

Dietary prevention of allergic disease in children: Are current recommendations really based on good evidence?

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We provide a critical appraisal of the literature on the effects of dietary prevention of atopic disease in children. In our view, currently available studies suffer from lack of blinding which is a major problem if the primary end point is subjective (such as the diagnosis of eczema). In addition, long-term follow-up suggests that atopic symptoms are delayed rather than truly prevented, and that only the mildest cases are prevented (or delayed). Although it has been reported that cow's milk allergy is truly prevented by dietary interventions in early life, this has never been demonstrated by double-blind placebo-controlled food challenges. No studies to date have shown effects of hypoallergenic formulae on objective markers of atopic sensitization, such as specific IgE levels. Finally, there is no universally accepted pathophysiological mechanism which could explain the usefulness of hypoallergenic formulae in allergy prevention. In conclusion, we feel that the currently available evidence on the allergy preventive effects of hypoallergenic formulae is insufficient to justify blanket advice being given to 'high risk' families. Such advice gives parents the hope that they can actually prevent allergy in their children which may not be justified. A cautious approach in advising interventions with hypoallergenic formulae to prevent allergy in high-risk infants is warranted.

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With the rising prevalence of atopic diseases in the Western world in the last decades of the 20th century, the importance of prevention of allergy has been increasingly recognized (1, 2). A number of randomized controlled trials on the dietary prevention of the development of atopic diseases in early childhood have been completed, and reviews of these studies conclude that such interventions are useful and effective in preventing childhood atopic disease (3–7). A Cochrane systematic review showed a relative risk of 0.57 for atopic eczema (AE) in babies receiving hypoallergenic formula as compared with those fed cow's milk formula (95% CI 0.44–0.73), with a number needed to treat of 6 (8).

A working group of the Section of Pediatrics of the European Academy of Allergy and Clinical Immunology (SP-EAACI) has concluded that 'a dietary regimen is unequivocally effective in the prevention of allergic disease in high-risk infants' (3). This regimen consists of breastfeeding combined with avoidance of solid foods and cow's milk for the first 4–6 months of life. If breastfeeding is insufficient or impossible, a hypoallergenic formula is recommended (3).

Although these recommendations are presented as firmly evidence-based, the SP-EAACI working group commented that the existing studies on dietary prevention of allergy have methodological shortcomings. These include

differences between studies in criteria of hypoallergenicity and in diagnostic criteria and intensity of atopic disease, lack of control for confounding factors, and insufficient adherence to the dietary avoidance programme (9, 10).

In this paper, we will argue that additional methodological issues, in particular problems in blinding of the study formula to parents and study staff, may limit the validity of the available evidence. Even if this is not considered to be of major importance, the results of most studies suggest that symptoms of allergic disease are postponed rather than prevented. No studies have been able to show objective supportive evidence of reduction of allergic sensitization. Furthermore, it is likely that prevention will primarily target the mildest cases of atopic disease, the importance of which is questionable. Finally, a universally agreed pathophysiological mechanism supporting dietary prevention appears to be missing.

Based on these issues, we feel that dietary prevention of allergy has not been unequivocally demonstrated to be effective, and that parents should be counselled with great caution in this area.

Methodological problems, in particular lack of blinding

A number of studies on dietary prevention of allergic disease are not designed in a blinded fashion. Eleven out of 18 studies in the Cochrane review on hypoallergenic formulae for prevention of allergy in infants included blinded assessment (8). Even when assessments are reported as 'blinded', however, unblinding of the study team is a potential source of bias. In studies in which patients or parents know what treatment (or formula) is being received but the examiner does not ('single blind' design), the odds of unblinding of the examiner by inadvertent disclosure by patient or parent are high (11). Such unblinding of the study team has been implicated as a flaw in a systematic review of the effects of maternal diet during lactation in allergy prevention (12). An illustration of this mechanism comes from a long-term study of a multifaceted intervention strategy, which was unblinded. At the age of 7 yr, the doctor's diagnosis of asthma was quite dramatically reduced in the intervention group as compared with the control group (15% vs. 23%), but there were no differences in objective markers (such as atopic sensitization or bronchial hyperresponsiveness) between the two groups (13). Apparently, physicians are less likely to diagnose atopic disorders when the child has been enrolled in a programme to prevent allergy.

Even when studies claim to be *double blind* (i.e., both parents and examiners are unaware of which formula the child is receiving), and study formulae are delivered in identical canisters, the large differences in taste and smell between hypoallergenic and standard infant formulae and between different hypoallergenic formulae will inevitably cause unblinding amongst parents and presumably also of the study team. It has been shown that blinded volunteers and professional taste panellists can distinguish different formulae based on their smell and taste (14, 15).

Prevention or delay?

Although hypoallergenic formulae are intended to *prevent* the development of allergy, results so far are more consistent with the hypothesis that symptoms of allergic disease are delayed rather than prevented. Studies with repeated follow-up invariably show that the effects of intervention with hypoallergenic formulae are strongest during the first year of life, and become smaller with follow-up until school age (8). Although delay of atopic symptoms may be useful, it is less desirable than true prevention.

A number of studies examined the preventive effects of hypoallergenic formulae on cow's milk allergy (CMA), without any co-intervention (16–22). The SP-EAACI working group review concludes that CMA is truly prevented (and not just delayed) by dietary intervention in early infancy (3). In none of these studies, however, was CMA diagnosed by double-blind, placebo-controlled food challenges (DBPCFC). In some of these studies, food challenges were not carried out at the end of the study period (16, 17). In most studies, open challenges were used to diagnose CMA (18, 19, 21, 22), which are known to carry a high risk of false positive results (23). In these studies, DBPCFC were only performed when the results of open challenges were equivocal. Only one study used DBPCFC in all cases, but the author of this paper was later unmasked as fraudulent (20). In the absence of systematic double-blind food challenges, it remains unclear whether the beneficial effects on symptoms are due to true prevention of allergy or to treatment of existing CMA.

