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Review

Can early life interventions prevent food allergies?

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ABSTRACT

Background. The incidence of food allergies is increasing all over the world. Prevention strategies intend to reduce food sensitization risk and subsequent allergies. In this review, we will discuss the recent data concerning different geographic regions for the prevention of food allergies in children.

Methods. This review provides recommendations for the prevention of food allergies based on the recent data available in the PUBMED database in English (up to December 2022).

Results. The best strategy to prevent food allergies is regarded as the early introduction of allergenic foods to an infant's diet. A healthy and diverse diet is recommended for infants and their mothers, in accordance with the family's eating habits and regional food culture, rather than avoiding certain foods or using supplements. Avoiding common food allergens in the maternal diet during pregnancy and/or breastfeeding is not recommended. Exclusive breastfeeding is generally recommended for all mothers for at least 6 months. There is no specific association between exclusive breastfeeding and the primary prevention of any specific food allergy. Where a breastmilk substitute is needed, the best alternative should be chosen according to the infant's nutritional needs. There is no substantial evidence to support the use of hydrolyzed or soy formula in infancy against food allergies or sensitization.

Conclusions. Feeding patterns in infancy play an important role in the risk of developing food allergies. Existing strategies to prevent allergies are relatively ineffective and further research is needed to figure out strategies for food allergy prevention, particularly in high-risk infants.

Key words: allergy, child, food allergy, prevention.

One of the main causes of chronic illness in children is food allergy (FA), a complex immunological disorder that appears to have become more prevalent over the past 20 years in many different nations.[1] A multifactorial interaction of genetic factors and nutritional-environmental exposures is blamed for the underlying reason.[1] The content and diversity of the human microbiome of the gut and skin have been negatively impacted by inappropriate antibiotic usage, altered diets, non-vaginal deliveries, ultra-sanitary lifestyles, and less time spent outdoors.[2,3] These factors also had significant effects on the maturation of the immune system, which in turn affected the emergence of allergy illnesses like FA.[2,3] The most significant modifiable risk factors for FA development early in childhood include skin barrier dysfunction and delayed introduction of allergic solid foods.[4,5] As the dual allergen exposure hypothesis suggests, exposure to solid foods through the skin can lead to allergic sensitization, while oral exposure to solid foods induces tolerance.[4] Early oral exposure to allergens produces T-cell deviation toward Th1 and Treg subtypes, whereas early cutaneous exposure to allergens causes T-cell deviation toward a Th2 type and subsequent FA.[5] When the skin's protective barrier is compromised, allergens and microorganisms penetrate the skin and compromise the immune system. The formation of IgE and the allergic cascade then begin. Skin barrier dysfunction is made worse

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by immunological dysfunction.[5] Primary oral exposure of antigens allowing for presentation via a healthy mucosal immune system, rather than through an impaired skin epidermal barrier, is crucial to prevent FA.[4,5] Years of research have been conducted to determine whether changes in a mother's or an infant's diet can affect the risk of FA. These studies have searched for dietary patterns during infancy, pregnancy, and breastfeeding, avoiding certain allergenic foods, when to introduce certain foods, and dietary supplements.[2,5]

Since 2002, documents on the prevention of FA have been reported globally.[4] The European Academy of Allergy and Clinical Immunology (EAACI) Guidelines[6], Japanese Society of Pediatric Allergy and Clinical Immunology (JSPACI)[7], Chinese Expert Consensus[8], Indian Society of Pediatric Gastroenterology, Hepatology and Nutrition (ISPGHAN)[9], American Academy of Allergy, Asthma, and Immunology (AAAAI)[10], American College of Allergy, Asthma, and Immunology (ACAAI)[10]; Canadian Society for Allergy and Clinical Immunology (CSACI)[10], Australasian Society of Clinical Immunology and Allergy (ASCIA)[11], and the Malaysia Allergy Prevention (MAP)[12]; are the ones that have been updated in the last two years among these guidelines. These recommendations include prevention strategies to stop the onset of allergy symptoms or their progression, and risk groups have been defined to specify the recommendations.[4] A child with a family history of allergies is considered at high risk for allergic disease, according to numerous previous international papers.[10,13] Halken et al.[6] defined an increased risk of FA due to having a condition associated with FA such as eczema or asthma or having close relatives with a history of any allergy. AAAAI, ACAAI and CSACI proposed a risk gradient for the development of FA among infants.[10] The bottom of the pyramid represents a standard risk for infants in the general population. The ascending gradient of risk assessment for the development of FA lines up with a family history of atopy, mild to moderate eczema, and other food allergies and peaks with severe eczema as the highest risk for the development of FA.[10] A summary of current guidelines for the prevention of food allergies is provided in Fig. 1.

