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Predicting probability of tolerating discrete amounts of peanut protein in allergic children using epitope-specific IgE antibody profiling

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ARTICLE SUMMARY

- Existing diagnostic testing is not predictive of severity or the threshold dose of clinical reactivity, and many patients still require an Oral Food Challenge (OFC). While OFCs are very useful for making an allergy diagnosis and determining clinical reactivity, they often cause anaphylaxis, which can increase patient anxiety. and are time and resource intensive.[1]
- An extensive validation was performed across 5 cohorts (all with confirmed oral food challenge results) across six different countries. Cohorts used: BOPI, OPIA, CAFETERIA, CoFAR6, and PEPITES with specimens from Australia, UK, US, Ireland, and Germany.
- This paper reports the first validated algorithm using two key peanut specific IgE epitopes to predict probabilities of reaction to different amounts of peanut in allergic subjects and may provide a useful clinical substitute for peanut oral food challenges.
- Using the algorithm, subjects were assigned into "high", "moderate", or "low" dose reactivity groups. On average, subjects in the "high" group were 4 times more likely to tolerate a specific dose, compared to the "low" group.[1] For example, 88% of patients in the high dose reactivity group were able to tolerate ≥ 144 mg of peanut protein whereas only 29% were able to tolerate the same amount in the low dose reactivity group.[1-2]

CLINICAL CONSIDERATIONS

- The new epitope test offers more granular information to help clinicians stratify treatment and peanut avoidance plans for their patients.
- See below for summary of clinical considerations based on threshold reactivity level.[1]

allergenis peanut diagnostic result	clinical considerations[1]
likely allergic – low dose reactor	• inform or avoid oral food challenge to reduce risk of anaphlyaxis • confirm strict avoidance of peanut • consider immunotherapy to reduce risk of reaction
likely allergic – moderate dose reactor	• consider a single oral food challenge (30 to 100 mg) to reduce anxiety and improve quality of life • less stringent avoidance of peanut regime • consider inclusions of precautionary labeled foods such as 'May contain peanut' • consider immunotherapy to reduce risk of reaction
likely allergic – high dose reactor	• consider a single oral food challenge (100 to 300 mg) to reduce anxiety and improve quality of life • less stringent avoidance of peanut regime • consider inclusions of precautionary labeled foods such as 'May contain peanut' • consider starting immunotherapy at higher doses to shorten time to maintenance dose
unlikely allergic	• oral food challenge to rule out the diagnosis of peanut allergy

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REFERENCES

1. Suprun M, Kearney P, Hayward C, et al. Predicting probability of tolerating discrete amounts of peanut protein in allergic children using epitope-specific IgE antibody profiling. ***Allergy.*** 2022;00:1-9. doi: 10.1111/all.15477
2. Sindher SB, Long A, Chin AR, Hy A, Sampath V, Nadeau KC, Chinthrajah RS. Food allergy, mechanisms, diagnosis and treatment: Innovation through a multi-targeted approach. ***Allergy.*** 2022 Jun 22. doi: 10.1111/all.15418. Epub ahead of print. PMID: 35730331.

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ORIGINAL ARTICLE

Emollients for prevention of atopic dermatitis: 5-year findings from the BEEP randomized trial

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Abstract

Background: The effectiveness of emollients for preventing atopic dermatitis/eczema is controversial. The Barrier Enhancement for Eczema Prevention trial evaluated the effects of daily emollients during the first year of life on atopic dermatitis and atopic conditions to age 5 years.

Methods: 1394 term infants with a family history of atopic disease were randomized (1:1) to daily emollient plus standard skin-care advice (693 emollient group) or standard skin-care advice alone (701 controls). Long-term follow-up at ages 3, 4 and 5 years

Abbreviations: AD, atopic dermatitis; BEEP, Barrier Enhancement for Eczema Prevention; CI, confidence interval; IPD, individual patient data; POEM, Patient-Oriented Eczema Measure; RR, relative risk; SAP, statistical analysis plan.

