EFFECTIVENESS OF ENHANCING THE SKIN BARRIER SINCE EARLY INFANCY TO PREVENT INFANTILE ATOPIC DERMATITIS AND FOOD SENSITIZATION: A RANDOMIZED CONTROLLED TRIAL

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Background: Atopic dermatitis (AD) mainly affects young children. The primary prevention of AD was investigated among high-risk infants.
Objective: The study aimed to determine whether enhancing the skin barrier since early infancy would affect primary prevention and food sensitization.
Methods: A randomized controlled trial of 60 high-risk infants with a family history of atopy, aged up to 10 weeks, were enrolled. They were randomly assigned to either the intervention group receiving an inhouse emollient (cold cream) or the control group receiving only routine skin care education. The dermatologic assessment was recorded at ages 2, 4, 6, 8, 9 and 12 months. The skin prick test (SPT) with the top eight food allergens was performed at nine months.
Results: Fifty-six infants contributed to the study. A total of 11 (19.6%) developed AD, comprising 7 (24.1%) in the intervention group and 4 (14.8%) in the control group, with $p = 0.380$. Only 39 infants undergoing SPT with food sensitization found among 6 (15.4%) infants were comparable between the two groups ($p = 0.674$).
Conclusion: We could not conclude that enhancing the skin barrier among high-risk infants could prevent AD and food sensitization.

Keywords: atopic dermatitis, emollient, food sensitization, skin prick test

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Introduction

Atopic dermatitis (AD) is a chronic inflammatory dermatosis affecting mostly high-risk infants with a family history of atopy. Infants with AD presented dry skin with chronic and recurrent pruritic eczematous rashes in particular areas of the skin. The well-known 1980 Hanifin and Rajka criteria have been the most recognized diagnostic criteria, which many institutes have modified.[1,2] The prevalence of AD in Thailand proposed by the International Study of Asthma and Allergies in Childhood or ISAAC Phase III, reported a prevalence of 13.5% in the age group 6 to 7 years, and 7.2% for the age group 13 to 14 years.[3] A prevalence study among adults ranged from 2.1 to 4.9%,[4] while the trends of disease occurrence are increasing globally. Children with AD are also at increased risk of allergic rhinitis (AR), asthma and food allergy. Furthermore, the impact of the disease can lead to a significant socioeconomic burden due to a chronic course and inevitably impact the quality of life among patients and their family members.[5-6] Recently, one online survey study in the US in 2019 reported the median annual AD expense at US $600.[7] Factors responsible for developing IAD are multifactorial, including genetic, environmental, immune dysregulation and dysfunctional skin barrier.[8] Skin barrier dysfunction and immune dysregulation are the key pathogenesis of IAD.[9] Thus, the hypothesis of the effectiveness of enhancing the skin barrier since early infancy to impede penetration of allergens may play an essential role in preventing AD. During the past ten years, efforts to study the modalities impacting disease prevention have become a concern worldwide.[10] Among those methods, studies have suggested that routine emollients used in early infancy could prevent AD, especially among high-risk infants. Several cohort studies provided evidence of both pros and cons for enhancing the skin barrier during the early life period.[11-14] The dual-allergen exposure hypothesis proposed that epicutaneous sensitization occurs through a damaged skin barrier, permitting allergen penetration leading to food allergy.[15-18] We conducted a study investigating whether enhancing the skin barrier since early infancy among infants from atopic families would affect primary prevention and food sensitization of AD.

Methods

The Institutional Review Board approved this clinical study, Royal Thai Army Medical Department (reference number: IRBRTA 256/2563), according to the ethics principles of the Declaration of Helsinki (1975), including its revision. The study was registered in the Thai Clinical Trials Registry and obliged to disclose details of the 24 mandatory items of the WHO International Clinical Trials Registry Platform (Trial identification number was 20201118001). Before enrolling infants, written informed consent to participate in the study was obtained from parents or legal guardians.

Participants

Babies born from families (first-degree relative) with at least one allergy problem, including AD, AR, food allergy or asthma, attending the labor rooms or well-baby clinic at Phramongkutklao Hospital, a tertiary care center in Bangkok, Thailand, from 17 June 2020 to 19 February 2021 were eligible for the study. A randomized controlled trial was conducted at the Pediatric Outpatient Department, Phramongkutklao Hospital.

