Early Nutritional Strategies for Preventing Allergic Disease

Hania Szajewska MD

Department of Paediatrics, Medical University of Warsaw, Poland

ABSTRACT: The rising number of children and adults with allergic disorders worldwide has prompted interest in strategies to prevent or reduce the risk of allergy. This article discusses the role of early nutritional strategies in the prenatal/postnatal periods that potentially may modify disease risk. Exclusive breastfeeding may help to prevent allergic disease by decreasing exposure to exogenous antigens, protecting against infections, promoting gastrointestinal mucosal maturation and the development of gut microbiota, and conferring immunomodulatory and anti-inflammatory benefits. However, the results of the studies are inconsistent, showing a protective effect, no effect, or even a predisposing effect. Still, breastfeeding should be promoted for its nutritional, immunological and psychological benefits. For infants with a documented hereditary risk of allergy (i.e., an affected parent and/or sibling) who cannot be breastfed exclusively, dietary products with confirmed reduced allergenicity are recommended. Previously, for complementary feeding, early exposure to solid foods during infancy was associated with the development of allergic diseases, particularly eczema. Currently, the guidelines downplay the role of solid foods in the development of allergies, stating that there is no convincing scientific evidence that the avoidance or delayed introduction of potentially allergenic foods beyond 4–6 months reduces allergies in infants considered to be at increased risk for the development of allergic diseases or in those not considered to be at increased risk. Evidence from some trials with probiotics or prebiotic oligosaccharides suggests some benefits, but at present there is insufficient evidence to support their routine use. Neither can specific recommendations be made for the use of long-chain polyunsaturated fatty acids, antioxidants, folate, and vitamin D.

IMAJ 2012; 14: 57–61

KEY WORDS: infants, feeding, breastfeeding, complementary feeding, hydrolyzed formula

The rising number of children and adults with allergic disorders worldwide is a major public health concern, although the origins of this increase are still not well understood. Consequently, there is an interest in understanding the reasons for this increase and in strategies to prevent or reduce allergic disease. With a better understanding of the immune system, it is now clear that, among other factors, impaired oral tolerance, which is a specific suppression of cellular and/or humoral immune responses to an antigen, contributes to the development of allergic diseases. Recognition of the oral tolerance mechanisms may provide measures for safe and effective primary prevention of allergic diseases either at the population level or in subgroups of individuals with increased genetic disease susceptibility. A number of strategies have been studied for preventing allergy. However, not all of them are equal. This article discusses evidence regarding the role of early nutritional interventions that potentially may modify developing immune tolerance and disease risk in the prenatal and postnatal periods.

MATERNAL DIET DURING PREGNANCY AND LACTATION

One systematic review [1] of five randomized controlled trials involving 952 participants evaluated the effects of maternal dietary avoidance of milk, eggs and other potentially antigenic foods during pregnancy and lactation. The investigators found that prescribing an antigen-avoidance diet to a high risk woman during pregnancy is unlikely to substantially reduce her child's risk of atopic diseases. Moreover, such a diet may adversely affect maternal or fetal nutrition, or both. Prescribing an antigen avoidance diet to a high risk woman during lactation did not reduce the risk of her infant developing atopic eczema during the first 18 months of life. In addition, evidence did not show a significant protective effect of maternal antigen avoidance on positive skin-prick tests to cow's milk, egg, or peanut antigen at 1, 2, or 7 years. Thus, current evidence is inadequate to recommend avoidance of specific foods during pregnancy or breastfeeding for preventing children from developing allergic diseases such as eczema and asthma. Since the evidence is not fully conclusive, large well-conducted studies are needed.

