

The Link Between Breastfeeding & Asthma - Tenuous or Trustworthy?

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CLINICAL HIGHLIGHTS

- The *Asthma Society of Ireland* reports that the current prevalence of childhood asthma in the Irish population is approximately 15%
- The *World Health Organization* (2002) and the Department of Health and Children in Ireland (2003) recommend breastfeeding for the first six months of life
- 1 out of every 3 Irish mothers breastfeed, at least initially
- High levels of soluble CD14 in breast milk have been suggested to play a pivotal immunomodulatory role in the protection against atopy development
- Breast milk contains Omega fatty acids which are thought to confer protection against atopy by decreasing the synthesis of pro-inflammatory lipid mediators such as prostaglandin E₂

ABSTRACT

Aim: The primary aim of this review was to examine the evidence for and against breastfeeding as a protective factor in the development of asthma in childhood. **Methods:** A literature search was carried out using the PubMed database, yielding 304 papers between the dates of 1-Jan-1999 and 2-Feb-2007. An English language restriction was imposed. Reviewers assessed study quality and extracted data. Relevant data were obtained from Irish, European and international bodies with respect to asthma, the percentage of mothers breastfeeding, and current recommendations for breastfeeding. **Results:** The prevalence of childhood asthma in Ireland is estimated to be 15%, and approximately 30% of children under the age of five have had at least one attack of asthma². Approximately one in three Irish mothers breastfeed, at least initially, and amongst this group 36% did so exclusively³. A number of constituents of breastmilk have been proposed to decrease the risk of asthma, including CD14 and omega fatty acids. A 1995 prospective follow-up study reported that exclusive breastfeeding of greater than one month's duration resulted in a significant reduction in respiratory allergy at age seventeen⁴. Of the four randomized controlled trials (RCTs) analyzed in this review, two reported that exclusive breastfeeding, of at least four months duration, significantly reduced the risk of childhood asthma^{5,6}. A third RCT found no evident link between breastfeeding and asthma⁷, while the final RCT reported that breastfeeding may in fact increase the risk of asthma⁸. **Conclusion:** Given the genetic and environmental variables at play in the phenotypic expression of asthma as a disease, the relationship between breastfeeding and asthma is still somewhat unclear. Four high-quality RCTs yield conflicting results. The World Health Organisation (WHO) and the Department of Health and Children in Ireland both recommend breastfeeding for the first six months of life^{9,10}. These evidence-based recommendations consider the benefits of breastfeeding, including reducing the risk of asthma.

INTRODUCTION

The relationship between breastfeeding, asthma, and other atopic diseases has been researched and debated for many years. In 1988, a landmark paper by Kramer described that year as being the "golden jubilee of [this] controversy"¹. Given the elaborate interplay between genetic, environmental factors and the complex phenotype of asthma as a disease, conflicting studies continue to be published.

The Asthma Society of Ireland reports the current prevalence of childhood asthma in the Irish population at approximately 15%, while an estimated 30% of children under five years of age have had at least one attack of asthma². Recent figures show that approximately 1 in 3 (36.97%) Irish mothers breastfeed at least initially, with greater than 36% doing so exclusively³.

In 1999, Oddy et al reported the incidence of asthma in children aged six was significantly reduced if exclusive breastfeeding continued for at least the first four months of life⁵. Prior to this, in 1995, Saarinen & Kajosaari reported that exclusive breastfeeding of greater than one month's duration resulted in a significant reduction in respiratory allergy at age seventeen⁴. More recently (2002), Kull et al published a study indicating, yet again, that children breastfed for the first four months of life went on to exhibit less asthma in childhood⁶. Severity and duration of episodes of wheeze have also been linked to duration of breastfeeding¹¹. The results of these studies should be carefully balanced with conflicting results from studies conducted by Sears et al¹² and Wright et al¹³, which found no evident link between breastfeeding and asthma. In fact, Sears et al reported that breastfeeding may even increase the risk of asthma.

The aim of this review is to explore the evidence for and against breastfeeding as a protective factor in the development of wheeze and asthma in childhood.