The inclusion criteria were all newborn babies from atopic families with a minimum gestational age of 37 weeks to 10 weeks postpartum. Exclusion criteria were infants with significant congenital anomalies, abnormal skin manifestations related to genetic abnormalities or immunodeficiency syndrome, emollient use within two weeks and disagreement of their parents to enter the enrollment.

Patient enrollment and randomization

At the maternity ward, nursery and Pediatric Outpatient Department, eligible babies were enrolled and randomly assigned by a block of four randomizations within sealed opaque envelopes to either the intervention group, using an inhouse emollient (cold cream) or a control group: routine baby skin care.

Procedures

The infants in the intervention group received an inhouse cold cream at every visit, the amount of emollient depending on their age, such as 60 g monthly for infants less than four months old, 90 g monthly for infants aged 4 to 8 months old and 120 g monthly for infants aged more than eight months old. In the inhouse, cold cream is a water-in-oil emulsion formulated and manufactured by the Department of Pharmacy, Phramongkutklao Hospital, which has a basic formulation containing white petrolatum, liquid paraffin, cetyl alcohol, sodium lauryl sulfate, methylparaben, propylparaben and purified water and no ingredients known to have a detrimental effect on the skin barrier suitable for the dry skin type. According to a study by Thitthiwong et al.[13], applying the inhouse cold cream and following good skin care practices from early infancy could effectively prevent atopic dermatitis among high-risk infants. Applying the inhouse cold cream to the whole body and face was recommended except for the perioral and periorbital areas at least once daily within 3 to 5 minutes after bathing. The parents were asked to carry the empty transparent bottles of the inhouse cold cream to the clinic or take a picture to show their compliance with the emollient used. Education to caregivers concerning feeding practices and good baby skin care was provided to parents in both groups at every visit. The infants were followed up at 2, 4, 6, 8, 9 and 12 months. Pediatric dermatologists assessed all patients at every visit to evaluate the development of AD using Hanifin and Rajka criteria. The record forms were completed by another investigator, reporting types of milk feeding (breastmilk or infant formula), bathing frequency and duration, other skin products used such as soap, pets, inhouse smoking, and compliance with emollient use (in the intervention group). In the intervention group, adverse events including skin infection, stinging, exanthema and allergic reaction to the emollient and urticaria from inhouse cold cream use, were obtained by interviews and recorded. The control group was advised not to use the emollient. Skin prick tests (SPT) with the eight common food allergens, including cow milk, soy, egg white, egg yolk, wheat, peanut, fish and mixed shellfish were performed at age nine months among all participants by the pediatric allergist who was also blinded to the infants' group assignment.

Statistical analysis

Based on a related study by Thitthiwong et al., we estimated a 10% dropout rate in Bangkok and calculated that 114 patients were needed for this study. Baseline variables were analyzed and presented as mean with standard deviation (SD) or median (min-max) for continuous variables and calculated using frequency and percentage for categorical variables. Comparisons between two independent data sets were analyzed using Chi-square or Fisher's exact tests for categorical data and independent sample t-test or Mann-Whitney U test for continuous data. Prevalence was compared between two independent data sets using Chi-square or Fisher's exact test. Mean age was compared between two independent data sets using an independent t-test or Mann-Whitney U test. The Chi-square test was used to compare the number of infants receiving a diagnosis of AD. Fisher's exact test was used to compare the number of infants undergoing SPT in both groups and multivariate analysis was employed between infants receiving a diagnosis of AD and nonAD. The analyses used STATA/MP12 Version (Stata Corp, TX, USA) and $p < 0.05$ was considered statistically significant.

