Expert Review of Clinical Immunology

ISSN: 1744-666X (Print) 1744-8409 (Online) Journal homepage: http://www.tandfonline.com/loi/ierm20

Timing and diversity of complementary food introduction for prevention of allergic diseases. How early and how much?

Joachim Heinrich, Berthold Koletzko & Sibylle Koletzko

To cite this article: Joachim Heinrich, Berthold Koletzko & Sibylle Koletzko (2014) Timing and diversity of complementary food introduction for prevention of allergic diseases. How early and how much?, Expert Review of Clinical Immunology, 10:6, 701-704, DOI: 10.1586/1744666X.2014.917049

To link to this article: http://dx.doi.org/10.1586/1744666X.2014.917049

Published online: 03 May 2014.

Timing and diversity of complementary food introduction for prevention of allergic diseases. How early and how much?

Expert Rev. Clin. Immunol. 10(6), 701–704 (2014)

Joachim Heinrich

Author for correspondence: Helmholtz Zentrum München – German Research Center for Environmental Health, Institute of Epidemiology I, Ingolstädter Landstraße 1, D-85764 Neuherberg, Germany
Tel.: +49 893 187 4150
Fax: +49 893 187 3380
heinrich@helmholtz-muenchen.de

Berthold Koletzko

Dr. von Hauner Children's Hospital, Ludwig Maximilians University, Munich, Germany

Sibylle Koletzko

Dr. von Hauner Children's Hospital, Ludwig Maximilians University, Munich, Germany

The timing of the introduction of complementary foods appears crucial to the development of allergic diseases later in life. The results from recent observational studies might be misinterpreted to suggest that introducing complementary food prior to the age of four months might have a beneficial effect on the induction of immune tolerance. Since these two recently published papers cannot completely account for reverse causation, as is the case for all observational studies, we recommend that the current ESPGHAN and American Academy of Pediatrics recommendations be maintained as long as new evidence from large randomized controlled intervention trials do not suggest otherwise. That is, complementary foods should be first introduced between the age of 17 to 26 weeks.

Complementary feeding in infancy may affect several health outcomes such as growth, neurodevelopment, obesity, cardiovascular diseases, celiac disease, Type 1 diabetes and oral health [1]. Infant nutrition and complementary feeding practices are also considered important for the development of the immune system and later allergic diseases. The exposure of the infant's digestive tract to food-derived components, for example, food antigens and/or bacteria, and their impact on the gut microbiota, along with the infant's host factors, such as genetic and epigenetic predispositions, is crucial for the development of allergic diseases [2,3]. While the WHO defines complementary foods as all nutrient-containing solid or liquid foods given to infants other than breast milk [4], pediatric organizations, such as ESPGHAN, do not consider human milk substitutes as complementary food [1].

Prior to 2008, it was recommended that for children at high risk for allergic diseases based on family risk of atopy, solids should be avoided during the first 6 months of life, and a delayed introduction of dairy products until the age of 12 months, hen's egg until 24 months, and peanut, tree nuts, fish and seafood until 36 months was recommended. However, since 2008, the ESPGHAN and the American Academy of Pediatrics (AAP) have recommended that complementary foods be first introduced between 4 and 6 months of age [1,2]. The earlier recommendations were largely based on findings in a birth cohort study published in 1990 which included 1650 infants followed using yearly questionnaires for 10 years [3]. In this study, the early introduction of four different solid foods by age 4 months was associated with an increased risk for eczema, particularly in infants at risk for allergic diseases. Based on these observations, it was hypothesized that a later introduction of solid foods might reduce the risk of allergic diseases. Recommendations for practice were thus provided, even though there was insufficient evidence to support them. Many parents followed these recommendations. Indeed, infants from families with allergic diseases and those with early signs of allergic

Keywords: allergy • food diversity • infancy • prevention • solid food

EXPERT REVIEWS

 10.1586/1744666X.2014.917049 ISSN 1744-666X

diseases were breastfed for longer and complementary feeding was delayed. Correspondingly, observational studies found that prolonged exclusive breastfeeding and delayed introduction of weaning foods were associated with an increased risk of allergic disorders.