BREASTFEEDING

Exclusive breastfeeding may help to prevent allergic disease by decreasing exposure to exogenous antigens, protecting against infections, promoting gastrointestinal mucosal maturation and the development of gut microbiota, and conferring immunomodulatory and anti-inflammatory benefits. Whether or not allergy prevention is feasible through breastfeeding has been frequently studied and hotly debated for more than 70 years. Several meta-analyses of data published before 2007 found prob-

able and possible evidence that exclusive breastfeeding protects against asthma, wheezing and atopic dermatitis [2,3]. However, more recent meta-analyses on the relationship between exclusive breastfeeding and atopic disease have not supported these conclusions [4]. Overall, there are studies that show a protective effect, no effect, or even a predisposing effect. Despite the fact that there is controversy in the literature, this does not mean that breastfeeding does not have significant effects. Rather, this is more likely a reflection of the methodological inadequacy of investigating breastfeeding in ways that take into account all the complexity of interactions. A variety of methodological problems are likely to contribute to these inconsistent results. First, these include the inability to randomize and blind. Thus, in general, the studies on breastfeeding are non-randomized, retrospective, or observational in design and thus produce inconclusive results. While randomization to formula feeding versus breastfeeding is unfeasible and unethical, randomizing subjects to an intervention that promotes breastfeeding is feasible and ethical and such studies have been carried out (e.g., PROBIT Study) [5]. A second methodological problem is the retrospective design of many studies addressing the association between breastfeeding and allergic disease. One threat to the validity of retrospective studies is the potential for parental recall bias (i.e., a bias arising from mistakes in recollecting events, both because of failures of memory and looking at things 'with hindsight' and possibly changed views). Although it is unlikely that a mother would forget whether she had breastfed, she might not recall whether the breastfeeding was totally exclusive. One may overcome this problem by obtaining prospective feeding histories. Moreover, most of the studies that examined the effect of breastfeeding on food allergy were carried out in unselected birth cohorts with regard to allergy risk. Only a limited number of studies have assessed the effect of breastfeeding in high risk infants. Inconsistencies may also be due to imprecise definitions of the intervention. Many studies do not make the distinction between "exclusive breastfeeding" and "any breastfeeding." Moreover, ideally, the diagnosis of allergic diseases should be based on widely agreed-upon criteria. However, in many of the studies on the effect of breastfeeding, heterogeneous definitions made comparisons between the studies difficult. One example is asthma. The terms "wheezing" and "asthma" are often used interchangeably, and the latter is sometimes diagnosed in very young children. However, the diagnosis of asthma cannot be reliably and objectively determined in children younger than 5 years of age. Equally important is who makes the diagnosis, i.e., parental/participant versus physician diagnosed outcome(s). Finally, reverse causation may contribute to inconsistent results. Infants at the highest risk of allergic diseases (because of a family history of allergy or the presence of early signs of allergy, such as infantile eczema or wheeze) might be breastfed for longer periods in the hope that breastfeeding might reduce the risk of allergic diseases.

Exclusive breastfeeding for 6 months is a desirable goal

What can be done? In 1988, Kramer proposed 12 criteria to apply to studies designed to assess the relationship between atopic disease and breastfeeding [6]. These criteria included non-reliance on the maternal recall of breastfeeding, sufficient duration of exclusive breastfeeding, strict diagnostic criteria for atopic outcomes, assessment of effects on children at high risk of atopic outcomes, and adequate statistical power. Unfortunately, there are no studies that fully meet these criteria. Thus, the issue remains controversial.

What to do in practice? Despite the controversy, everyone agrees that even if breastfeeding does not provide a strong protective effect, it should be promoted for its nutritional, immunological and psychological benefits. Exclusive breastfeeding for 6 months is a desirable goal [7,8].

