

Chapter 17

THE LONG-TERM EFFECTS OF BREAST-FEEDING ON ASTHMA AND ATOPIC DISEASE

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1. EPIDEMIOLOGICAL EVIDENCE

In this review, the primary objective is to assess the evidence of whether breastfeeding protects against asthma and atopic disease for the long-term (long-term is defined here as >5 years of age). Two main types of observational epidemiological studies have been used to test this hypothesis. These are cohort studies of random samples of children and cohort studies of children with a family history of asthma or atopy. In each study type, exposure and outcome data are collected either prospectively or retrospectively. The 12 criteria for assessing the adequate measurement of exposure, outcome and statistics of cohort studies in this context are given in Table 17-1.¹

1.1 Retrospective and prospective studies

In retrospective studies asthma and atopy may be measured currently. Retrospective studies of breastfeeding and asthma have shown no association²⁻⁵, a reduced risk^{4, 6-8} or an increased risk.⁹ According to the criteria in Table 17-1, late maternal recall of breastfeeding is not acceptable. Only prospective studies are included in this review.

Table 17-1. Criteria for assessing the adequacy of cohort studies for the effect of breastfeeding on the development of asthma and allergy (see reference 1)

Measurement	Criteria
Exposure	1. Non-reliance on late maternal recall of breastfeeding 2. Blind ascertainment of infant feeding history 3. Sufficient duration of breastfeeding 4. Sufficient exclusivity of breastfeeding
Outcome	5. Strict diagnostic criteria 6. Blind ascertainment of outcomes 7. Consideration of severity of outcome 8. Consideration of age of onset of outcome
Statistics	9. Control for confounding factors 10. Assessment of dose-response effects 11. Assessment of effects in children at high risk of outcome 12. Adequate statistical power

Prospective cohort studies classify subjects in the study on the basis of presence or absence of exposure. The relevant events, both exposures and the outcomes of interest have not yet occurred when the study is initiated. In some prospective studies, the exposure may have occurred but the outcomes have not yet occurred. The studies that met the criteria in Table 17-1 with children followed to more than five years, are reviewed below after a brief discussion of the excluded studies.

1.2 Studies considered in this review

1.2.1 Excluded studies

For 2 studies it was unclear as to whether they met the criteria in Table 17-1.¹¹⁻¹² A cohort of 1661 infants recruited between 1972 and 1973 was assessed from ages 9 to 26 years using respiratory questionnaires, pulmonary function tests and allergy skin tests.¹¹ Following multifactor adjustment breastfeeding showed odds ratios of 1.94 (95%CI: 1.42-2.65 $p<0.0001$) for current asthma at 9 years and 1.83 (1.35-2.47 $p<0.0001$) for current asthma at 9-26 years by repeated measures analysis. This study has a number of limitations. Children were enrolled at the age of 3 years when data on breastfeeding recall were collected from mothers. As with most historical studies, the results of this study cannot be easily generalised to present times when health and lifestyle practices have changed. The cohort was at a time (early 1970s) when breastfeeding rates were low. In the hospital, suckling times and number of feeds were restricted and built up over several days. In

addition, long periods of separation of mother and baby and nightly formula feeds could have limited establishment of breastfeeding. This study might provide useful information about partial breastfeeding which could contribute to one of the important aspects of biological plausibility, i.e. a dose-response. In the cohort, 47% of babies were never breastfed and the modal time of cessation of breastfeeding was just 5-11 weeks. The second study¹² does not meet criteria 1, 3, 4, 9, 10 and 11 in Table 17-1.

1.2.2 Included studies

In relation to scientific rigour, to study the effect of breast-milk on the development of asthma and allergy, all of the 12 criteria in Table 17-1 were met in the studies briefly summarised below.

In Finland a long-term study of 256 healthy babies followed from before birth to 17 years showed significant protection by breastfeeding at least for the first 17 years of life.¹³ The value of this study lies in the duration of the follow-up and in the comprehensive collection of exposure and outcome data. In this study a clear prophylactic relationship between breastfeeding and atopic disease was found that was not modified by family history of atopic illness.