Although allergic sensitization *per se* does not reflect allergic disease, reduction of allergic sensitization would be supportive evidence of the efficacy of dietary interventions in preventing allergic disease. A number of studies examined the effects of hypoallergenic formulae (without any other co-intervention) on allergic sensitization (skin prick test or specific IgE levels in

blood) (16–20). According to the Cochrane review, some of these studies suffered from major methodological flaws concerning randomization and allocation concealment (8). One of these studies only reported specific IgE levels in those children with clinically suspected CMA (which was not confirmed by DBPCFC) (19). Thus, the effect of the intervention on atopic sensitization rates *per se* were unknown in this study. The other study reported a 50% reduction of sensitization rates at the age of 5 yr in children fed partial whey hydrolysate (20), but the conclusions of this paper were later drawn into question because the author of this paper was unmasked as fraudulent (24). The three remaining studies found no effect of intervention with hypoallergenic formulae on atopic sensitization (16–18).

Only the mildest cases are prevented

The results of prevention studies with hypoallergenic formulae are most impressive for symptoms of AE, with an almost 50% reduction during the first year of life (8, 21). Given the fact that the distribution of severity of AE in the population is highly skewed, with most cases of AE at the mildest end of the spectrum (25), it can be assumed that any intervention aimed at preventing the development of AE will involve the mildest cases of eczema. The usefulness of preventing such very mild cases of AE, which can be easily managed with skin care advice and intermittent use of steroid ointments (26, 27), and which carry a favourable long-term outcome (28), has never been weighed against the effort involved and against the possible side effects of such an intervention (29). More specifically, it can be argued that treating six infants at risk for prolonged periods of time with a hypoallergenic formula to delay the skin manifestations of one case of mild AE are not worth the effort.

Obviously, preventing more serious cases of eczema would be worthwhile. Scoring the severity of eczema (rather than just recording the presence or absence) in studies of allergy prevention is therefore advisable (10). Until now, no such data have been published. In the large German study of prevention of allergy with different hypoallergenic formulae, it was stated that the severity of eczema was recorded with a scoring system, but the results of eczema severity were not presented; only the presence of eczema was analyzed (21). The only study with data on reduced eczema severity in children receiving hypoallergenic formula (20) cannot be appraised because the author was unmasked as fraudulent (24).

No universally accepted pathophysiological explanation for effects of hypoallergenic formula in preventing atopic disease

The usual pathophysiological explanation for the development of atopic disease is that exposure causes sensitization, and that sensitization is a major risk factor for disease (9). Recent studies have shown, however, that there is no direct link between early life exposure and atopic disease in later life, neither for inhaled allergens such as house dust mite (30) or for food allergens during the first days of life (31). Sensitization may already be demonstrated in early life, and this may be due to prenatal exposure or to inadvertent postnatal exposure to the relevant allergens (9). Furthermore, it has been shown that not only sensitization, but also clinical reactivity to common allergenic foods on the first known exposure may develop in children avoiding these foods (32–34).

Other observations raise the possibility that the absence of exposure to a given allergen does not affect the prevalence of allergic disease, but only causes sensitization to shift to another allergen. For example, the rates of allergic asthma in Tucson, Arizona, where house dust mite is not found in the environment, are the same as in other parts of the world where house dust mites flourish. In the Tucson population, *Alternaria* takes the place of house dust mite as principle asthma associated environmental allergen (35). Similarly, whilst Australian children living in the coastal area become sensitized to house dust mite and children living inland to pollen, the prevalence of bronchial hyperresponsiveness and asthma in the two areas is comparable (36). These observations suggest that whilst exposure plays a role in developing sensitization to that allergen, prevention of exposure to a certain allergen does not prevent either sensitization to other allergens or the development of atopic disease. Studies of prevention of allergic disease by avoiding cow's milk should thus ensure that lower prevalences of clinical reactivity to one food (such as cow's milk) is not offset by higher prevalences to other foods (such as egg or peanut) or to inhalant allergens. None of the available studies have addressed this issue.

Current knowledge suggests that immunological events in early life involving regulatory T cells determine whether or not atopy is likely to develop (37, 38). It is unclear how feeding high-risk infants hypoallergenic formulae could influence this process. Another possible explanation would be the induction of oral tolerance to certain foods, but tolerance induction by hypo-

allergenic formulae has never been demonstrated *in vivo*. The limited available evidence appears to suggest that it is controlled *exposure* rather than avoidance that can induce oral tolerance (39, 40). It has even been suggested that long-term avoidance of cow's milk can increase the likelihood of anaphylaxis upon re-exposure (41, 42).

Conclusion

We feel that the methodological problems in the available studies (in particular with blinding) and the lack of a universally accepted pathophysiological mechanism urge for caution before translating the results of dietary prevention studies into blanket advice for whole populations at risk. Even if one considers the studies performed to be valid, the effects of hypoallergenic formulae on the development of allergy in children appear to be limited to delaying the skin manifestations of AE during early life. Although prevention of CMA has also been reported this has not been confirmed by DBPCFC. It is likely that the preventive effect of hypoallergenic formulae on atopy involves only the mildest cases.

The current practice of giving blanket advice to children from atopic families gives parents the hope that they can actually prevent the development of atopy in their children. Based on a number of issues, we have argued that this may not be justified. We feel that counselling parents on the limitations of the current scientific knowledge in this area, and a cautious approach in advising interventions with hypoallergenic formulae in high-risk infants are warranted.

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