DIETARY PRODUCTS WITH REDUCED ALLERGENICITY

Formulas that contain protein that has been hydrolyzed to reduce the potential risk associated with intact cow's milk protein are widely available. These formulas are differentiated by the protein source (whey and casein) and by the degree of hydrolysis (partially or extensively hydrolyzed). The American Academy of Pediatrics defines partially hydrolyzed formulas as those containing reduced oligopeptides that have a molecular weight of generally < 5000 Da and defines extensively hydrolyzed formulas as those containing only peptides that have a molecular weight < 3000 Da [8]. A number of meta-analyses have evaluated the effects of using these hydrolyzed formulas in the prevention of allergy. Among them, the *Cochrane Review* [9] (search date: March 2006) found that in high risk infants who are unable to be completely breastfed, there is limited evidence that prolonged feeding with a hydrolyzed formula compared to a cow's milk formula reduces infant and childhood allergy and infant cow's milk allergy. It was also stated that in view of the methodological concerns and inconsistency of the findings, further large well-designed trials comparing formulas containing partially hydrolyzed whey or extensively hydrolyzed casein to cow's milk formulas are needed. Despite this evidence, there is still uncertainty regarding the choice of a hydrolyzed formula for allergy prevention as well as the actual efficacy of a particular hydrolyzed formula. Clearly, not all hydrolyzed formulas are equal. Efficacy and safety should be established for each hydrolyzed formula, as factors such as the protein source, hydrolysis method, and degree of hydrolysis that often depend on the manufacturer contribute to differences among hydrolysates. A 2010 meta-analysis [10] compared the efficacy of a partially hydrolyzed 100% whey formula with that of standard infant formula in reducing the risk of allergy in healthy infants at high risk for atopic disease. This meta-analysis showed that the pHF compared to standard infant formula reduced the risk of all allergic diseases, particularly atopic dermatitis/eczema, at some time points among children

at high risk for allergy. Limited data suggest that the use of the pHF compared with standard infant formula reduced the risk of gastrointestinal symptoms and food allergy. The pooled results did not provide evidence of a difference in the effect of the pHF versus standard infant formula on the incidence of either wheezing/asthma or rhinitis. Few significant differences in outcomes were found between children who received the pHF versus an extensively hydrolyzed whey formula. No significant differences in outcomes were found between children who received the pHF versus an extensively hydrolyzed casein formula. These results should be interpreted with caution due to a lack of methodological rigor in many trials. However, the studies were carried out in different settings with similar results consistently being seen in the various trials, and reassuringly, the strongest evidence comes from a well-designed and conducted, independently funded randomized clinical trial (GINI Study). Therefore, the effects of the pHF have generalizability. Similar conclusions were reached by the authors of another meta-analysis comparing use of pHF with standard infant formula [11]. In all the studies, a reduced incidence of atopic dermatitis was found among infants who received a pHF versus cow's milk formula, regardless of the study design, infant population, follow-up time or study location.

Infants with a documented hereditary risk of allergy (i.e., an affected parent and/or sibling) who cannot be breastfed exclusively should receive a formula with confirmed reduced allergenicity

The most recent evidence comes from a study that was published subsequent to the latest meta-analyses [12]. This was a single-blind, randomized controlled trial involving 620 infants designed to assess the effect of using a partially hydrolyzed whey infant formula at weaning on the risk of allergic disease. The participants were randomized to receive, at partial or full cessation of breastfeeding, one of three infant formulas: cow's milk formula (n=206), soy formula (n=208), or partially hydrolyzed whey formula (n=206). Study formulas were offered until the end of the first year of life. The methods of randomization and allocation concealment were unclear. The first 97 infants were randomized to two arms only (cow's milk formula or soy formula); later, when partially hydrolyzed formula became available, a new randomization list was generated with a higher proportion of infants allocated to the partially hydrolyzed formula group to obtain equal numbers in each formula group. The primary outcome measure was the development of any allergic manifestations (eczema, food reaction, positive skin-prick test) assessed during 18 telephone interviews with parents. The investigators reported that at 2 years, 575 (93%) infants of 620 were followed, and at 6 to 7 years, 495 (80%). Feeding with the pHF compared with cow's milk formula did not significantly affect the risk of any allergic disease at 0–1 year or at 0–2 years. There was also no difference between the group fed the pHF and the group fed cow's milk formula for any of the secondary outcomes within the first 2 years and at 6–7 years. The authors concluded that there was no evidence that introducing pHF at the cessation of breastfeeding reduced the risk of allergic manifestations, including eczema, asthma and allergic rhinitis. There were some issues with the trial [13,14], in addition to unclear allocation concealment, that call for caution when interpreting the results. These include the unclear reason for publishing the results 15 years after collecting the data, outcome assessment through telephone interviews with parents, and changing definitions of outcome parameters compared to previous publications on this cohort.

For clinical practice, based on the current evidence, currently recommendations state that infants with a documented hereditary risk of allergy (i.e., an affected parent and/or sibling) who cannot be breastfed exclusively [15] should receive a formula with confirmed reduced allergenicity, i.e., a partially or extensively hydrolyzed formula, as a means of preventing allergic reactions, primarily atopic dermatitis [8].

