Is asthma prevention possible with dietary manipulation?

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ABSTRACT

What we know

- Primary prevention of asthma should be possible because the recent increase in asthma is due to environmental factors.
- The major modifiable dietary environmental risk factors for childhood asthma are lack of breastfeeding and low intake of omega-3 fatty acids.
- Randomised controlled trials (RCTs) have shown that interventions using probiotics, hydrolysed milk formulas, and combined dietary manipulation plus airborne allergen avoidance reduce asthma and/or atopy in newborns.
- Observational studies have shown a 30%–50% reduction in childhood asthma with exclusive breastfeeding for three months, and similar reductions in children who eat fish regularly (ie, have a high intake of omega-3 fatty acids).

What we need to know

- Will further RCTs using intervention with probiotics reveal identifiable subgroups of children who respond and children who do not respond?
- Will supplementation of the diet with omega-3 oil reduce the rate of significant clinical atopic disease, particularly asthma? If so, for how long will supplements need to be given?
- Will effective primary prevention require multiple intervention strategies? If so, how feasible are these as public health interventions?
- What are the benefits and harms of allergen-avoidance diets in high-risk women who are breastfeeding?
- Can protein hydrolysate formulas reduce rates of atopy and/or asthma?

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ALTHOUGH MOST PUBLISHED REPORTS on asthma prevention deal with tertiary prevention (ie, reducing morbidity in established asthma with the use of preventive agents such as inhaled corticosteroids), there is increasing interest in primary prevention (ie, the prevention of asthma in those genetically "at risk").

Logically, primary prevention should be possible given that asthma results from a complex interaction between genetic susceptibility and environmental risk factors, rates of childhood asthma are increasing,[1,2] and therefore the recent increase must be due to environmental factors rather than a change in genetic susceptibility. If we can identify the modifiable environmental risk factors that have led to increasing rates of asthma, then primary prevention should be possible. Peat and Li[3] have developed a useful classification of these risk factors (see Box 1).

A number of randomised controlled trials (RCTs) have been conducted to test the hypothesis that primary asthma prevention is possible. However, a major problem with these studies has been the difficulty of accurately defining asthma in children under five years of age.[4] Further, most of the RCTs are recent and have had limited follow-up. Therefore, the focus has been on measuring outcomes that are assumed to be on the causal pathway to asthma rather than assessing rates of actual asthma. These outcomes have included the development of atopy (as defined by positive allergen skin-prick testing or detection of specific IgE) or the development of clinical atopic disease, particularly atopic dermatitis/eczema.

What is known?

Primary prevention

Most reported RCTs of primary asthma prevention use a "high-risk" selection strategy rather than a population-based strategy[5] (ie, the subjects recruited have been identified as being at high risk of asthma, usually on the basis of a positive family history of asthma and/or atopy). Moreover, since the development of clinical atopy occurs in early life, studies have either recruited the subjects *in utero* (during the last trimester) or during the neonatal period.

A meta-analysis of maternal dietary allergen avoidance during pregnancy to prevent atopic disease in infants at high risk concluded that such avoidance is "unlikely to substantially reduce the risk of atopy in the child. Moreover, such a diet may have an adverse effect on maternal and/or fetal nutrition".[6] This meta-analysis was based on three RCTs involving a total of 504 women. Although several trials suggested a lower incidence of positive allergen skin-prick testing initially, by the age of 18 months there was no benefit. Given the potential harm to the fetus (lower mean gestational weight gain), elimination diets during pregnancy are not recommended.

Another meta-analysis of three RCTs, involving a total of 209 women, assessed the efficacy of a maternal allergen-avoidance diet during lactation for preventing atopic disease in infants of women at high risk.[7] Combined data from these trials suggest a strong protective effect on atopic eczema during the child's first 12–18 months of life. However, the author of the review noted substantial methodological weaknesses in all three trials.

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1: Risk factors for childhood asthma (modified from Peat and Li[3])

Factors that identify "high-risk" children

Family history/genetic markers
Ethnicity, affluence, socioeconomic status
Male sex

Factors that provide insight into mechanisms

Early infections ("hygiene hypothesis")
Vaccination status and antibiotic use
Exposure to other children (eg, number of siblings, shared bedroom, daycare attendance)
Perinatal factors
Preterm birth
Head circumference (HC), birthweight (BW) and HC:BW ratio
Maternal age (very young or very old)

Factors that have potential for primary prevention

Indoor allergens:
Beds, pillows, floor coverings, pets
Dampness or mould
Heating, ventilation, house construction
Parental smoking:
Prenatal and postnatal exposures
Lack of breastfeeding:
Time of breast-feeding cessation
Timing of introduction of cow's milk and cereals
Dietary fatty acids:
Omega-3 fatty acids (eg, from fish and polyunsaturated foods)