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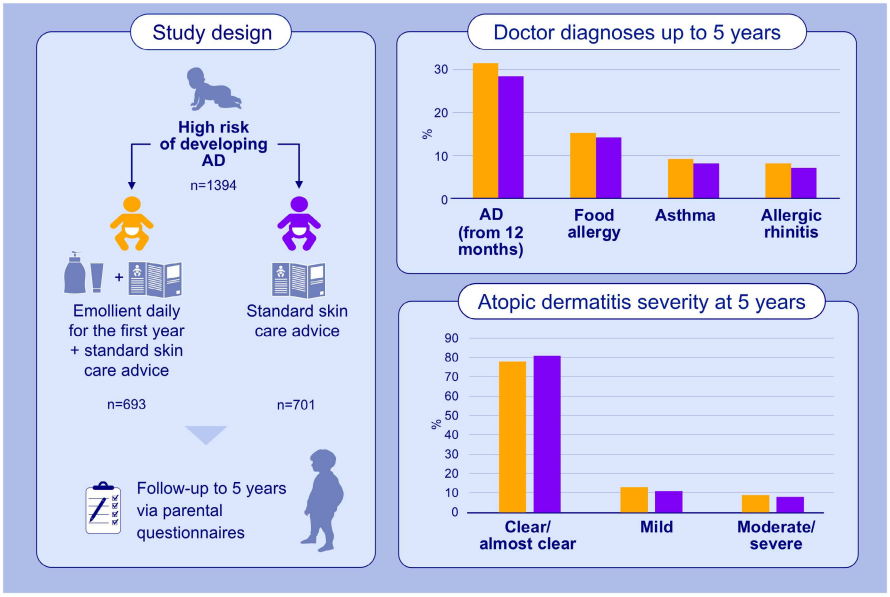
was via parental questionnaires. Main outcomes were parental report of a clinical diagnosis of atopic dermatitis and food allergy.

Results: Parents reported more frequent moisturizer application in the emollient group through to 5 years. A clinical diagnosis of atopic dermatitis between 12 and 60 months was reported for 188/608 (31%) in the emollient group and 178/631 (28%) in the control group (adjusted relative risk 1.10, 95% confidence interval 0.93 to 1.30). Although more parents in the emollient group reported food reactions in the previous year at 3 and 4 years, cumulative incidence of doctor-diagnosed food allergy by 5 years was similar between groups (92/609 [15%] emollients and 87/632 [14%] controls, adjusted relative risk 1.11, 95% confidence interval 0.84 to 1.45). Findings were similar for cumulative incidence of asthma and hay fever.

Conclusions: Daily emollient application during the first year of life does not prevent atopic dermatitis, food allergy, asthma or hay fever.

KEYWORDS
asthma, atopic dermatitis, food allergy, prevention, rhinitis



GRAPHICAL ABSTRACT

Graphical Abstract1394 newborns at high risk of atopic dermatitis randomized to either daily emollients (Doublebase Gel [Dermal Laboratories] or Diprobase Cream [Bayer]) for 12 months or standard skin care advice. Regular emollients did not prevent atopic dermatitis, food allergy, asthma or allergic rhinitis during the first 5 years of life. Severity of atopic dermatitis similar in the two groups at 5 years.

1 | BACKGROUND

Atopic dermatitis (syn, atopic eczema, eczema) is a global problem affecting around 1 in 5 children[1] and 1 in 20 adults.[2,3] The prevalence of atopic dermatitis (AD) seems to be increasing especially in cities undergoing rapid demographic development.[4] Genetic factors such as genes coding for skin barrier proteins and immunological responses appear to be important,[5] but the increased prevalence over time, increased risk in smaller families, and migrant studies suggest that environmental factors also play a role.[6]

While many effective topical and systemic treatments are available for established AD,[7] prevention of AD has remained elusive.[8,9] Most previous preventive strategies focused on allergen reduction during pregnancy and during infancy with little evidence of benefit.[10] Some evidence exists for a possible role of probiotics,[11] but the exact combination of bacterial strains and timing is still unclear and issues such as selective reporting may have impacted the evidence base. Interest in the role of a defective skin barrier preceding AD development led to the hypothesis that enhancement of the skin barrier from birth might prevent a chain of events resulting in skin

inflammation and establishment of AD.[12] The risk of atopic dermatitis is strongly associated with mutations in the gene encoding filaggrin - a protein that contributes to skin barrier integrity that suggests an impaired skin barrier as a critical defect in the development of AD.[13] Dysfunction in the skin barrier starts soon after birth, making enhancement of the skin barrier a possible target for AD prevention by reducing inflammation from irritants and sensitization through the skin.[14] The "outside-in" hypotheses suggests that there is a complex interplay between epithelial barriers, environmental factors and the immune system in the development of systemic allergic diseases such as AD.[15]