COMPLEMENTARY FOOD

Previously, early exposure to solid foods during infancy was associated with the development of allergic diseases, particularly eczema. Nowadays, we are witnessing a shifting of the paradigm. Oral tolerance induction is being investigated to determine if early weaning onto allergenic foods after at least 3–4 months of exclusive breastfeeding will result in the reduced prevalence of food allergies. Extended avoidance/delayed introduction of solid foods, specifically of potentially allergenic foods, is being replaced by early exposure. No effect of the delayed introduction of solid foods on the prevalence of food allergies has been suggested by the results of a number of prospective birth cohort studies, e.g., the GINI Study [16], LISA Study [17] and the KOALA Study [18]. Consequently, current recommendations from scientific societies agree that there is no convincing scientific evidence that the avoidance or delayed introduction of potentially allergenic foods (e.g., cow's milk, egg, peanut, tree nut, fish and seafood) beyond 4–6 months reduces allergies in infants considered to be at increased risk for the development of allergic diseases or in those not considered to be at increased risk [8,19]. However, different opinions exist [20]. Still, even if the available evidence suggests that early exposures may modify tolerance development, further research on these exposures continues. Such studies are currently underway. One example is the EAT study (**E**nquiring **A**bout **T**olerance; www.eatstudy.co.uk). This study is designed to determine whether early (at 3 months of age) introduction of six allergenic foods (cow's milk-based yogurt, egg, fish, wheat, sesame, peanut) into the diet of unselected infants, together with

pHF = partially hydrolyzed 100% whey formula

continued breastfeeding, compared with later (at 6 months of age) introduction with continued breastfeeding will have an impact on the risk of food allergies at 3 years of age. Another example is the LEAP study (**L**earning **E**arly **A**bout **P**eanut Allergy; www.leapstudy.co.uk), which plans to compare the effects of peanut avoidance until 3 years of age with early peanut introduction in 640 high risk infants (age 4–10 months) with atopic dermatitis and/or egg allergy. The preventive effect of early consumption of peanuts during infancy has been suggested by the results of a cross-sectional study demonstrating a low prevalence of peanut allergy in Jewish children in Israel who consumed large quantities of peanuts during their first year of life compared with Jewish children in the United Kingdom who avoided peanuts [21].

There is no convincing evidence that the avoidance or delayed introduction of potentially allergenic foods beyond 4–6 months reduces allergies in infants considered to be at increased risk for the development of allergic diseases or in those not considered to be at increased risk

Further research is also needed to explore whether very early (first weeks of life) exposure to cow's milk protein reduces the risk of immunoglobulin E-mediated cow's milk protein allergy, as suggested by a recent prospective cohort study involving more than 13,000 infants [22]; however, these results have been challenged by other investigators [23].

PROBIOTICS AND/OR PREBIOTICS

The rationale for using probiotics in the prevention of allergic disorders is based on several concepts. It has been suggested that improved hygiene and the reduced exposure of the immune system to the microbial stimulus early in childhood contribute to the rising number of allergic disorders worldwide [24]. Second, there are differences in the neonatal gut microbiota that may precede or coincide with the early development of atopy. Atopic subjects have more clostridia and tend to have fewer bifidobacteria than non-atopic subjects [25]. Finally, there is evidence suggesting a crucial role for a balanced commensal gut microbiota in the maturation of the early immune system.

A number of recent meta-analyses have suggested that probiotics are effective in preventing eczema, particularly if the probiotics are administered both pre- and postnatally [26-28]. However, one major limitation of all these meta-analyses is that all of them pooled data obtained from different probiotic strains, with no analyses based on individual probiotic strain(s). It is well accepted that all probiotics are not created equal. The most recent meta-analysis by Doege et al. [29] included seven randomized double-blind placebo-controlled trials published until 2009. The pooled results of six of these trials showed a significant reduction in the risk of atopic eczema in children aged 2–7 years by the administration of probiotics during pregnancy. However, this effect was only significant for lactobacilli, but not for a mixture of various bacterial strains as probiotics. This most recent meta-analysis by Doege et al. differs from those previously published. While it presents pooled data, it also separately presents data from studies that used mixtures of probiotics and studies that used lactobacilli. Of note, only the lactobacilli proved to be effective. Still, different lactobacilli were pooled together, calling for caution when interpreting the pooled effect.