Primary and Secondary Outcomes

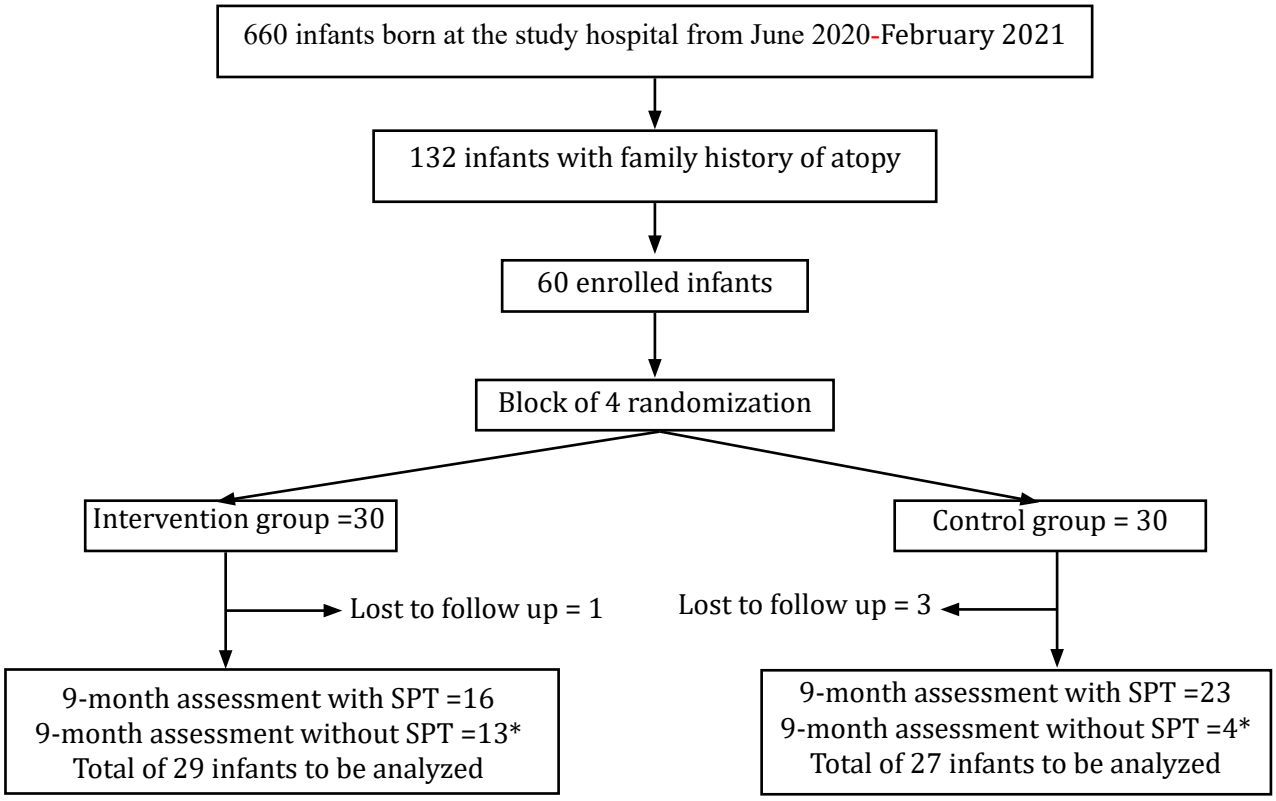
The primary outcome was to compare the prevalence of AD between the intervention and control groups using Hanifin and Rajka diagnostic criteria.[1,2] The secondary outcomes were to investigate the average age of developing AD, to compare the prevalence of food sensitization by SPT for common food allergens assessed by a pediatric allergist at the age of 9 months, to study adverse events of an inhouse cold cream in the intervention group and to study factors affecting AD development and food sensitization.

Results

We informed 132 families whose infants were eligible to participate in this study. Due to COVID-19 restrictions during this study from

17 June 2020 to 19 February 2021, we could not enroll more infants to achieve the total of 114 infants as calculated. Of those 132 families, 60 infants were enrolled and randomly allocated to one of the two groups: 30 in the control group and 30 in the intervention group. Four families were lost to follow-up during the clinical trial: one infant in the intervention group and three in the control group. The remaining 56 infants, 29 in the intervention group and 27 in the control group, participated until the end of this study. However, 17 infants (13 in the intervention group and 4 in the control group) could not be followed up at the hospital due to COVID-19 restrictions. After receiving permission, we had to assess their clinical symptoms and interview their parents via phone and video. These 17 infants were also lost to appointments for SPT at nine months old. The flow chart of all participants is shown in **Figure 1.** The baseline characteristics of the 56 infants were comparable in both groups such as sex, body weight, family history of atopy, bathing duration, detergent use, types of feedings, inhouse smoking and pets, as shown in **Table 1.**

Primary and secondary outcomes



*Number of infants being assessed for skin lesion and interviewed by video calls due to pandemic of COVID-19

Figure 1. Participants flow chart in the study

Table1. Baseline characteristics of participants

	Control group (n=27)	Intervention group (n=29)
	n (%)	n (%)
Gender		
Male	14 (51.85)	12 (41.38)
Bodyweight (grams)		
Mean ± SD	3106.67 ± 415.14	3072.45 ± 447.81

Table1. Baseline characteristics of participants (Cont.)