Food sensitization may be initiated through an impaired skin barrier, especially in those with AD, so prevention of AD may also prevent the development of subsequent food allergy[16,17] . Furthermore, if associated conditions such as asthma and allergic rhino-conjunctivitis truly follow-on from AD in predisposed individuals in the so-called 'allergic march',[18] then it might also be possible to prevent such co-morbidities by preventing early-onset AD with emollients.[16] Two pilot studies had suggested an efficacy signal for preventing AD using such an approach.[19,20] The rationale for the follow-on BEEP (Barrier Enhancement for Eczema Prevention) study was to conduct a definitive large randomized controlled trial to evaluate whether whole-body daily emollient application for the first year of life could prevent AD in high-risk children, compared with standard skin care.[21] Results for the 2-year primary outcome of AD did not show any protective effect of daily emollient on AD development (adjusted relative risk 0.95 [95% confidence interval (CI) 0.78 to 1.16], $P = .61$).[22] Secondary outcomes for AD were consistent with the primary outcome. Parental reported skin infections were more common in the emollient group during the first year (adjusted incidence rate ratio 1.55, 95% CI 1.15 to 2.09). There was also no evidence that emollient reduced the risk of food allergy (adjusted relative risk 1.47, 95% CI 0.93 to 2.33). Other studies have found similar results on risk of AD[23] but findings are controversial, with some small studies and systematic reviews reporting positive effects.[24]

The purpose of the five-year follow-up of children in the BEEP trial was to evaluate the longer-term effects of daily emollient application during infancy on AD and other atopic outcomes up to 5 years of age.[21]

2 | METHODS

2.1 | Study design and participants

BEEP was a multicentre, 2-arm, parallel-group randomized controlled trial which recruited participants from 12 hospitals and four general practice sites in the UK. The trial was approved by the West Midlands Ethics Committee, UK (14/WM/0162). The protocol[21] and results for the primary outcome at 2 years have been published.[22] Briefly, between November 2014 and November 2016 after informed consent from the parent/guardian, term newborns (≥37 weeks gestation) at high-risk of developing AD (at least one first-degree relative with parent-reported doctor-diagnosed AD, allergic rhinitis or asthma) were randomized (1:1) to apply emollient all over the body daily for the first year plus standard skin-care advice (emollient) or standard skin-care advice only (control). Standard general skin care advice was provided in booklet and video format at the time of randomization and included guidance to use mild cleansers and shampoos specifically formulated for infants, and to avoid soap, bubble bath, and baby wipes.[22] Randomization was stratified by recruiting centre and number of first-degree relatives with atopic disease (1, 2, or >2). Participating families were not blinded to group allocation. Parents whose children were allocated to the emollient group were initially sent both Doublebase Gel (Dermal Laboratories, Herts, UK) and Diprobase Cream (Bayer, Berks, UK) and specified which emollient they wanted when reordering. No emollients were supplied after the child reached 1 year of age. Adherence was assessed by asking parents about emollient use at 3, 6, and 12 months and was deemed satisfactory if emollients were applied at least 3–4 times per week to most of the child's body. We used a similar definition for contamination in the control group.

The sample size for the trial was calculated for the primary outcome of a diagnosis of AD in the last year as defined by the UK working party refinement of the Hanifin and Rajka diagnostic criteria for eczema at age 2 years[25] assessed by research nurses blinded to treatment allocation. The original target sample size of 1282 was based on a *relative* reduction of 30% in the primary AD outcome at the 5% significance level (two-sided) with 90% power assuming 30% of children would have AD in the control group, and 20% dropout. Faster than expected recruitment prompted a review by the Trial Steering Committee (August 2016), who permitted all pregnant mothers who had already given consent by that point to be randomized upon the birth of the baby, resulting in 1394 infants being randomized (693 emollient, 701 control).