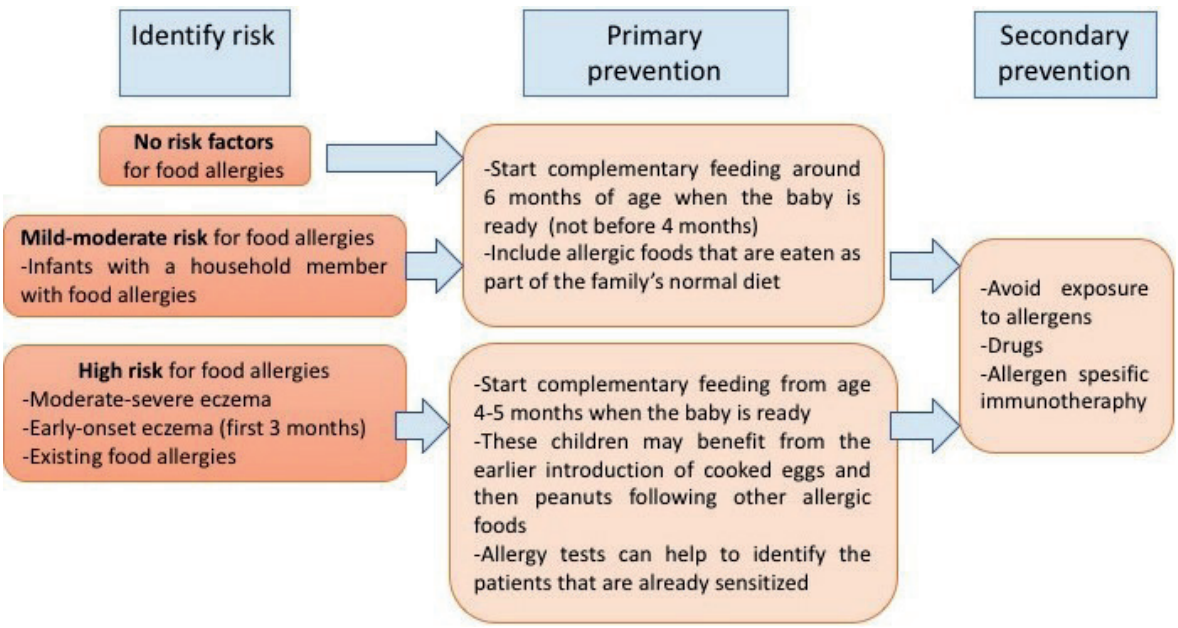

Fig. 1. Summary of current international guidelines for the prevention of food allergies.
Primary prevention refers to inhibiting the development of clinical disease before it occurs.[38]
Secondary prevention refers to the prevention of symptoms in those who have food allergies.[38]

Maternal diet in pregnancy and lactation

According to the World Health Organization (WHO), infants should be breastfed exclusively for the first six months of life and for the next two years to ensure their health.[14] Although most of the international food allergy guidelines recommend breastfeeding, there is no consistent evidence of allergy prevention through breastfeeding.[4,6,10,15-18] The EAACI guideline makes no recommendations for or against using breastfeeding to avoid FAs, but the guideline emphasizes that breastfeeding has many benefits for infants and mothers and supports WHO's global breastfeeding advice.[6] The American Academy of Pediatrics (AAP) and Japanese Pediatric Guideline for Food Allergy (JPGFA) reported that no implications can be made about the effect of breastfeeding on preventing or delaying any specific FAs.[7,19] In a systematic review and meta-analysis it was reported that breastfeeding of any duration does not seem to be an effective way to prevent FA, but that there is some weak evidence for the prevention of the development of AD in infants.[20]

