ideally need support from prospective trials.

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Breast feeding and childhood asthma

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Asthma is the most chronic disease of childhood and the leading cause of morbidity in children globally as measured by emergency department visits, hospitalisations and days of missed school.[1] Susceptibility to asthma may be increased by factors present early in life, including low birth weight, preterm birth, young maternal age and male gender. Environmental allergens including household smoking, house dust mite, grasses or pollens are also implicated. Conversely, early exposure to respiratory infections may be protective, although certain infections are suspected to increase the risk. Against this complex aetiological background, there is some evidence that breast feeding may protect against the development of asthma in children.[2 3]

In this issue of *Thorax*, a birth cohort study by Scholtens and colleagues assesses whether the association between breast feeding and asthma measured longitudinally from 1 to 8 years of age is influenced by maternal and paternal allergy (***see page 604***). The main finding of the study confirmed that breast feeding for >16 weeks was significantly associated with reduced asthma prevalence from 3 to 8 years without evidence of attenuation and regardless of family history.[4]

The study population consisted of 3963 Dutch children born in 1996/1997 who participated in the Prevention and Incidence of Asthma and Mite Allergy (PIAMA) birth cohort study and who were followed every year for 8 years. Asthma was defined as at least one attack of wheeze and/or dyspnoea and/or prescription of inhalation steroids in the last year. Chronic asthma was defined as asthma diagnosis at 8 years with asthma diagnosis in at least two other years. Specific immunoglobulin E (IgE) to common airborne allergens and bronchial hyper-responsiveness were measured according to a standard protocol. Breast feeding was measured at 3 months and at 1 year, and was defined as the duration of any breast feeding (no breast feeding, 1–16 weeks breast feeding and breast feeding for >16 weeks). In this study, the investigators took advantage of the longitudinal analytical method of generalised estimating equations (GEE) to study the associations between breast feeding and repeated measures of the respiratory outcomes every year until 8 years of age. Adjustment was made in all models for child age, gender, maternal and paternal allergy, maternal education and smoking during pregnancy, as well as current parental smoking. In addition, the analysis was stratified by maternal and paternal allergy. Missing data were imputed several times because 10% of baseline data were missing in this study and imputation did not make any difference to the final outcome of the study.

Scholtens and colleagues found that asthma risk was lower in children breast fed for >16 weeks compared with those not breast fed. Children breast fed for the longer duration had significantly fewer chronic asthma symptoms, and having an allergic or non-allergic mother did not change these associations. Breast feeding for >16 weeks was inversely associated with sensitisation to airborne allergens at 8 years, although this was not significant, and there was no association observed for bronchial hyper-responsiveness. From ages 3 to 8 years, breast feeding was associated with a lower asthma risk at all years, and maternal or paternal allergy did not affect the association between breast feeding and asthma. Because breast feeding has been associated with protection against early respiratory infections,[5] the observed association between breast feeding and asthma at early ages may be mediated by the protection against infections afforded by breast feeding. Although breast feeding is shown to be protective against lower respiratory tract infection during infancy, such protection has not been demonstrated for asthma in all studies. Issues pertaining to study design, analytical methods and theoretical problems such as confounding have greatly complicated the interpretation and comparison of studies. Furthermore, asthma has a complex phenotype in which numerous genetic and environmental

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determinants interact. Consequently, the effect of any single determinant is likely to be small and the independent effects difficult to quantify. However, because asthma is so common at a population level, and because breast feeding is amenable to intervention, a relatively small effect may well have important implications for public health. Therefore, it is important to establish whether breast feeding does modify the risk of developing childhood asthma, even if the effect is relatively small. In the PIAMA study, the repeated measures analysis (GEE) showed that a lower risk of wheeze and asthma was apparent for all years from 1 to 8 years, although not significantly at each year, and asthma, wheeze and dyspnoea did not decrease by 8 years of age, suggesting that breast feeding had an effect on the long-term outcomes of asthma. Strengths of the study were the longitudinal design and follow-up until 8 years of age, with ongoing data collection, a large study population and low attrition rate, as well as multiple imputation making efficient use of the available data.

Breast feeding is highly recommended for all infants irrespective of atopic heredity,[6] although epidemiological studies provide conflicting results in the debate as to whether breast feeding can have a role in protection against asthma and allergic disease in young children. The issues of breast feeding with other factors may not have been considered in these previous studies. The protective effects of breast feeding on asthma have been reported for young children,[2 3 7] but other studies of children at high risk,[8] at low risk[9] or of adults[10 11] have shown no such effects. One recent study[12] found that a longer duration of breast feeding favourably influenced lung growth in children, with minimal effects on airflows of children from non-asthmatic mothers; however, in the presence of maternal asthma, a longer duration of breast feeding was associated with decreased airflows. The assumption that breast feeding protects against asthma has been cast into doubt from these studies.

Nevertheless, there are a number of biologically plausible mechanisms through which breast feeding may impact on the aetiology of asthma. For example, there may be interactions of asthma with overweight with a shorter duration of breast feeding, in addition to overweight significantly increasing the risk for asthma as seen in one study (odds ratio 1.81: 95% CI 1.11 to 2.95).[13] Furthermore, there is evidence that breast feeding protects against wheeze in infancy, and several components of human milk have been postulated as conferring this effect. Breast milk may provide an immediate line of defence against infectious agents, which compensates directly for the immaturity of the newborn immune system to resist infection. Protection may also be through the myriad of factors in milk, including bioactive enzymes, hormones, growth factors, cytokines and immunological agents, which augment and stimulate the development of the immature host defence.[14] Early milk has an abundance of cytokines at a time when neonatal organ systems are immature, suggesting that these bioactive components of milk may be important in neonatal development.

Animal and human studies suggest that the bioactive components in milk contribute to the protective effects of breast milk. Investigators in a recent murine study examined the role of transforming growth factor β (TGFβ) in milk by exposing lactating mice to an airborne allergen and assessed the development of asthma in the progeny. They found that breast feeding-induced tolerance relied on the presence of TGFβ during lactation, and was mediated by regulatory $CD4^+$ T lymphocytes and depended on TGFβ signalling in T cells.[15] The data showed that airborne allergens could be transferred from mother to newborn through breast milk and that this exposure could induce antigen-specific tolerance in the offspring, resulting in protection against allergic airway disease. The authors concluded that breast milk-mediated transfer of an antigen and TGFβ to the neonate resulted in oral tolerance induction and antigen-specific protection from allergic airway disease. This report provides new insights into the mechanisms underlying tolerance induction in neonates and pinpoints a maternal influence through breast milk-mediated antigen transfer as a crucial factor in this process. In addition, the amount of TGFβ in maternal milk has been shown to be less in mothers with atopic disease.[16 17] Overall, these and other findings[18] suggest that this particular cytokine in milk may influence the development of atopic disease.

The results of the PIAMA birth cohort study measured over 8 years and using a repeated measures analysis correspond to the results of many other studies on breast feeding and asthma and is in agreement with the findings from animal studies. Because a modern birth cohort study design with repeated measures analysis was used, the authors were able to show that breast feeding was protective against asthma throughout the years of early childhood both with and without a family history of asthma or allergy. This interesting study contributes to the debate related to breast feeding and childhood asthma.

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