Follow-up after the 2-year primary outcome time point was via questionnaires sent to parents at 3, 4 and 5 years, either in an email with link or in the post. Reminders were sent after 2 and then 3 weeks, respectively, if a questionnaire had not been completed. Results for the 2-year primary outcome of AD were published in February 2020, at which point parents were also sent a summary of the results.[26]

2.2 | Outcomes

Long-term follow-up outcomes (defined as tertiary in the protocol) were:

- Presence of AD in the previous year at 3, 4 and 5 years based on parental report of a clinical diagnosis of AD.
- Any parental report that in their opinion their child had AD at 3, 6, 12, 18 months, 2, 3, 4 and 5 years.
- Presence of AD at 3, 4 and 5 years based on parental completion of UK Working Party diagnostic criteria for AD[25]

- Severity of AD at 3, 4 and 5 years as measured by the Patient-Oriented Eczema Measure (POEM)[27]
- Presence of other atopic diseases:
  - Parental reported wheezing, allergic rhinitis and food allergy symptoms at 3, 4 and 5 years.
  - Parental report of a clinical diagnosis of asthma or allergic rhinitis by 5 years.
  - Parental report of a clinical diagnosis of food allergy at 3, 4 and 5 years

The questions used for these outcomes are presented in the Supporting Information. A summary of the parental reported outcomes at 2 years are also presented in the Supporting Information.

Two additional long-term outcomes were specified in version 2.0 of the Statistical Analysis Plan (SAP), prior to database lock and unblinding of 3-, 4- and 5-year outcome data: parental report of a clinical diagnosis of AD from the age of 12 months to 60 months and parental report of a clinical diagnosis of food allergy by 5 years. These outcomes were added to capture the lifetime experience and fluctuating nature of AD and food allergy. The first 12 months were not included for AD as transient eczematous rashes are common in the first year of life and often reported by parents as "eczema" but are less likely to be true AD.[28]

Health-related quality of life and health economic long-term outcomes will be reported separately. No additional long-term safety data was recorded between years 2 and 5 of follow-up.

2.3 | Statistical analysis

Details of the analyses of the long-term outcomes were added to the SAP[29] by the trial statistician after the analysis of the primary and secondary outcomes at which point, the investigators, trial management, data management, statisticians and participants were aware of the results. Full details of definitions and derivations of the long-term tertiary outcomes are given in version 2.0 of the SAP, which was finalized prior to the database lock for the analysis of the long-term outcomes at 60 months. All analyses were carried out using Stata 17.0 (StataCorp LP, College Station, TX, USA).

Analysis was according to randomized group regardless of adherence with the allocation in the first year. The main analyses made the assumption that missing outcomes were missing at random, that is, did not depend on the unobserved outcomes given the observed data. All analyses adjusted for randomization stratification variables using a fixed effect for number of immediate family members with atopic disease and a random effect for the recruiting centre.

Analysis of binary long-term outcomes at 3, 4 and 5 years used mixed effects logistic regression models including the outcome collected at earlier time points (i.e. 12 and 24 months where applicable) with a random effect for participant. Models included an allocated treatment-by-time interaction to estimate the between-group difference at each follow-up time point. Adjusted risk differences and risk ratios along with corresponding 95% confidence intervals (CI) were obtained using Stata's Margins command with standard errors computed using the delta method.[30]

Multiple imputation was used to impute missing outcomes collected at 5 years only and the cumulative incidence outcomes. Between-group effects in each imputed dataset were estimated using mixed effects logistic regression. Adjusted risk differences and risk ratios were obtained, as described above, and combined using Rubin rules for multiply imputed data. Further details of the multiple imputation model and sensitivity analyses are in the Supporting Information and SAP. Exploratory subgroup analyses for *FLG* genotype was done by including an interaction term in the analysis model for the parental report of clinical diagnosis of AD from the age of 12 months to 60 months.

3 | RESULTS

3.1 | Follow-up rates and baseline characteristics

Follow-up for the outcomes at 3, 4 and 5 years took place between November 2017 and November 2021. Overall completion was 70% at each time point; however, completion was slightly higher in the control group at all time points, particularly at 4 and 5 years (Figure 1).