	Control group (n=27)	Intervention group (n=29)
	n (%)	n (%)
Family history of atopy		
2 parents with atopy	5 (18.52)	5 (17.24)
Siblings with atopy	4 (14.81)	5 (17.24)
Families with food allergy	4 (14.81)	2 (6.90)
Environmental exposures		
Bathing duration		
≤10 minutes	27 (100.00)	28 (96.55)
>10 minutes	-	1 (3.45)
Detergent use	9 (33.33)	7 (24.14)
Types of milk ingestion		
Breast-feeding only	14 (51.85)	13 (44.83)
Infant formula ± breast-feeding	13 (48.15)	16 (55.17)
Smoking in house		
None	25 (92.59)	21 (72.41)
Smoking	2 (7.41)	8 (27.59)
Pets; cats	3 (11.11)	3 (10.34)
Pets; dogs	7 (25.93)	8 (27.59)

The 56 high-risk infants received clinical assessment visits up to 12 months old by pediatric dermatologists in our institute to determine whether they met the AD diagnostic criteria based on Hanifin and Rajka diagnostic criteria for AD. Of those, 11 (19.6%) infants developed AD, 7 (24.1%) in the intervention group compared with 4 (14.8%) in the control group, without statistical significance (p = 0.380). The primary outcome is shown in **Table 2.** The median age of developing AD was four months in the control group and six months in the intervention group. The median age of onset of AD was comparable between the two groups. To compare the prevalence of food sensitization, the pediatric allergist in our hospital performed SPT among high-risk infants at the age of 9 months for the eight top food allergens, including cow milk, soy, egg white, egg yolk, wheat, peanut, fish and mixed shellfish. Overall, 39 infants underwent SPT with food sensitization,revealing6(15.4%)infants,3(13.04%) in the control group, comparable with 3 (18.75%) in the intervention group (p = 0.674). Egg white was the most common food allergen sensitized in both groups. The food sensitization in both groups is shown in **Tables 3 and 4.** None of the participants diagnosed with AD developed food sensitization with clinical food allergy. No complications including skin infection, stinging, exanthema or allergic reaction to emollient and urticaria, were found using the inhouse cold cream in the intervention group during this study.

Discussion

In this study, we investigated the hypothesis of enhancing the skin barrier during early infancy as the primary prevention of AD and possibly decreasing food sensitization among at-risk infants. This clinical trial was conducted a second time after the positive result in our related study.[13] Theoretically, emollients reduce skin permeability, improve hydration and repair a defective stratum corneum. Various studies have proposed

Table 2. Atopic dermatitis (AD) between the two groups

	Control group (n=27)	Intervention group (n=29)	*p-value*
	n (%)	n (%)	
			0.380
NonAD	23 (85.2)	22 (75.9)	
AD	4 (14.8)	7 (24.1)	

Table 3. Infants undergoing skin prick tests between the two groups

	Control group (n=23)	Intervention group (n=16)	*p-value*
	n (%)	n (%)	
			0.674†
No sensitization	20 (86.96)	13 (81.25)	
Food sensitization	3 (13.04)	3 (18.75)	

Abbreviation: †, Fisher's exact test

Table 4. Food allergen sensitization among infants receiving SPT between the two groups

	Control group (n=23)	Intervention group (n=16)	*p-value*
	n (%)	n (%)	
Cow milk			0.503†
No sensitization	21 (91.30)	16 (100.00)	
Sensitization	2 (8.70)	-	
Soy			NA
No sensitization	23 (100.00)	16 (100.00)	
Sensitization	-	-	
Egg white			0.631†
No sensitization	21 (91.3)	13 (81.25)	
Sensitization	2 (8.70)	3 (18.75)	
Egg yolk			0.162†
No sensitization	23 (100.00)	14 (87.50)	
Sensitization	-	2 (12.50)	
Wheat			NA
No sensitization	23 (100.00)	16 (100.00)	
Sensitization	-	-	
Peanut			NA
No sensitization	23 (100.00)	16 (100.00)	
Sensitization	-	-	

Table 4. Food allergen sensitization among infants receiving SPT between the two groups (Cont.)