Almost 10 years ago, Zutavern and colleagues described the phenomenon of 'reverse causality' in a German birth cohort; dairy products and egg were introduced later if the infant had presented with symptoms of eczema during the first 4 months of life. This resulted in significantly less doctor-diagnosed eczema in children with early solid feeding [5]. When children with early skin symptoms were excluded from the analysis, the introduction of solids between 5 and 6 months of age was no longer a risk factor for eczema and later allergic diseases [5,6]. Based on these and further publications which considered potential reverse causality effects, both ESPGHAN [1] and AAP [7] concluded that complementary foods should be introduced between the ages of 17 and 26 weeks. These organizations concluded that there is no convincing evidence that avoidance or delayed introduction of potentially allergenic foods, such as fish or egg, reduces the risk of allergic diseases in infants, regardless of their risk of allergic diseases [1,7].

Since the publication of these two guidelines in 2008, the controversial debate on dietary recommendations for the prevention of allergic diseases during infancy has continued. This controversy was recently stimulated by two published papers using data from two cohort studies, the PASTURE/EFRAIM study [8,9] and the DIPP study [10,11]. The results of these publications have been interpreted as evidence that the introduction of complementary feeds prior to age 4 months has allergy-preventive effects.

The DIPP cohort includes only children with HLA-conferred susceptibility of Type 1 diabetes born since 1994 in three different areas in Finland. Nwaru *et al.* analyzed data from age-specific dietary questionnaires on the introduction of different food items at 3, 4, 6 and 12 months of age in relation to the occurrence of asthma and other allergic manifestations during childhood [10,11]. The authors found that delayed introduction of solids (wheat, rye, barley, oats and other grains, meat fish and egg) was associated with eczema within the first 6 months of life, which again may reflect reverse causation. After adjusting for different possible confounders, the authors reported that the introduction of cereals between 5 and 5½ months of age and egg and fish before 8–9 months was associated with a reduced risk for later asthma and allergic rhinitis, when compared to introduction at later time points [11]. When they specifically addressed the diversity of complementary food during the first year of life, they did not find any association between solid food introduction at 4 months of age with atopic outcomes [10]. Stratified analyses by eczema showed that the association between an increased risk for asthma and allergic rhinitis by the age of 5 years with less diversity of food items at the age of 6 months was only significant for children with early-life eczema. No association was found among children without skin lesions during the first year of life (Table E1 in [10]). Again, this finding supports the occurrence of reverse causation.

The PASTURE/EFRAIM birth cohort study recruited infants from rural areas in five European countries. Approximately half of the participants were born to mothers who lived and worked on a farm with livestock. For 1041 children, information on feeding during the first year of life was available and was associated with reported allergic disease occurrence until the age of 6 years. In their first paper on atopic dermatitis, the authors stratified the analysis by skin symptoms early in life to reduce the likelihood of reverse causation [9]. However, in their most recent paper examining the impact of solid feeding during infancy on respiratory allergies until age 6 years, the authors only excluded children whose respective end points had occurred before solid food introduction [8]. This analytic strategy may be insufficient to exclude reverse causality as eczema during the first 6 months of life is closely associated with later asthma and allergic rhinitis. No stratified analysis for children with and without early skin symptoms was reported. The authors concluded that less food diversity during the first year of life appears to increase the risk of asthma and allergic diseases in childhood. However, four or more food items as early as four months of age increased the risk for non-atopic asthma. When (even insufficient) adjustment for reverse causation was considered, the presumably protective effects were attenuated. Furthermore, the results were no longer statistically significant when the extreme group of infants which were given less than four food items until the age of 12 months (<5 % of the study population) were excluded (Table 2 in [8]). Gene expression analysis was performed in relation to food diversity as a novel approach to increase our understanding of the mechanisms inducing tolerance. Increased food diversity was associated with an increased expression of forkhead box protein 3 and a decreased expression of Cϵ germline transcript [8]. However, significant differences were found only in a very small subgroup of 22 children, 15 of which had an allergic parent and who were exposed to no more than three food items by 1 year of age. Such a low number of complementary food items during the first year of life is highly unusual. It is conceivable that restricting the number of complementary foods to such an extent could occur primarily among families with a strong motivation to reduce allergy risk, possibly because of family burden or early manifestations of allergic symptoms, such as eczema. The gene expression findings were not presented separately for children with and without early eczema. Thus, one must consider the possibility that these results in this very special subgroup were influenced by reverse causation.