Uncertainty exists about the effect of maternal diet during pregnancy and lactation on a child's immune development and risk of allergic diseases.[4] Some earlier studies and guidelines recommended avoiding highly allergenic foods, but these were not supported by later studies.[4,21] There is no evidence that maternal avoidance of known food allergens during pregnancy reduces the risk of their children developing allergic diseases.[4] Studies investigating diet indices on allergy outcomes have also failed to prove a consistent eating pattern based on the Healthy Eating Index, Dietary Inflammatory Index, or Mediterranean diet, during pregnancy and subsequent allergy prevention in the infant.[22] According to a review that considered 11 randomized controlled trials and 32 cohort studies including over 40 000 children, eating patterns including vegetable oils, margarine, nuts, and fast food are associated with a higher risk of developing atopy.[21] The authors also stated that Mediterranean dietary patterns, diets rich in fruits and vegetables, fish and vitamin D-containing foods are dietary patterns that are more likely to be associated with a lower risk of allergic diseases.[21] In a systematic review, Garcia et al.[20] indicated that a mother's diet during pregnancy and lactation might influence her child's risk of occurrence of the atopic disease. The authors found that supplementation with probiotics during late pregnancy and lactation may diminish the risk of eczema, and fish oil supplementation may reduce the risk of sensitization to food allergens.[20] The World Allergy Organization (WAO) guideline panel does not have a recommendation about prebiotic supplementation in pregnancy or during breastfeeding due to a lack of evidence.[23] Similarly, the EAACI task force does not have a recommendation for or against the use of vitamin supplements, fish oil, prebiotics, probiotics or symbiotics during pregnancy or lactation.[6] As a consequence, mothers should consume a healthy diet during pregnancy or breastfeeding and should neither reduce nor increase the intake of potentially allergenic foods to prevent the development of FA.[4]

Complementary foods

Infant feeding habits change according to local eating habits and food culture.[18] The introduction of allergenic foods into an infant's diet and the prevention of FA is not part of the WHO recommendations.[24] Early reports about preventing FA stated that eliminating allergenic foods or delaying the introduction of allergenic foods might reduce sensitization by preventing the transition of allergens through the increased permeability of the immature infant gut.[4] However, numerous subsequent studies demonstrated no benefits of allergen avoidance.[25]

The 2015 randomized trial Learning Early About Peanut Allergy on a sizable cohort of high-risk infants showed that early peanut introduction dramatically reduced the likelihood of peanut allergy in high-risk infants.[26] Early and frequent consumption of peanuts lowered the relative risk of developing a peanut allergy

by 81% at the age of five years.[26] According to a meta-analysis of 5 studies, consuming eggs between the ages of 4-6 months was found to be associated with a lower risk of developing an egg allergy than introducing eggs later in life.[27] Early introduction of fish into an infant's diet was found to reduce fish sensitization with very low certainty evidence.[27] There is no consistent evidence that the early introduction of cow's milk (CM) reduces the risk of CM allergy.[27] In 2016, a randomized trial involving breastfed infants evaluated whether the early introduction of six allergenic foods (CM, hen's egg, peanut, sesame, codfish, and wheat) in the diet would protect against the development of FA. In this trial, lower relative risks of peanut allergy and egg allergy were observed in the early-introduction group than in the standard-introduction group.[28] After these studies, updates were made to the guidelines; allergen avoidance gave way to the early consumption of certain solid foods.[5]