The Tucson Children's Respiratory Study of 1246 healthy infants was designed to investigate risk factors for lower respiratory tract illness. Established between 1980 and 1984, detailed pediatric assessments were conducted at defined intervals. When the cohort was 6 years of age, recurrent wheeze was less common in non-atopic children who were breastfed as infants, compared to non-atopic children who were not breastfed.¹⁴ At 11 years an association between breastfeeding and asthma differed with maternal asthma status.¹⁵ Among children with a maternal history of asthma, the percent of children who developed asthma was 9% for the never breastfed, 36% for those breastfed for three months or less and 57% for those breastfed for four months or longer. However, breastfed children were significantly less likely to wheeze at age 6, 9 or 11 years if they had not been diagnosed with asthma at any age. A limitation of this study was that formula feeding was prevalent in the United States at the time of study recruitment¹⁶ (more than 50%) and data on formula introduction were not collected, therefore a measure of exclusive breastfeeding was not possible.

In the Dundee Infant Feeding Study, 674 children were followed from birth to seven years.¹⁷ The prevalence of wheeze, breathlessness or cough at age 7 was significantly reduced if a child had been exclusively breastfed for at least 15 weeks ($P < 0.05$).

The Western Australian Pregnancy Cohort Study included 2187 children followed to 6 years.¹⁸ There was a significant reduction in the risk of childhood asthma at age 6 years if other milk was introduced before 4 months in either atopic or non-atopic children.¹⁸⁻¹⁹

The strengths of this study include its representativeness of the general population, its sample size and high response rate.²⁰ Collection of outcome data (including respiratory history) was prospective, by diary card, at frequent intervals and based on validated questionnaires.^{18, 21}

1.3 Summary

Studies that met the criteria for inclusion in this review of the long term effects of breastfeeding on asthma and atopic disease demonstrate a pattern of protection with breastfeeding and an increased risk with formula. In studies that met all recommended standards the odds ratios consistently exhibited an expected direction of effect that suggest biological plausibility and specific protective effects of breast-milk. Although the range of magnitude of effect is not large (1.2-1.5), in population terms this is large enough to be of public health significance.

Inconsistency in the literature is due to researchers measuring different aspects of atopy and asthma in children of different ages and using different ways of measuring those outcomes. The use of multivariate statistical models does not allow for entire control of confounding variables as there are many factors that may influence both the mother's likelihood of breastfeeding and the risk of children developing asthma or atopy.

1.4 Meta analyses

A meta analysis of nine studies examined the association between breastfeeding and the development of asthma.²² The meta analysis showed that children breastfed for at least three months of age were significantly protected against developing asthma by an estimated odds of 0.80. Other meta-analyses²³⁻²⁵ suggest a similar protective effect of between 26% - 30% from exclusive breastfeeding during the first 3 months of life against developing asthma, allergic rhinitis and atopic eczema later in childhood.

1.5 Studies of children with a family history

The prospective family cohort study classifies subjects on the basis of presence or absence of the disease in the mother or father or both. As in the population cohort study, the relevant exposure and outcome events, both have not yet occurred when the study is initiated.

A large randomised controlled trial of 519 high risk infants born in two maternity hospitals in South Wales was conducted. Subsequent follow-up²⁶ until seven years showed that the protection afforded by breastfeeding persisted for wheezing (any breastfeeding 22% wheeze; never breastfed 43% wheeze) ($P < 0.001$).

In Canada, researchers assessed the effect of different formulas on atopic disease in a double-blind study of high-risk infants.²⁷ A protective effect of exclusive breastfeeding for four months or longer against atopic disease until at least five years (OR: 0.42 95% CI: 0.20, 0.89) compared to infants fed cow's milk-based or soy formula was apparent. Whey hydrolysate reduced the incidence of atopic symptoms in high-risk infants (OR: 0.32 95% CI: 0.16, 0.65) and this approach appeared beneficial compared to breastfeeding without maternal dietary restriction, or soy-based formula feeding.²⁷⁻²⁸

2. MAKING SENSE OF THE EPIDEMIOLOGICAL EVIDENCE

A number of key issues complicate the interpretation of the available evidence and are often not taken into full and proper consideration. These issues include: low statistical power; misclassification of information; causal pathway modeling; and effect modification (statistical interaction).