In addition to findings from the DIPP and PASTURE/EFRAIM cohort, a few more observational studies published during the past 5 years concluded that early introduction of solids reduces the risk of allergic diseases [12–14]. The results of these recent publications seem to be more homogenous than the heterogeneous picture of past papers which did not show a beneficial effect of later food introduction or even an increased risk for atopic eczema in relation to the early introduction of solids or greater food diversity [15,16]. However, even some of these more recent studies did not consider possible reverse

causation [12] and hence must be interpreted with caution. Some authors considered an adjustment for medical history of allergic diseases to be sufficient [8,10], while more cautiously performed analyses excluded children with early skin symptoms [5,6,9,14]. Most of the presumed protective effects relating to the timing of solid food introduction were no longer statistically significant if subjects with early skin symptoms were excluded [5,6,8,14].

These two recent published papers were selected on the subjective opinion of the authors and because the most recent systematic review on primary prevention of food allergy by de Silva *et al.* [17]. did not include these two observational studies [8–11].

In addition to potential effects on allergy prevention, other aspects relevant to child health must also be considered. In breastfed infants, an earlier start of complementary feedings will lead to a reduced duration of exclusive breastfeeding and a reduced total amount of breast milk consumed because complementary feeds tend to partly replace breast milk. Solid foods have a higher caloric density, and an earlier introduction of solids increases the total energy intake [18,19] and hence the risk for more rapid early weight gain and increased later obesity risk [20,21].

We conclude that the currently available data from observational cohort studies do not provide reason to modify the guidelines on complementary feeding practices established by ESPGHAN and AAP. It is simply not possible for any observational study to completely account or correct for reverse causation. Interventional studies are thus needed to clarify these issues [1,7]. A randomized controlled intervention trial approach focused on different times of complementary feeding introduction has been shown to be feasible [22,23]. Several large ongoing randomized controlled intervention trials on the role and timing of the introduction of solids might provide more conclusive evidence on their potential effects on later health. The currently available evidence does not justify the conclusion that the introduction of complementary feeds prior to the age of 4 months would be beneficial for allergy prevention. As long as the results of new large RTCs do not suggest otherwise, the introduction of solids/complementary foods is recommended between 17 and 26 weeks of age.

Financial & competing interests disclosure

The Ludwig-Maximilians-University of Munich and it's employee S Koletzko have received support for scientific and educational activities by companies that market food products for infants, including Abbott, Danone, Hipp, Mead Johnson, and Nestlé. B Koletzko is a member of the National Breastfeeding Committee and tends to be biased towards breastfeeding. The Ludwig-Maximilians-University of Munich and it's employee B Koletzko have received support for scientific and educational activities by companies that market food products for infants, including Abbott, Danone, Fonterra, Hipp, Mead Johnson, and Nestlé, predominantly as part of publically funded research projects with financial support by the European Commission or German governmental research funding. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