Pathogenesis of Asthma and its links with Atopy

The International Consensus Report describes asthma as a “chronic inflammatory disorder of the airways ...[where,] in susceptible individuals, inflammatory symptoms are usually associated with widespread but variable airflow obstruction and an increase in airway response to a variety of stimuli. Obstruction is often reversible, either spontaneously or with treatment”¹⁴.

The airway wall of patients with asthma is characterized by increased smooth muscle mass, mucous gland hypertrophy and vascular congestion. These changes lead to a thickened airway wall and markedly narrowed airways. The underlying inflammatory process involves the binding of sensitising antigens to Immunoglobulin (IgE) on mast cells. This binding triggers degranulation and the release of inflammatory mediators, such as histamine, proteoglycans and cytokines¹⁵.

According to the Th1/Th2 hypothesis, the immune system is regulated by a balance between T-helper 1 (Th1) and T-helper 2 (Th2) activity¹⁶. Th1 cells stimulate the type-1 pathway (cellular immunity) to fight viruses and other intracellular pathogens. In contrast, Th2 cells stimulate the type-2 pathway (humoral immunity) by increasing antibody production in response to allergen exposure. In extrinsic asthma, there is a shift towards increased Th2 activity¹⁷. This shift is associated with atopic sensitization, causing low to moderate airway inflammation¹⁸ and asthma.

Mechanisms by which Breast milk may decrease the risk of developing Asthma

In theory, factors which affect the Th1/Th2 balance by promoting the Th1 pathway or inhibiting the Th2 pathway could infer protection against the development of asthma.

One factor that may influence the Th1/Th2 balance in children is soluble CD14, a constituent of breast milk¹⁸. CD14, a receptor expressed on macrophages and B-cells, recognizes and binds bacterial cell wall components¹⁹. After such binding, it initiates signal transduction via the Toll-like receptor 4 (TLR4) resulting in increased secretion of IL-12. IL-12 tends to promote a strong Th1 response¹⁹.

High levels of soluble CD14 in breast milk have been suggested to play a pivotal immunomodulatory role in the protection against atopy development^{20,21}. An evaluation of several small scale studies suggested that low soluble CD14 levels in breast milk is associated with development of atopy²². However, studies of large populations are lacking.

In addition, breast milk contains Omega fatty acids¹⁸. Omega-3 (or ω -3) polyunsaturated fatty acids are thought to confer protection against atopy by decreasing the synthesis of pro-inflammatory lipid mediators such as prostaglandin E2 (PGE2)²³. PGE2 is known to enhance the synthesis of Th2-like cytokines and IgE antibodies as well as inhibiting the differentiation of Th1-like lymphocytes²³. Hence, by blocking PGE2, ω -3 polyunsaturated fatty acids may favor a Th1 immune response and reduce atopy²³.

Breast milk also contains the ω -6 fatty acids gamma-linolenic acid (GLA) and di-homo-gamma linolenic acid (DGLA), both thought to reduce the risk of asthma²⁴. GLA and DGLA can be converted by inflammatory cells to 15-(S)-hydroxy-8, 11, 13-eicosatrienoic acid and prostaglandin E1(PGE1) compounds, which possess anti-inflammatory and anti-proliferative properties²⁵. It is notable that neither cow nor soy milk contain significant GLA.

The ratio of ω -3 to ω -6 fatty acids can also affect the Th1/Th2 response. A higher ratio of ω -6 to ω -3 long chain polyunsaturated fatty acids favours a Th1 response, and vice versa²⁴. Because breast milk is rich in ω -6 fatty acids (Table 1), the protective effect of breast feeding against atopy might be attributed to its high content of these beneficial fatty acids. In addition, these fatty acids form precursors to various eicosanoids, which also have influences on Th1 and Th2 responses²⁴.