Recently, some authors have suggested introducing common allergenic solid foods at 4 to 6 months of age[6,19,28] indeed, some of them recommend not delaying the introduction of allergenic foods.[7] Asia Pacific Association of Pediatric Allergy, Respirology & Immunology (APAPARI) consensus statement's recommendations for infant feeding and the introduction of allergenic foods in infants differ according to the risk status of the infant.[18] APAPARI indicates that healthy infants should be introduced to complementary foods at 6 months of age however, the introduction of allergenic foods in healthy infants with a family history of atopy (at-risk infants) and in high-risk infants with severe eczema should not be delayed.[18] Regardless of risk status, the EAACI 2020 guideline on the prevention of the development of FA in children recommends introducing allergenic foods (cooked eggs and peanuts) to the infant's diet between the ages of 4 and 6 months as a part of complementary feeding.[6] Australian guidelines and ASCIA recommend introducing allergic foods within the first year of life.[11,15] AAP indicates that there is no evidence that delaying the introduction of allergenic foods, including peanuts, eggs, and fish, beyond 4 to 6 months, prevents allergic disease.[19] ACAAI, AAAI, and CSACI recommend that all infants irrespective of risk should be given cooked eggs and peanuts at around the age of 6 months, but not before 4 months of life, at home when the infant is developmentally ready.[10] Before allergen introduction, screening is not required, but the decision to screen is optional.[10] A medical assessment may be advisable in infants with severe AD and/or FA, before introducing common food allergens into the infant's diet.[29] In conclusion, it is difficult to make a standardized recommendation on when to introduce complementary foods and when to defer the introduction of solids for all infants. Recent guidelines in the USA and Europe advising early peanut introduction for high-risk infants with severe eczema or egg allergy have been published as a result of the high prevalence of peanut allergy in Western societies.[18,26] Due to the comparatively low prevalence of peanut allergy in most of Asia compared to the West, Asian recommendations diverge from US and European recommendations, which are primarily focused on preventing peanut allergy.[18] Early peanut introduction should be encouraged in nations with a high frequency of peanut allergy.[18,26] In Asian countries, egg allergy is more prevalent; therefore, the early introduction of a cooked egg is considered in infants with severe AD.[18]

How to begin complementary feeding is a controversial issue. It is advised to introduce new foods singly and a few days apart so that the responsible food can be identified in the event of an allergic reaction.[30] Current ASCIA[11] and BSACI[17] guidelines recommend introducing one new common allergen alone, but updated European[6] and the US/Canadian[10] guidelines have now removed this recommendation. The AAP indicated that it is safe to introduce multiple foods at once.[31] The order in which foods should be introduced varies according to studies. The recent US/Canadian consensus guideline stated that there

is no set order for these foods to be started.[10] The infant's developmental stages, nutritional needs, and cultural dietary practices should be taken into account for the introduction of complementary foods (eg, grains, fruits, or vegetables first followed by a cooked egg and then a peanut).[10] The family's needs and the local food culture should be taken into account when making recommendations about other common allergens like tree nuts and shellfish.[10] Ongoing exposure is needed to maintain tolerance; an introduction without ongoing consumption may be counterproductive.[30]

According to the EAACI position paper, high diet diversity in the first year of life was significantly associated with reduced food allergy risk up to 6 years of age.[32] The authors recommend that infants in any risk category for an allergic disease should have a diverse diet.[32] It has been proposed that a varied diet during infancy can affect allergy outcomes by exposing the gut microbiota to a variety of foods, increasing the intake of fiber, prebiotics, and omega-3 fatty acids, and promoting the development of immunological tolerance.[32] The introduction of solid foods during the weaning phase and greater dietary variety may increase the gut microbiome's diversity, positively impact its structure and function, and indirectly influence the development of tolerance through the microbiome.[10,32] A more diverse diet may also lead to exposure to different food antigens that impact the development of immune tolerance.[10,32] Consequently, diet diversity in the first year of life is associated with reduced food allergy outcomes and is recommended by allergen prevention strategies.[6,10]

A recent study has shown that commercial baby foods are low in common food allergen content.[33] If the infant's diet is heavily reliant on commercial infant food products, there would be a risk of limited exposure to allergens.[33] This low food allergen content may be disadvantageous for infants fed mostly with commercial infant foods because they are at risk of consuming insufficient amounts of the major food allergens on a regular basis during infancy.[33] Decreased levels of food variety can disrupt nutrient variety and a balanced diet.[33]

Based on recent data, consumption of solid foods (including allergenic foods) is recommended during the first year of life, according to the infant's neuro-developmental abilities and familial or cultural habits.[29] The use of home-prepared foods including the major food allergens according to regional food culture and considering the infant's readiness seems best.[29]