2.1 Low statistical power

Asthma and atopy are complex multifactorial diseases and therefore it is inevitable that most single causes (i.e. breastfeeding) will have relatively small effects on overall disease prevalence. On the basis of published meta-analyses, the true relative risk linking breastfeeding to childhood asthma may be 1.2 to 1.3.²⁹ In terms of breastfeeding where a large proportion of infants are exposed to early formula feeding, small odds ratios such as this have public health importance. Consequently, studies that appear large by conventional standards may be under-powered and the interpretation of individual non-significant results may be misleading.³⁰⁻³¹

2.2 Misclassification of information

Both the primary exposure (breastfeeding) and the primary outcomes (asthma, atopic disease, and eczema) are subject to serious potential misclassification, particularly when assessed retrospectively. Study results may be confounded by the early introduction of infant formula as small

amounts of early formula milk may be damaging to the developing infant immune system.

2.3 Causal pathway modeling

A complex disease such as asthma is likely to arise from the action of a series of etiological determinants extended along several complex causal pathways. A given secondary exposure may either be a confounder and therefore we need to adjust for it or may be part of the causal pathway linking the exposure to the outcome of interest and therefore we must not adjust for it. In other words, inappropriate adjustment for determinants lying on a causal pathway of interest may lead to shrunken estimates and inflated standard errors and will reduce an already limited statistical power.

2.4 Effect modification (statistical interaction)

There is the possibility that the association between breastfeeding and asthma and atopy varies at different levels of a key third variable such as the underlying genetic risk of atopy. In fact, evidence would suggest that this may be the case.^{15, 32} Such interactions not only complicate interpretation, but also reduce statistical power.

2.5 Resolving the conflict

Given these considerations for the effect of breastfeeding, we would expect relatively small relative risks with large standard errors. This means that, even if a real association between breastfeeding and asthma/atopy exists many studies will generate non-significant estimates, and a non-trivial proportion will produce estimates that apparently go in the opposite direction. Two complementary solutions to this problem are to 1) carry out meta-analyses²²; and 2) undertake large population-based studies with careful assessment of exposures, outcomes and relevant confounders.

When the exposure is both common and modifiable and the outcome is costly in terms of mortality, morbidity and economics, a small relative risk is of major public health relevance. The putative association between childhood asthma/atopy and breastfeeding unquestionably meets these criteria.

2.6 Causality

Previous studies that have shown a protective effect of breastfeeding on asthma and atopy have fulfilled strict criteria for assessing causality from

observational studies³³, that is biological plausibility, consistency of findings, strength of association, temporality (exposure to breastfeeding before atopy develops) and a dose-response relationship.

2.7 Biological plausibility

A large body of literature on the biochemistry of human milk provides biological plausibility for the hypothesis that breastfeeding protects against the development of asthmatic and allergic symptoms. Breastmilk contains a vast array of beneficial and multifunctional compounds including antimicrobial, immunomodulating and bioactive molecules that may have imprinting and subsequent long-term effects.³⁴⁻⁴⁰ These molecules exhibit pleiotropic functionality⁴¹, are well adapted to infants' mucosal sites and are not well represented in infant formula. Breastmilk is also a rich source of n-3 fatty acids, which have anti-inflammatory effects. It is not currently known which of the many components in milk may account for the protective effect but several mechanisms are likely.⁴¹⁻⁴⁴

3. Mechanisms whereby breastfeeding could impact on asthma and atopic disease

There are five mechanisms whereby breastfed children may show a reduced occurrence of asthma and atopic disease.