Table 1. Polyunsaturated fatty acid composition of mature human milk²⁴

Fatty Acid	Type of Fatty Acid	%wt/wt
Linolenic acid (18:2)	ω -6	10.76
γ -Linolenic acid (18:3)	ω -6	0.16
Dihomo- α -linolenic acid (20:3)	ω -6	0.26
Arachidonic acid (20:4)	ω -6	0.36
α -Linolenic acid (18:3)	ω -3	0.81
Eicosapentaenoic acid (20:5)	ω -3	0.04
Docosapentaenoic acid (22:5)	ω -3	0.17
Docosahexaenoic acid (22:6)	ω -3	0.22
Total ω -6 PUFAs		11.54
Total ω -3 PUFAs		1.24
Total ω -6 PUFAs / Total ω -3 PUFAs		9.31

PUFA: Polyunsaturated fatty acid

Mechanisms by which Breast milk may increase the risk of developing Asthma

It has been hypothesised that exposure to bacteria in early life promotes dendritic cell maturation and stimulates the production of IL-12, provoking a Th1 response⁸. According to the TH1/TH2 hypothesis, this exposure would be expected to decrease the risk of developing asthma later in life.

Exclusively breast fed infants have been found to have lower levels of Gram negative enterobacteria in their gastrointestinal tract²⁶ and less of a diversity of colonizing species²⁷. These infants may experience less dendritic cell maturation and IL-12 production which, consequently, may result in an under-developed Th1 response. In other words, breast fed infants who have had less exposure to bacteria in early life may experience greater Th2 responses and increased risk of asthma.

What if the breastfeeding mother is an Asthmatic?

Breast milk from women with asthma has been found to contain higher levels of IL-4, IL-8 and IgE¹³. All of these compounds are thought to induce sensitisation to allergens, thereby increasing the risk of developing atopy¹³.

A prospective, longitudinal study of 1246 newborns, in their first 2 years of life, determined that exclusive breastfeeding was associated with a significantly lower rate of wheeze irrespective of concomitant maternal asthma²⁸. However, by age six, exclusive breastfeeding was actually related to a higher rate of asthma in children of mothers with asthma²⁸. On the other hand, an Australian study found no statistically significant association between maternal asthma and the development of asthma in breastfed children²⁹. Taken together, these studies have been interpreted as displaying an overall protective effect of breastfeeding on the development of atopy and asthma in early childhood, indicating breastfeeding should be encouraged, even by mothers with asthma^{7,30}.

Does the duration of breastfeeding have any effect?

In one Swedish prospective study, infants breastfed for four months, or more, were less likely than those not breastfed to develop wheeze, asthma, atopic dermatitis and multiple allergic manifestations, at age two years⁶. An additional protective effect was seen in children with a family history of atopy who were breastfed for 6 months⁶. Furthermore, a German prospective study found that a longer duration of breastfeeding decreased the risk of asthma in early childhood³¹. The beneficial effects of breastfeeding might be further supported by high levels of soluble CD14 in breast milk³¹.

Selection of studies and extraction of data

Using the keywords 'Asthma' and 'Breastfeeding', a preliminary search on the Pubmed database yielded 304 papers published in English between the 1-Jan-1999 and 2-Feb-2007. The search was subsequently narrowed by selecting cohort studies done in developed countries, and by applying the criteria proposed by Kramer et al¹ for appraisal of the studies concerning the effect of breastfeeding on development of atopy (Table 2).

Table 2. Kramer Criteria¹

(1) Exposure
<ul style="list-style-type: none"> • Non-reliance on late maternal recall of breastfeeding • Blind ascertainment of infant feeding history • Sufficient duration of breastfeeding • Sufficient exclusivity of breastfeeding
(2) Outcome
<ul style="list-style-type: none"> • Strict diagnostic criteria • Blind ascertainment of outcomes • Consideration of severity of outcomes • Consideration of age of onset of outcome
(3) Statistics
<ul style="list-style-type: none"> • Control for confounding • Assessment of dose-response effects • Assessment of effects in children at high risk of outcome • Adequate statistical power

The result was four Randomised Control Trials (RCTs). Two of the studies concluded that breastfeeding had a protective effect in the development of asthma; Oddy et al^{5, 32} (Australia) and Kull et al⁶ (Sweden). Similarly, two studies concluded that breastfeeding had no such protective effect; Sears et al¹² (New Zealand) and Wright et al¹³ (USA).