Like probiotics, prebiotics may contribute to more favorable gut microbiota and may have a direct effect on the immune system. The *Cochrane Review* published in 2006 concluded that there is insufficient evidence to determine the role of prebiotic supplementation of infant formula for the prevention of allergic disease and food hypersensitivity [30]. One small trial of prebiotic oligosaccharides (with excessive losses) reported a reduction in eczema in high risk formula-fed infants. A very recent study carried out in 440 healthy term infants, unselected for allergy risk, from five European countries demonstrated that formula supplementation with a specific mixture of neutral oligosaccharides and pectin-derived acidic oligosaccharides compared with unsupplemented formula reduced the risk of atopic dermatitis from 9.7% in the control group to 5.7% in the prebiotic group ($P = 0.04$) [31].

For synbiotics, one randomized controlled trial (n=925) found that treatment with *L. rhamnosus*, *B. breve*, and *P. freudenreichii* plus galacto-oligosaccharides did not have a significant effect on all allergic diseases, but significantly reduced eczema and, particularly, atopic eczema [32].

Overall, research in the area of prevention of allergic disorders through modification of intestinal microbiota is relatively new. According to recommendations by the American Academy of Pediatrics [33], "the results of some studies support the prophylactic use of probiotics during pregnancy and lactation and during the first 6 months of life in infants who are at risk of atopic disorders. However, further confirmatory evidence is necessary before a recommendation for a routine use can be made." This recommendation is hard to argue against. In particular, there is a need to determine which microorganisms or prebiotic products are suitable for use and in which type of population.

OTHER NUTRITIONAL INTERVENTIONS

A number of other nutritional factors, including long-chain polyunsaturated fatty acids, antioxidants (e.g., vitamin C, vitamin E, beta-carotene, zinc) [34], folate [35] and vitamin D [36], are considered to have effects on immune function. Among them, supplementation with LCPUFA has been studied most extensively, both pre- and postnatally. The rationale for the use

LCPUFA = long-chain polyunsaturated fatty acids

of LCPUFA is based on the observations that the low consumption of n-3 LCPUFA (e.g., oily fish), typical of the diet in many westernized countries, results in reduced maternal consumption of n-3 LCPUFA, favors more pro-inflammatory n-6 LCPUFA, and contributes to the development of allergy and asthma [37]. Epidemiological studies suggest an association between the intake of fish oil and a reduced risk of allergy [38]. However, in contrast to the epidemiological data, a meta-analysis of 10 publications (representing 6 studies) found no clear evidence of a benefit with regard to reducing the risk of allergic sensitization or a favorable immunological profile with use of n-3 or n-6 LCPUFA [39].

Correspondence:
Dr. H. Szajewska
Dept. of Paediatrics, Medical University of Warsaw, 01-184 Warsaw, Dzialdowska 1, Poland
Phone/Fax: (48-22) 452-3309
email: hania@ipgate.pl