Formulas

Current evidence do not support that partially hydrolyzed formula (pHF) or extensively hydrolyzed formula (eHF) prevents FA in children, even in infants at high risk of allergy, but discrepancies among guidelines exist.[4] In a recent review of the Cochrane database, HF was compared with a CM-based formula for the prevention of allergic disease in infants who were not able to exclusively breastfeed however, no evidence was found for the suggestion of the use of HF.[34] According to the consensus approach of AAAAI, ACAAI and CSACI, the use of HF in infancy has not been shown to have any superiority in preventing FA or food sensitization.[10] The BSACI 2017[17] guideline doesn't recommend a hypoallergenic formula for the prevention of FA in children however the Japanese guideline does not have a recommendation. If possible, the BSACI guideline indicates that infants should be breastfed while starting complementary foods.[17] If breastmilk is unavailable, a CM-based formula should be used rather than a hypoallergenic formula, unless the infant has been diagnosed with CM allergy.[17] Irregular consumption of CM-based formula has been shown to enhance the risk of CM allergy, regularity appears to be crucial to promoting ongoing tolerance, with a few ingestions per week.[35] For this reason, continuous consumption of CM-based formula (as little as 10 mL daily) is crucial as not to lose tolerance.[35] The EAACI Task Force indicates that breastfed infants should not be given CM-based formula in the first week of life to prevent CM allergy.[6] No suggestion has been made for

or against using pHF or eHF to prevent CM allergy.[6] In case of not being able to breastfeed, the choice is up to families, including HF.[6] The EAACI Task Force recommends against utilization the of soy protein formula in the first 6 months of life to prevent FA.[6]

Dietary supplements

There is no common consensus for the utilization of dietary supplements globally.[4] In studies to date, no substantial evidence indicates that dietary supplementation diminishes the risk of any allergic findings in children.[4] In the EAACI 2020 update guideline, no suggestion is made for or against the use of vitamin supplements, fish oil, prebiotics, probiotics or symbiotics in infancy to prevent FA in infants and young children.[6] The 2020 ASCIA guideline[11] does not recommend their use however, the WAO guideline suggests the use of prebiotic supplements in not-exclusively breastfed infants but does not suggest their usage in exclusively breastfed infants, based on the very low certainty of the evidence.[23] The researchers concluded that prebiotic supplementation in infants reduces the risk of developing recurrent wheezing and possibly also the development of FA.[23] They also emphasized that prebiotic-containing formulas should not be used instead of breast milk.[23]

Consumption of omega-3 fatty acids and fibres/prebiotics may be significant, but the optimal dosage and the target group expected to benefit the most are not obvious yet.[29] There is no sufficient evidence to advise vitamin D, omega 3, or pre-or-probiotic supplements to prevent FA in infants. A diverse range of food ingestion in infancy may enhance the intake of nutrients and positively influence the gut microbiome composition and subsequently FA.[4,29]

Others

Atopic dermatitis is accepted as the initial step of allergic diseases. The development of AD often represents the beginning of the "atopic march", and usually proceeds with the development of FA, allergic asthma and allergic rhinitis.[2] It is not clear whether AD is the main pathology or the earliest finding of the underlying condition. Many studies showed a causal role for the skin barrier and cutaneous sensitization in the development of FA.[2] Although reported studies point to a shred of strong evidence for improving the skin to prevent AD and thus FA, two preventative emollient trials "Barrier Enhancement for Eczema Prevention (BEEP)[36]" and "Preventing Atopic Dermatitis and ALLergies in Children (PreventADALL)[37]" found no decrease in AD or FA. Brough et al.[2] suggested that improving the skin's integrity may prevent epicutaneous sensitization or give the possibility of gaining oral tolerance through early food consumption. It is expected that maintaining skin integrity and preventing AD would positively impact the prevention of allergic diseases, especially FAs.[2] Despite discrepancies, AD seems to be a significant risk factor for FA and may have an important role in FA prevention.[2]

Th1-stimulating infant vaccines are expected to act to prime the immune response away from a Th2-driven allergic phenotype.[6] The EAACI Task Force suggests against using the Bacillus Calmette-Guérin (BCG) vaccination to prevent FA in infants and young children.[6] No recommendation has been made for or against using emollients as skin barriers or using preventive oral immunotherapy to prevent FA in infants and young children.[6]

Conclusion

- Infant feeding recommendations alter according to regional public health priorities (Table I).
- Eliminating allergenic foods from the diet during pregnancy or breastfeeding to prevent sensitization is not suggested.
- Infants in any risk group for allergic disease and their mothers should consume a healthy and diverse diet, similar to what is ordinary for the family.