	Control group (n=23)	Intervention group (n=16)	*p-value*
	n (%)	n (%)	
Fish			NA
No sensitization	23 (100.00)	16 (100.00)	
Sensitization	-	-	
Shellfish			
No sensitization	23 (100.00)	16 (100.00)	NA
Sensitization	-	-	

Abbreviations: NA, not analyzed; †, Fisher's exact test

positive effects of this modality such as those by Simpson and Horimukai, and negative effects in a recent study.[11, 12, 19] Skjerven conducted a multicenter, cluster-randomized trial using a large sample size and did not support using these interventions to prevent AD before one year.[19] In addition, Chalmers et al.[14] in the UK used Diprobase cream or DoubleBase gel, which are common in the UK National Health Service and have mechanistic evidence for their skin barrier function but without clear benefit of emollients for AD prevention. Our study might have reached the same conclusion due to the small sample size. However, one of the distinctive features of our study compared with related negative studies is that Thailand is situated in the tropical dry forest biome. This may have affected the results to differ from the negative studies by Chalmers et al.[14] in the UK and Skjerven et al.[19] in Norway and Sweden,which are situated in or near the cool, temperate, moist forest biome. Overall, 11 (19.6%) high-risk infants in this study developed AD at 4 to 6 months without exhibiting significant differences between groups (p = 0.380). To enhance the skin barrier in our study, participants in the intervention group received an inhouse cold cream, a hospital formulation consisting of liquid paraffin, white petrolatum, cetyl alcohol, sodium lauryl sulfate, methylparaben, propylparaben and purified water, applied to the whole skin within 3 to 5 minutes after bathing and padding. The emollient in our study might not have used the same formulation as those in other studies. Our study showed no association between our inhouse cold cream use and other adverse effects for up to one year. We could not discover any other factors such as the family history of atopy, skin product use, bath duration, types of milk feeding, smoking or pets inhouse to have influenced AD development.

We could not demonstrate any significant effects of emollients on preventing allergic sensitization to food allergens, especially the top eight. The SPT results at nine months in our study showed similar proportions of infants sensitized in both groups. We also could not conclude whether emollient use influenced the risk of developing food allergies. In addition, a systematic review showed the adverse effects of this modality for the primary prevention of AD and food allergy.[20] Due to the restrictions imposed by the COVID-19 pandemic, we could not recruit the target number of participants we planned for our study. As a result, we did not find any difference between infants with and without IAD. This study's limitations included the short follow-up visits and the small number of participants. More evidence for the primary prevention of IAD still needs further investigations. Emollients might have to be applied multiple times daily to exert a protective effect. Intervention for longer than one year and a more significant number of participants might be required. Although we could not reach the target number of participants, we hope this research will inspire and advance the development of preventive modalities for atopic dermatitis.

Conclusion

We could not conclude that enhancing the skin barrier among high-risk infants could prevent AD and food sensitization.

Availability of data and material

The data supporting the findings of this study are available upon reasonable request from the corresponding author. The data are not publicly available due to privacy or ethics restrictions.

Conflict of interest

The authors declare they have no conflict of interest.

Authors' contributions

All authors were involved in patients' care, collected, analyzed and interpreted the patient's data and wrote the manuscript. The corresponding author read and approved the final manuscript.

