluded. It is therefore of particular interest that the hypothesis was tested in a birth cohort in the Philippines, where breast feeding is inversely associated with socioeconomic status and healthy maternal behaviour [56••]. Comparing IQ at 8.5 years between those who were breast-fed for 12–18 months and those breast-fed for less than 6 months, the advantage of longer breast feeding was 1.6 IQ points in normal-birth-weight infants and 9.8 IQ points in low-birth-weight infants. The greater effect in low-birth-weight infants supports the suggestion that the effect is due to long-chain polyunsaturated fatty acids (LCPUFA), especially the $n-3$ fatty acid docosahexaenoic acid (DHA), as low-birth-weight infants have a lower LCPUFA and DHA status. An effect in low-birth-weight infants (+6 IQ points), but not in infants with normal birth weight, was also found in a follow-up of men from the Caerphilly study at the age of 60–74 years [57]. The associations could be weakened by differences in age-related decline in cognitive function and poor recall of infant feeding. The LCPUFA hypothesis is also supported by a Swedish study [58], in which IQ at 6.5 years was tested. LCPUFA were measured in colostrum and breast milk 1 and 3 months after birth. Duration of breast feeding had a strong effect on IQ, while there was no direct effect of LCPUFA levels. In a model including duration of breast feeding and gestational age, however, the ratio between $n-3$ and $n-6$ fatty acids (DHA/arachidonic acid) had a significant positive effect, and this model could explain a surprisingly high 76% of the variation in total IQ. Further support

for a beneficial effect of DHA on cognitive development comes from a large multi-centre trial in which mothers received a daily DHA supplement or a placebo for the first 4 months after delivery [59]. There was a significant effect of the DHA supplement, with a higher Bayley psychomotor development index at 30 months ($P = 0.008$), but not at 12 months. There were no differences in other tests or in visual acuity during the first year of life.

In the offspring of diabetic mothers, those ingesting the largest volume of breast milk during the first week of life achieved major developmental milestones earlier, but showed a delay in onset of speaking [60]. This is in line with an intervention study in which mothers were randomized to fish oil or a placebo during the first 4 months of breast feeding [61]. In the fish oil group, passive vocabulary was smaller at 1 year compared with the placebo group, and word comprehension at 1 year was inversely associated with erythrocyte DHA at 4 months. There was no effect on passive vocabulary at 2 years or problem solving at 9 months. The apparent delayed language development in those receiving more breast milk or higher DHA levels in the milk is not necessarily a problem with regard to cognitive development.

Conclusion

During the last 2 years, many studies have provided new and exciting information on the long-term effects of breast feeding. Most remarkable has been a marked increase in the number of comprehensive meta-analyses and systematic reviews providing more solid evidence.

The existing studies suggest that breast feeding, in addition to its well-established beneficial effects during the breast-feeding period, also confers beneficial long-term effects. The most important effect is better cognitive development. Also, breast feeding may provide protection against some immune-related diseases, such as type 1 diabetes, coeliac disease and inflammatory disease. Furthermore, breast feeding seems to be associated with lower blood pressure and serum cholesterol, but the relevance of these associations remains unclear, since it is not clear if breast feeding is associated with a reduced risk of cardiovascular disease or death. Moreover, a large numbers of studies have shown a small but consistent protective effect of breast feeding against risk of obesity. In addition to the beneficial effects of breast feeding for the infant, there is increasing evidence that it also has beneficial effects on the long-term health of the mother. The most convincing evidence is the protective effect against breast cancer. In general, the potential beneficial effects of breast feeding on long-term health are not strong at the individual level, but are likely to be of importance at the population level.

A major limitation of most of the studies on potential health effects of breast feeding is that they are observational, wherefore residual confounding and reverse causality (for example in the association with atopic disease) can never be completely ruled out, despite well-conducted statistical analyses. Duration of breast feeding and several outcomes such as obesity, cognitive development, and risk of some lifestyle diseases are significantly associated with parental education and socioeconomic status. The parameters used to control for these factors might be too crude to pick up all details, and other factors such as ability to care for and stimulate the child could also confound the association. The only randomized studies are on preterm infants randomized to different feeding regimes for short periods, while they are still in hospital [4], and a large intervention study in Belarus [62], where hospitals were randomized to interventions to promote breast feeding or no intervention. Future follow-up of these randomized trials will be of great interest. Publication bias (whereby studies are more likely to be published if they show an effect) has also been shown in meta-analyses to be a problem. Other problems are that the definition of breast feeding, the way duration is classified, and the inclusion and definition of potential confounders vary considerably between studies, making pooled analysis difficult. With retrospective cohort studies, where data were collected many decades ago, it is difficult to improve this, but future studies should be more systematic in collecting these data.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 336).

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This review includes 61 studies on breast feeding and obesity in later life and shows a protective effect that is still evident, although markedly reduced, after control for relevant confounders.

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