References

1. 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
2. Fiocchi A, Assa'ad A, Bahna S. Food allergy and the introduction of solid foods to infants: a consensus document. Adverse Reactions to Foods Committee, American College of Allergy, Asthma and Immunology. Ann Allergy Asthma Immunol 2006;97:10-20
3. Fergusson DM, Horwood LJ, Shannon FT. Early solid feeding and recurrent childhood eczema: a 10-year longitudinal study. Pediatrics 1990;86(4):541-6
4. WHO. Available from: www.who.int/nutrition/databases/infant-feeding/en/index/html
5. Zutavern A, Brockow I, Schaaf B, et al. Timing of solid food introduction in relation to atopic dermatitis and atopic sensitization: results from a prospective birth cohort study. Pediatrics 2006;117(2): 401-11
6. Zutavern A, Brockow I, Schaaf B, et al. 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(1):e44-52
7. Greer FR, Sicherer SH, Burks AW. 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(1):183-91
8. Roduit C, Frei R, Depner M, et al. Increased food diversity in the first year of life is inversely associated with allergic diseases. J Allergy Clin Immunol 2014; 133(4):1056-64
9. Roduit C, Frei R, Loss G, et al. Development of atopic dermatitis according to age of onset and association with early-life exposures. J Allergy Clin Immunol 2012;130(1):130-6.e135
10. Nwaru BI, Takkinen HM, Kaila M, et al. Food diversity in infancy and the risk of childhood asthma and allergies. J Allergy Clin Immunol 2014;133(4):1084-91
11. Nwaru BI, Takkinen HM, Niemela O, et al. Introduction of complementary foods in infancy and atopic sensitization at the age of 5 years: timing and food diversity in a Finnish birth cohort. Allergy 2013;68(4): 507-16
12. Koplin JJ, Osborne NJ, Wake M, et al. Can early introduction of egg prevent egg allergy in infants? A population-based study. J Allergy Clin Immunol 2010;126(4): 807-13
13. Sariachvili M, Droste J, Dom S, et al. Early exposure to solid foods and the development of eczema in children up to 4 years of age. Pediatr Allergy Immunol 2010;21(1 Pt 1):74-81
14. Snijders BE, Thijs C, van Ree R, et al. 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(1):e115-22
15. Sausenthaler S, Heinrich J, Koletzko S. Early diet and the risk of allergy: what can we learn from the prospective birth cohort

studies GINIplus and LISAplus? Am J Clin Nutr 2011;94(6 Suppl):2012S-7S

16. Chuang CH, Hsieh WS, Chen YC, et al. Infant feeding practices and physician diagnosed atopic dermatitis: a prospective cohort study in Taiwan. Pediatr Allergy Immunol 2011;22(1 Pt 1):43-9
17. de Silva D, Geromi M, Halken S, et al. Primary prevention of food allergy in children and adults: systematic review. Allergy 2014;69(5):581-9
18. Schiess S, Grote V, Scaglioni S, et al. Introduction of complementary feeding in 5 European countries. J Pediatr Gastroenterol Nutr 2010;50(1): 92-8
19. Grote V, Theurich M, Koletzko B. Do complementary feeding practices predict the later risk of obesity? Curr Opin Clin Nutr Metab Care 2012;15(3):293-7
20. Koletzko B, von Kries R, Monasterolo RC, et al. Infant feeding and later obesity risk. Adv Exp Med Biol 2009;646:15-29
21. Koletzko B, Brands B, Poston L, et al. Early nutrition programming of long-term health. Proc Nutr Soc 2012;71(3):371-8
22. Hogen Esch CE, Rosen A, Auricchio R, et al. The PreventCD Study design: towards new strategies for the prevention of coeliac disease. Eur J Gastroenterol Hepatol 2010; 22(12):1424-30
23. Wells JC, Jonsdottir OH, Hibberd PL, et al. Randomized controlled trial of 4 compared with 6 mo of exclusive breastfeeding in Iceland: differences in breast-milk intake by stable-isotope probe. Am J Clin Nutr 2012;96(1):73-9