Table I. Summary of current recommendations about infant feeding, maternal diet and dietary supplements for food allergy prevention.

Guideline	Complementary foods /formulas / dietary supplements in infants	Maternal diet in pregnancy, during lactation
WHO, 2003[24]	- Suggest CF to be introduced no earlier than 6 mo of age, with no specific allergen advice	-
APAPARI, 2018[18]	-Healthy infants; Introduce CF at 6 mo of age	-
	-At-risk infants (healthy infants with a family history of atopy or non-severe eczema); No delay in the introduction of allergenic foods (including egg, cow's milk, peanut, soy, wheat, and shellfish).	
	-High-risk infants with severe eczema; Introduction of all allergenic foods should not be delayed and aggressive control of eczema	
BSACI, 2018[17]	- Suggest CF to be introduced at around 6 mo	-
	-Introduce cooked egg/peanut before 1 year (high-risk infants from 4 mo) and continue as part of a usual diet	
AAP, 2019[19]	-Healthy infants; peanut should be introduced together with other solid foods, in accordance with family preferences	-
	- Infants with mild-to-moderate eczema; should be introduced to peanut at around 6 mo, in accordance with family preferences	
	-High-risk infants (presence of severe eczema and/or egg allergy); should be introduced to peanut at 4–6 mo.	
Japanese guidelines, 2020[7]	-Healthy infants; peanut should be introduced together with other solid foods, in accordance with family preferences	-Food elimination is not recommended
	- Infants with mild-to-moderate eczema; should be introduced to peanut at around 6 mo, in accordance with family preferences	- Insufficient evidence supporting the use of probiotics
	-High-risk infants (presence of severe eczema and/or egg allergy); should be introduced to peanut at 4–6 mo.	
ASCIA, 2020[11]	- Suggest CF to be introduced at around 6 mo	- Food elimination is not recommended
	-Cooked egg in the first year (high-risk infants from 8 months)	
	- Wheat, fish, peanut, and other nuts before 12 months	
	- There is no consistent evidence to support a protective role for partially or extensively hydrolyzed formulas	
EAACI, 2021[6]	-Suggest introducing well-cooked egg and peanut from 4 to 6 mo	-Advise against restricting consumption of potential food allergens
	- Suggest avoidance of cow's milk-based formula for breastfed infants in the first week of life	
	- Advise against using soy protein formula in the first 6 months to prevent cow's milk allergy	
	No recommendation for or against for the use of vitamin supplements, fish oil, prebiotics, probiotics or symbiotic	
American and Canadian Consensus, 2021[10]	-Introduce peanut/cooked egg-containing products to all infants, irrespective of their relative risk of developing food allergy, at around 6 months of life, not before 4 months of life.	- Food elimination is not recommended
	-Do not delay the introduction of other potentially allergenic CF	-No recommendation to support any particular food or supplement
	-Infants should be fed a diverse diet	
	-Recommends against the routine usage of any hydrolyzed formula	
	- Use of supplements has no clear role	

*AAP: American Academy of Pediatrics, APAPARI: Asia Pacific Association of Pediatric Allergy, Respirology & Immunology, BSACI: British Society of Clinical Immunology and Allergy, EEACI: European Academy of Allergy and Clinical Immunology, WHO: World Health Organization, CF: complementary foods

- For optimal health of the infant exclusive breastfeeding is strongly suggested.
- Early introduction of allergenic foods (in the first year of life) into an infant's diet and increased diet diversity is currently the most promising prevention strategies for FA. However, there is no trial-based comparative data regarding the quantity or the frequency of allergen intake that is clearly associated with tolerance.
- Hydrolyzed (partially or extensively) infant formula or soy protein formula for the prevention of allergic disease is not recommended. Where a breastmilk substitute is needed, the best alternative should be chosen according to the infant's nutritional needs.
- Protecting skin integrity with the use of appropriate emollient care against proinflammatory conditions may prevent the development of AD and subsequently sensitization to foods.
- Th1-stimulating infant vaccines such as BCG vaccination to prevent FA are not suggested.

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: ÖS, AE; data collection: ÖS, AE; analysis and interpretation of results: ÖS, AE; draft manuscript preparation: ÖS, AE. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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