The studies fulfilled the Kramer criteria but differed in the age of the children at the end of follow-up. The Oddy et al^{5, 32} and Kull et al studies conducted follow-up until 6 and 2 years, respectively, while Sears et. al. and Wright et. al. until 26 and 13 years, respectively. In addition, Oddy, Kull and Wright studied infants exclusively breastfed for ≥ 4 months, Sears studied infants with duration of breastfeeding of ≥ 4 weeks.

It was decided to compare the outcome of breastfeeding on development of asthma in the samples as a whole rather than concentrating on high risk groups – for example, those with a family history of atopy. The term 'non-exclusively breastfed' was used to include both partial and non-breastfed infants. Diagnostic criteria defined asthma as that diagnosed by a physician, rather than a recurrent wheeze reported by parents, and was applied to all four studies.

Table 3. Characteristics of 4 RCTs which show the relationship between breast feeding and childhood asthma

Study	Country	Sample size	Age at follow-up	% EBF developing asthma	% NEBF developing asthma	p value
Oddy et al	Australia	2012	6	7.8	10.6	0.029
Kull et al	Sweden	1246	2	7.7	12	<0.05
Wright et al	USA	1043	13	16.5	12.2	<0.05
Sears et al	New Zealand	1037	26	9	2	0.0008

EBF= exclusively breastfed, NEBF = non-exclusively breastfed

DISCUSSION

The discrepancy between studies is difficult to interpret, with many methodical difficulties to overcome in research of this kind.

The standard measure of statistical significance in most medical research is defined as $p \leq 0.05$. Taking this into account, all the trials reviewed were statistically significant. However, although a $p \leq 0.05$ implies a statistical difference, it does not quantify or qualify whether the difference is a large one or if it is clinically significant.

Asthma is a multifactorial disease. The studies adjusted their data to account for confounding variables such as genetic predisposition, socio-economic status and other environmental factors.

Many of the infants in the studies would have been exposed to cow’s milk formula at some stage in their infancy. The potential effect of this exposure on the development of asthma was discounted as negligible in the studies.

To summarize, Oddy et al concluded that introduction of milk other than breast milk increased the risk of developing asthma, while prolonged breastfeeding had a protective effect. Similarly, Kull et al found that infants exclusively breastfed had a lower risk of developing asthma. In fact, they found that even partial breastfeeding (> 6months) was protective, especially in infants with atopic heredity.

Conversely, Wright et al concentrated on the children of atopic mothers and, in this group, any breastfeeding was found to increase the child’s risk of developing asthma. Sears et al found that breastfeeding in all groups (including children with a family history of atopy) was associated with a higher incidence of asthma.

CONCLUSION

Asthma is a condition that affects 15% of Irish children and is characterised by airway inflammation, reversible airflow obstruction and hypersensitivity of airway walls. Breastfeeding is postulated to influence the immunological balance between Th1 and Th2 responses in many ways, some of which may contribute to the atopic sensitisation of airways seen in childhood asthma. Nevertheless, some studies have shown breastfeeding to confer no benefit at all and, in some cases, even an increased risk of asthma in childhood.

In 2003, the World Health Organisation (WHO) published the "Global Strategy on Infant and Young Child Feeding", which recommends exclusive breastfeeding for the first six months of life⁹. Shortly after this, the Department of Health and Children in Ireland published a press release¹⁰ endorsing these WHO recommendations for exclusive breastfeeding in the first six months of life. While these recommendations provide no definitive conclusion to the debate over breastfeeding and asthma they serve to remind readers that there are a myriad of other benefits associated with breastfeeding.

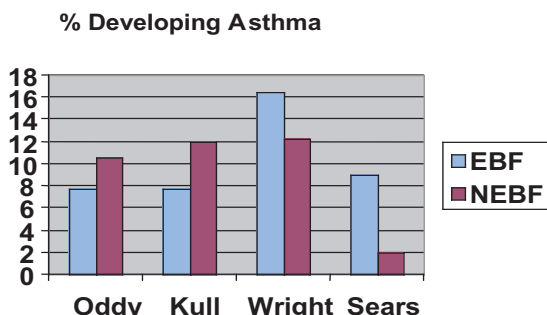


Figure 1: The relationship between the development of asthma & exclusive/non-exclusive breastfeeding.

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