References

1. Kramer MS, Kakuma R. Maternal dietary antigen avoidance during pregnancy or lactation, or both, for preventing or treating atopic disease in the child. *Cochrane Rev* 2006; 3. Art. No.: CD000133. DOI: 10.1002/14651858.CD000133.pub2.
2. Dutch State Institute for Nutrition and Health. Van Rossum CMT, Buchner FL, Hoekstra J. Quantification of health effects of breastfeeding. Review of the literature and model situation. RIVM Report 350040001/2005. Available at: http://www.rivm.nl/bibliotheek/rapporten/350040001.pdf. Accessed December 13, 2008.
3. Agency for Healthcare Research and Quality. Breastfeeding and maternal and infant health outcomes in developed countries. AHRQ Publication No. 07-E007, April 2007, 524 pages. Available at: http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=hstat1b.chapter. 106732. Accessed December 13, 2008.
4. Yang YW, Tsai CL, Lu CY. Exclusive breastfeeding and incident atopic dermatitis in childhood: a systematic review and meta-analysis of prospective cohort studies. *Br J Dermatol* 2009; 161: 373-83.
5. Kramer MS, Matush L, Vanilovich I, et al; Promotion of Breastfeeding Intervention Trial (PROBIT) Study Group. Effect of prolonged and exclusive breast feeding on risk of allergy and asthma: cluster randomised trial. *BMJ* 2007; 335: 815.
6. Kramer MS. Does breast feeding help protect against atopic disease? Biology, methodology, and golden jubilee of controversy. *J Pediatr* 1988; 112: 181-90.
7. ESPGHAN Committee on Nutrition, Agostoni C, Braegger C, Decsi T, et al. Breast-feeding: a commentary by the ESPGHAN Committee on Nutrition. *J Pediatr Gastroenterol Nutr* 2009; 49: 112-25.
8. Greer FR, Sicherer SH, Burks AW; American Academy of Pediatrics Committee on Nutrition, American Academy of Pediatrics Section on Allergy and Immunology. Effects of early nutritional interventions on the development of atopic disease in infants and children: the role of maternal dietary restriction, breastfeeding, timing of introduction of complementary foods, and hydrolyzed formulas. *Pediatrics* 2008; 121: 183-91.
9. Osborn DA, Sinn J. Formulas containing hydrolysed protein for prevention of allergy and food intolerance in infants. *Cochrane Rev* 2006; (4):CD003664. PubMed PMID: 17054180.
10. Szajewska H, Horvath A. Meta-analysis of the evidence for a partially hydrolyzed 100% whey formula for the prevention of allergic diseases. *Curr Med Res Opin* 2010; 26: 423-37.
11. Alexander DD, Cabana MD. Partially hydrolyzed 100% whey protein infant formula and reduced risk of atopic dermatitis: a meta-analysis. *J Pediatr Gastroenterol Nutr* 2010; 50: 422-30.
12. Lowe AJ, Hosking CS, Bennett CM, et al. Effect of a partially hydrolyzed whey infant formula at weaning on risk of allergic disease in high-risk children: a randomized controlled trial. *J Allergy Clin Immunol* 2011; 128: 360-5.e4.
13. Haschke F. Effect of partially hydrolyzed whey infant formula and prolonged breast-feeding on the risk of allergic disease in high-risk children. *J Allergy Clin Immunol* 2011; 128: 688-9; author reply 689.
14. Koletzko S, Filipiak-Pittroff B, Koletzko B, et al; German Infant Nutritional Intervention study group. No reason to change the current guidelines on allergy prevention. *J Allergy Clin Immunol* 2011 [Epub ahead of print] PubMed PMID: 22035876.
15. ESPGHAN Committee on Nutrition: Agostoni C, Decsi T, Fewtrell M, et al; Complementary feeding: a commentary by the ESPGHAN Committee on Nutrition. *J Pediatr Gastroenterol Nutr* 2008; 46 (1): 99-110.
16. Filipiak B, Zutavern A, Koletzko S, et al; GINI-Group. Solid food introduction in relation to eczema: results from a four-year prospective birth cohort study. *J Pediatr* 2007; 151: 352-8.
17. Zutavern A, Brockow I, Schaaf B, et al; LISA Study Group. Timing of solid food introduction in relation to eczema, asthma, allergic rhinitis, and food and inhalant sensitization at the age of 6 years: results from the prospective birth cohort study LISA. *Pediatrics* 2008; 121: e44-52.