The baseline characteristics of infants in whom the 5-year questionnaire was completed were similar in the two groups (Table 1). Families of infants in both groups in whom the 5-year questionnaire was not completed were more likely to have joined the study after the birth of their baby rather than consenting antenatally, had slightly younger mothers on average, were more likely to be of non-white ethnicity, were more likely to be in a household with other children, lived in areas on average with lower deciles of the Index of Multiple Deprivation and were less likely to have a first degree relative with a history of AD at randomization (Table 1).

3.2 | Moisturizer use during follow-up

At 3 years, parent-reported application of a moisturizer at least 3 times per week over all or most of the child's body in the past year was still increased in the emollient group (139/449, 31%) compared with the control group (94/471, 20%), and differences remained at 4 years (25% vs 18%) and 5 years (22% vs 16%). In both groups and at all time points, this frequent whole-body moisturizer use was more common in children with reported AD.

3.3 | AD outcomes

Diagnosis of AD at 3, 4 and 5 years was consistently slightly higher in the emollient group when compared to the control group, but

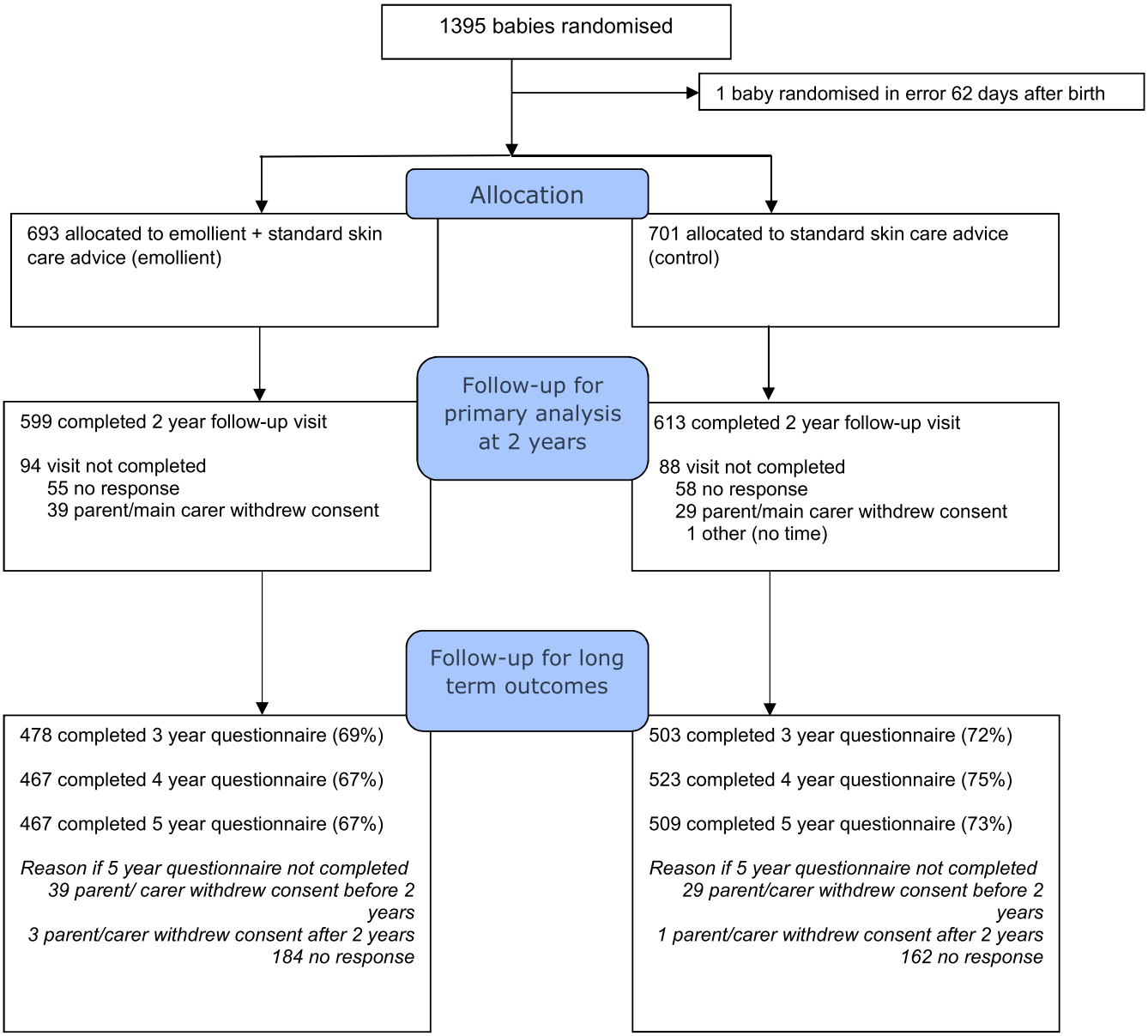


FIGURE 1 Participant flow diagram

adjusted differences were small, and none were statistically significant. The lack of difference between emollient and control groups for AD diagnosis was consistent for different methods of defining AD in the last year, including parental report of a clinical diagnosis, UK Working Party Diagnostic Criteria for AD (Table 2) and parental opinion of whether their child had developed AD (Table S2). AD of moderate severity or worse as measured by parent-reported symptoms on the POEM was also very similar between the groups at 3, 4 and 5 years (Table 2).

3.4 | Food allergy outcomes