The role of protein hydrolysed formulas on the development of atopy and asthma remains uncertain, and further studies are warranted. In a relatively small RCT (involving 177 subjects), early feeding of a protein hydrolysate (casein hydrolysate, "Pregestimil") formula to infants at risk of allergies had a long-term preventive effect on the prevalence of eczema, but not of asthma.[8]

The role of exclusive breastfeeding in protecting against asthma is controversial. Although most studies have shown a protective effect, several have found an increased rate of asthma in breastfed infants. A systematic review of prospective studies[9] identified 12 relevant studies of adequate methodological quality. The summary odds ratio for the protective effect of at least three months' exclusive breastfeeding was 0.70 (95% CI, 0.60–0.81), indicating a 30% reduction in the development of childhood asthma. This protective effect was even greater in children with a family history of atopy (50% reduction). These results indicate a valid and important protective effect of breastfeeding on subsequent development of asthma.

Dietary supplementation with probiotics has shown encouraging results. In a double-blind, randomised, placebo-controlled trial, *Lactobacillus* (given prenatally to mothers and then postnatally for six months to their infants) resulted in a 50% reduction in the rate of atopic eczema at the age of two years (23% v 46%).[10] As no definitive information concerning asthma can be derived at this early stage, the long-term results of this trial will be awaited with great interest. A key factor with probiotic intervention is that it does not cause any harm. Indeed, probiotics almost certainly result in a more "friendly" gut flora, which may have other beneficial effects on health apart from reducing rates of atopic disease.

Two RCTs have examined combined dietary manipulation and airborne allergen avoidance.[11,12] The Isle of Wight study[11] involved 120 "at risk" infants randomly allocated during pregnancy to an intervention group or a control group. The intervention group were either breastfed (with mothers excluding foods regarded as highly allergenic from their diet) or given a soy-based protein hydrolysate. In addition, exposure to house-dust mites was reduced by encasing the child's mattress and treating the home with an acaricide four times during the first nine months of life. The combined intervention resulted in a significant reduction in the rate of eczema and atopy (sensitisation to both dietary and aeroallergens) at four years of age. The rate of doctor-diagnosed asthma was also lower (24% v 35%), although this was not statistically significant. Clearly, this is an encouraging result and should be repeated in other countries, using larger numbers, and with prolonged follow-up of the subjects.

The second combined intervention RCT was conducted in Vancouver, Canada.[12] This examined the effectiveness of a multifaceted intervention. A total of 545 "high-risk" infants were prenatally randomly assigned to either a multiple intervention group or a control group. The intervention involved avoidance of house-dust mite, pet allergens and environmental tobacco smoke; encouragement of breastfeeding; and supplementing the diet with a partially hydrolysed formula. The result of the intervention was a modest but statistically significant ($P = 0.04$) reduction in the risk of *possible* or *probable* asthma and rhinitis at the age of 12 months. The incidence of positive allergen skin-prick tests to one or more aeroallergens was similar in both groups (4.4% in the intervention group v 4.6% in the control group). Clearly, more prolonged follow-up of these infants will be essential to determine whether these differences in possible or probable asthma persist.

In the western suburbs of Sydney, a large placebo-controlled RCT (involving about 600 "high-risk" newborns recruited in pregnancy) is now in progress.[13] The design is factorial, allowing two interventions to be evaluated in the one trial: a dietary supplement (omega-3 fatty acid) and comprehensive house-dust mite avoidance measures. Although this trial is only in its early stages, initial results show an impressive reduction in Der p 1 (dust mite) exposure levels in the intervention groups, plus good compliance with taking the omega-3 fatty acid supplement. When the children are old enough (ie, 5–6 years) for reliable medical outcome measures of asthma rates, this trial will supply definitive data on the effectiveness of omega-3 fatty acid supplementation alone and in combination with house-dust mite avoidance measures in the Australian environment.

In summary, RCTs have shown a consistent protective effect of a variety of dietary manipulations on subsequent asthma and/or atopy (see Box 2). Studies combining dietary manipulation with reduction in airborne allergen exposure

2: Recommendations for dietary measures to reduce asthma and/or atopy (with levels of evidence[14])

- Cease strict elimination diets during pregnancy (Level I)
- Ideally, exclusively breastfeed for 3–4 months (Level III)
- Consider *Lactobacillus* probiotic supplements (before and after delivery)* (Level II)

If breastfeeding is not possible:

- Consider supplementing infant with omega-3 fatty acids (Level III)
- Consider *Lactobacillus* probiotic supplements* (Level II)
- Consider protein hydrolysed formula (for 6–12 months)* (Level II)

*Data relate to atopy only, not asthma.

suggest added protection. However, longer follow-up of the children in all these studies is essential to determine the long-term benefits of these preventive measures on rates of childhood asthma.

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