3.1 Exposure to foreign dietary antigens

A breastfed infant is less exposed to foreign dietary antigen in cow's milk⁴⁵ although there are antigens in mothers milk. Some exclusively breastfed infants develop allergic reactions to cow's milk protein (β -lactoglobulin)⁴⁶ but the incidence of this is very low (0.5-1.7%) in comparison to the incidence in unselected populations of infants (2%-3%).⁴⁷ Studies in partially breastfed infants might help clarify whether the key factors were derived from foreign proteins or protection from breast milk factors.

The young infant's gut is immature, and may poorly exclude multiple allergens or large quantities of allergens that can react with the system of sensitisation. The benefits of exclusive breastfeeding derive not only from elimination of cow's milk protein but from local protection of human milk in the bowel. For example secretory IgA coats the mucosa and blocks entrance of antigens.⁴⁸

Many children do receive proteins from cow's milk formula in the first days of life that may initiate sensitisation in susceptible individuals.^{45, 49} Subsequent exposure even to minute quantities of β -lactoglobulin in breast-milk may elicit an allergic manifestation that may be associated with IgE mediated adverse reactions.

3.2 Maturation of gastrointestinal mucosa

Human milk contains factors that promote gastro-intestinal mucosa maturation thereby allowing early 'closure' of macromolecular absorption. The most striking interaction between diet and intestinal development occurs immediately following the first feed of mother's milk, and may be due to an expression of genes triggered by milk constituents.

3.3 Gut microflora and reduced sensitivity

By decreasing the incidence of infection and possibly altering the gut microflora that can act as an adjuvant for ingested food proteins, the possibility of sensitisation may be reduced. Control of colonisation of mucosal surfaces by organisms is the most important task of the mucosal immune system. In addition to respiratory microbial agents, the commensal (normal, healthy) microbial flora of the gastrointestinal tract stimulate the functional maturation of the immune system.⁵⁰ This is accomplished through humoral and cellular mechanisms which control the growth of bacterial, viral and parasitic organisms and non-cellular elements. Microbial products of the gastrointestinal flora may activate the antigen presenting mechanism of dendritic cells, polarising towards a Th1 memory.⁵¹⁻⁵² In early life Th1 and Th2 cell populations possess the potential of reversibility towards the alternate cytokine type but the reversibility is lost after long term stimulation by microbes.⁵³ Possible causal pathways are also discussed in detail in Chapters by Ogra, Kramer and Hanson.

Oligosaccharides in human milk may promote the development of bifidus flora by the provision of substrate for *Lactobacillus bifidus*, the 'healthy' bacteria, while limiting the growth of potentially pathogenic bacteria.⁵⁴

Nucleotides in human milk have multiple functions⁵⁵⁻⁵⁷ which include effects on gut microflora⁵⁸, intestinal growth and development⁵⁹ and the response to immunization.⁶⁰

Milk leukocytes survive in the gastrointestinal tract tolerating pH, temperature, osmolarity and resist proteolytic degradation by trypsin. They adhere to the gut epithelium and persist in the intestine for up to 60 hours. It is thought that the ability of milk immunocompetent cells to survive in the gastrointestinal tract, to secrete cytokines and to migrate across the neonatal

intestinal mucosa to the systemic circulation allows them to potentate not only the local response of the gastrointestinal tract but also their systemic immune responses³⁷.

Human milk lipids contain preformed long chain polyunsaturated fatty acids (n-3) in large amounts, which serve as precursors of biologically potent mediators (e.g. the eicosanoids; prostaglandins, thromboxanes and leukotrienes) as well as vital structural components of membrane systems in all tissues.⁶¹ It is thought that fatty acids are important cell signalling molecules⁶² acting rapidly and directly to alter the transcription of specific genes⁶³ involved in inflammation such as IL-1 β . The very long chain fatty acids (EPA and DHA) suppress IL-1 β mRNA, a finding that may be important in asthma prevention.⁶⁴

The fatty acid composition of breast-milk from the mothers of children with newly developed atopic dermatitis was observed to be lower than normal demonstrating an abnormal fatty acid status in atopic subjects.⁶⁵ This may account for some of the inconsistent results from studies of the effect of breastfeeding on the subsequent development of atopic dermatitis⁶⁶ and more recently asthma.⁶⁷ Infants need the correct amount and balance of fatty acids for normal immune system development and an imbalance may lead to hypersensitisation. One study investigated the supplementation of pregnant mothers with fatty acids and subsequent fatty acid in cord blood, and found that fatty acid levels were higher in the cord blood of infants of supplemented mothers.⁶⁸