18. Snijders BE, Thijs C, van Ree R, van den Brandt PA. Age at first introduction of cow milk products and other food products in relation to infant atopic manifestations in the first 2 years of life: the KOALA Birth Cohort Study. *Pediatrics* 2008; 122: e115-22.
19. Agostoni C, Decsi T, Fewtrell M, et al; ESPGHAN Committee on Nutrition: Complementary feeding: a commentary by the ESPGHAN Committee on Nutrition. *J Pediatr Gastroenterol Nutr* 2008; 46: 99-110.
20. Cattaneo A, Williams C, Pallas-Alonso CR, et al. ESPGHAN's 2008 recommendation for early introduction of complementary foods: how good is the evidence? *Matern Child Nutr* 2011; 7: 335-43.
21. Du Toit G, Katz Y, Sasieni P, et al. Early consumption of peanuts in infancy is associated with a low prevalence of peanut allergy. *J Allergy Clin Immunol* 2008; 122: 984-91.
22. Katz Y, Rajuan N, Goldberg MR, et al. Early exposure to cow's milk protein is protective against IgE-mediated cow's milk protein allergy. *J Allergy Clin Immunol* 2010; 126: 77-82.e1.
23. Koletzko S, Filipiak-Pittroff B, von Berg A, et al; German Infant Nutritional Intervention Study Group. Supplementation with cow's milk at birth is not recommended. *J Allergy Clin Immunol* 2011; 127: 836-8; author reply 839-40.
24. Prescot SL. Allergy: the price we pay for cleaner living? *Ann Allergy Asthma Immunol* 2003; 90: 64-70.
25. Kalliomaki M, Kirjavainen P, Eerola E, et al. Distinct patterns of neonatal gut microflora in infants in whom atopy was and was not developing. *J Allergy Clin Immunol* 2001; 107: 12934.
26. Osborn DA, Sinn JK. Probiotics in infants for prevention of allergic disease and food hypersensitivity. *Cochrane Rev* 2007; 4: CD006475.
27. Lee J, Seto D, Bielory L. Meta-analysis of clinical trials of probiotics for prevention and treatment of pediatric atopic dermatitis. *J Allergy Clin Immunol* 2008; 121: 116-21.
28. Betsi GI, Papadavid E, Falagas ME. Probiotics for the treatment or prevention of atopic dermatitis: a review of the evidence from randomized controlled trials. *Am J Clin Dermatol* 2008; 9: 93-103.
29. Doege K, Grajecki D, Zyriax BC, Detinkina E, Zu Eulenburg C, Buhling KJ. Impact of maternal supplementation with probiotics during pregnancy on atopic eczema in childhood – a meta-analysis. *Br J Nutr* 2011; 26: 1-6.
30. Osborn DA, Sinn JK. Prebiotics in infants for prevention of allergic disease and food hypersensitivity. *Cochrane Rev* 2007; 4: CD006474.
31. Gruber C, van Stuijvenberg M, Mosca F, et al; MIPS 1 Working Group. Reduced occurrence of early atopic dermatitis because of immunoactive prebiotics among low-atopy-risk infants. *J Allergy Clin Immunol* 2010; 126: 791-7.
32. Kukkonen K, Savilahti E, Haahtela T, et al. Probiotics and prebiotic galacto-oligosaccharides in the prevention of allergic diseases: a randomized, double-blind, placebo-controlled trial. *J Allergy Clin Immunol* 2007; 119: 192-8.
33. Thomas DW, Greer FR; American Academy of Pediatrics Committee on Nutrition; American Academy of Pediatrics Section on Gastroenterology, Hepatology, and Nutrition. Probiotics and prebiotics in pediatrics. *Pediatrics* 2010; 126: 1217-31.
34. Allan K, Kelly FJ, Devereux G. Antioxidants and allergic disease: a case of too little or too much? *Clin Exp Allergy* 2010; 40: 370-80.
35. Whitrow MJ, Moore VM, Rumbold AR, Davies MJ. Effect of supplemental folic acid in pregnancy on childhood asthma: a prospective birth cohort study. *Am J Epidemiol* 2009; 170: 1486-93.
36. Lange NE, Litonjua A, Hawrylowicz CM, Weiss S. Vitamin D, the immune system and asthma. *Expert Rev Clin Immunol* 2009; 5: 693-702.
37. Hodge L, Salome CM, Peat JK, Haby MM, Xuan W, Woolcock AJ. Consumption of oily fish and childhood asthma risk. *Med J Aust* 1996; 164: 137-40.
38. Oddy WH, de Klerk NH, Kendall GE, Mihrshahi S, Peat JK. Ratio of omega-6 to omega-3 fatty acids and childhood asthma. *J Asthma* 2004; 41: 319-26.
39. Anandan C, Nurmatov U, Sheikh A. Omega 3 and 6 oils for primary prevention of allergic disease: systematic review and meta-analysis. *Allergy* 2009; 64: 840-8.