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References

1. Hanifin, Rajka G. Diagnostic features of atopic dermatitis. Acta Derm Venereol 1980; 92: 44-7.
2. Eichenfield LF, Tom WL, Chamlin SL, Feldman SR, Hanifin JM, Simpson EL, et al. Guidelines of care for the management of atopic dermatitis: Section 1. Diagnosis and assessment of atopic dermatitis Work Group. J Am Acad Dermatol 2014; 70: 338-51.
3. Odhiambo JA, Williams HC, Clayton TO, Robertson CF, Asher MI, AÃ¯t-Khaled N, et al. Global variations in prevalence of eczema symptoms in children from ISAAC Phase Three. J Allergy Clin Immunol 2009; 124: 1251-8.
4. Barbarot S, Auziere S, Gadkari A, Girolomoni G, Puig L, Simpson EL, et al. Epidemiology of atopic dermatitis in adults: Results from an international survey. *Allergy: Eur J Allergy Clin Immunol* 2018; 73: 1284-93.
5. Carlsten C, Dimich-Ward H, Ferguson A, Watson W, Rousseau R, Dybuncio A, et al. Atopic dermatitis in a high-risk cohort: Natural history, associated allergic outcomes, and risk factors. Ann Allergy Asthma Immunol 2013; 110: 24-8.
6. Birdi G, Cooke R, Knibb RC. Impact of atopic dermatitis on quality of life in adults: a systematic review and meta-analysis. Int J Dermatol 2020; 59: e75-91.
7. Begolka WS, Chovatiya R, Thibau IJ, Silverberg JI. Financial Burden of Atopic Dermatitis Out-of-Pocket Health Care Expenses in the United States. Dermatitis 2021; 32: S62-70.
8. Kim BE, Leung DY. Epidermal barrier in atopic dermatitis. Allergy Asthma Immunol Res 2012; 4: 12-6.
9. Sandilands A, O'Regan GM, Liao H, Zhao Y, Terron-Kwiatkowski A, Watson RM, et al. Prevalent and rare mutations in the gene encoding filaggrin cause ichthyosis vulgaris and predispose individuals to atopic dermatitis. J Invest Dermatol 2006; 126: 1770-5.
10. Foisy M, Boyle RJ, Chalmers JR, Simpson EL, Williams HC. The prevention of eczema in infants and children: an overview of Cochrane and non-Cochrane reviews. Evid Based Child Health 2011; 6: 1322-39.
11. Simpson EL, Chalmers JR, Hanifin JM, Thomas KS, Cork MJ, McLean WHI, et al. Emollient enhancement of the skin barrier from birth offers effective atopic dermatitis prevention. J Allergy Clin Immunol 2014; 134: 818-23.
12. Horimukai K, Morita K, Narita M, Kondo M, Kitazawa H, Nozaki M, et al. Application of moisturizer to neonates prevents development of atopic dermatitis. J Allergy Clin Immunol 2014; 134: 824-30.
13. Thitthiwong P, Koopitakkajorn T. The good skin care practices and emollient use since early infancy as the primary prevention of infantile atopic dermatitis among infants at risk: A randomized controlled trial. Siriraj Med J 2020; 72: 41-6.

14. Chalmers JR, Haines RH, Bradshaw LE, Montgomery AA, Thomas KS, Brown SJ, et al. Daily emollient during infancy for prevention of eczema: the BEEP randomised controlled trial. Lancet 2020; 395: 962-72.
15. Lack G, Fox D, Northstone K, Golding J. Factors Associated with the Development of Peanut Allergy in Childhood. N Engl J Med 2003348: 977-85.
16. Samady W, Warren C, Kohli S, Jain R, Bilaver L, Mancini AJ, et al. The prevalence of atopic dermatitis in children with food allergy. Ann Allergy Asthma Immunol 2019; 122: 656-7.
17. Lowe AJ, Su JC, Allen KJ, Abramson MJ, Cranswick N, Robertson CF, et al. A randomized trial of a barrier lipid replacement strategy for the prevention of atopic dermatitis and allergic sensitization: the PEBBLES pilot study. Br J Dermatol 2018; 178: e19-21.
18. Tham EH, Rajakulendran M, Lee BW, van Bever HPS. Epicutaneous sensitization to food allergens in atopic dermatitis: What do we know?. Pediatr Allergy Immunol 2020; 31: 7-18.
19. Skjerven HO, Rehbinder EM, Vettukattil R, LeBlanc M, Granum B, Haugen G, et al. Skin emollient and early complementary feeding to prevent infant atopic dermatitis (PreventADALL): a factorial, multicentre, cluster-randomised trial. Lancet 2020; 395: 951-61.
20. Kelleher MM, Cro S, van Vogt E, Cornelius V, Lodrup Carlsen KC, Ove Skjerven H, et al. Skincare interventions in infants for preventing eczema and food allergy: A cochrane systematic review and individual participant data meta-analysis. Clin Exp Allergy 2021; 51: 402-18.