3.4 Immunomodulatory and anti-inflammatory factors in human milk

Human milk has functional immunomodulatory and anti-inflammatory factors that curtail macromolecular uptake. Breastfed infants appear to have a more effective immune function, reflected by an ability to mount a targeted response to a potential pathogen.⁶⁹ Human milk may have systemic immunomodulating properties⁷⁰ which are long lasting and which may protect against a number of diseases⁷¹⁻⁷⁵ including allergy.⁷⁶ Such clinical and experimental observations suggest that human milk has the ability to modulate the development of the infant's own mucosal and systemic immune systems which may be associated with immunoregulatory agents present in colostrum and mature milk.

Immunomodulating factors in human milk include α -tocopherol, β -casomorphins, prolactin and anti-inflammatory agents. These direct-acting factors protect by non-inflammatory mechanisms, including enzymes that degrade inflammatory mediators. The anti-inflammatory agents in human colostrum and mature milk include lactoferrin, lysozyme, antioxidants,

cytokines, secretory IgA and hormonal factors that down-regulate inflammation³⁴. Specifically, lactoferrin and sIgA inhibit endotoxin induced inflammatory cytokine release.⁷⁷⁻⁷⁸

Mammalian cells have developed an elaborate antioxidant defence system that includes both non-enzymatic antioxidants (e.g. glutathione, vitamins C and E [α -tocopherol] and β -carotene) and lactoferrin as well as enzymatic activities (e.g. glutathione peroxidase, catalase, and other hemoprotein peroxidases) both of which play a significant part in the anti-inflammatory system of human milk.

3.5 Cytokines and growth factors in human milk

Cytokines and growth factors in human milk may play an important role in modulating the development of asthma. The presence of cytokines, hormones and growth factors in human milk play an important role in modulating the development of atopic disease. Cytokines are soluble glycoproteins with established actions on the immune system.⁷⁹ They are pluripotent polypeptides that act in autocrine/paracrine fashions binding to specific cellular receptors, operating in networks and orchestrating immune system development and functions.⁸⁰ See also workshop summary (Chapter 24). Early milk has an abundance of these components at a time when neonatal organ system immaturity exists, suggesting that the bioactive compounds of milk may be important in neonatal development.⁸¹

Human milk contains several known growth factors including Epidermal Growth Factor (EGF) and Transforming Growth Factor (TGF)⁸². Both promote the maturation of gastrointestinal and respiratory mucosa restricting the penetration of harmful antigenic material and contributing to the anti-inflammatory effect of human milk.

4. CONCLUSION

Human milk feeding appears to be of considerable relevance to the development of the immune system in infancy and may therefore impact upon the incidence and severity of subsequent asthma and atopy later in life. As evidenced by the studies that met the strict criteria for the study of breastfeeding and atopic disease, all demonstrated a protective effect of breast-milk feeding or conversely, a risk of formula feeding. However, the continuing protective effect of breastfeeding on asthma and atopy later in adolescence and adulthood has yet to be confirmed in larger longitudinal studies. Because achievements in promoting breastfeeding have been based on consistent scientific evidence, they should not be eroded on the basis of a

few studies that show a negative relation to asthma. It is essential that scientists strive to collect better evidence to support or refute causal associations between breastfeeding and childhood illnesses.

Until more rigorous and more direct evidence is collected, links between breastfeeding and the development of allergic illness in adulthood based on studies in which bias and confounding cannot be controlled and mechanisms have not been investigated, should not be incorporated in public health messages. Given the many benefits conferred by breast-milk, breastfeeding should continue to be promoted as the preferred infant feeding method for the first 6 months and up to two years, as recommended by WHO.⁸³

ACKNOWLEDGEMENTS

This work was supported by a research fellowship grant from the National Health and Medical Research Foundation.

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