A greater proportion of parents reported a reaction to any food within the previous year at 3 and 4 years in the emollient group than in the control group (3 years 81/430 (19%) emollient, 56/455 (12%) control, adjusted relative risk (RR) 1.37, 95% CI 1.02 to 1.85, Table 3). Parental report of immediate reactions to foods containing cow's milk, egg or nuts and of a clinical diagnosis of food allergy in the previous year were also slightly higher in the emollient group than in the control group at 3 and 4 years (Table 3). At 5 years, all outcomes relating to food allergy were similar between the two groups (Table 3).

3.5 | Wheezing and allergic rhinitis outcomes

At 3 years, 96/449 (21%) parents in the emollient group and 134/472 (28%) parents in the control group reported wheezing or whistling in their child's chest in the previous year (adjusted RR 0.79, 95% CI 0.64 to 0.98). The percentage of parents reporting wheezing or whistling in the previous year decreased in both groups at 4 and

TABLE 1 Baseline characteristics according to allocated group and follow-up at 5 years

	Emollient—completed 5-year questionnaire (n = 467)	Emollient—did not complete 5-year questionnaire (n = 226)	Control—completed 5-year questionnaire (n = 509)	Control—did not complete 5-year questionnaire (n = 192)
Age of mother at randomization – mean [SD]	32.5 [4.6]	30.2 [6.2]	32.2 [4.9]	29.7 [5.6]
Parental-reported number of first-degree relatives with atopic disease				
1	179 (38%)	75 (33%)	191 (38%)	62 (32%)
2	192 (41%)	108 (48%)	214 (42%)	82 (43%)
3 or more	96 (21%)	43 (19%)	104 (20%)	48 (25%)
At least one first degree relative with history of AD (parent-report of doctor diagnosis)	388 (83%)	175 (77%)	428 (84%)	152 (79%)
Ethnicity of mother				
White	413 (88%)	176 (78%)	449 (88%)	152 (79%)
Asian	28 (6%)	17 (8%)	29 (6%)	11 (6%)
Black	11 (2%)	20 (9%)	7 (1%)	15 (8%)
Other	15 (3%)	13 (6%)	24 (5%)	14 (7%)
Number of other children in household at screening				
0	199 (43%)	76 (34%)	232 (46%)	61 (32%)
1	195 (42%)	91 (40%)	200 (39%)	71 (37%)
2	55 (12%)	40 (18%)	56 (11%)	40 (21%)
3 or more	18 (4%)	19 (8%)	21 (4%)	20 (10%)
Decile of English index of multiple deprivation 2015, median [25th, 75th centile]	7 [4, 9]	4 [3, 7]	6 [4, 9]	4 [2, 7]

Note: Other ethnicities include mixed ethnicity, Middle Eastern and south American.

TABLE 2 Parental reported presence of AD and severity of AD at 3, 4 and 5 years

	Emollient	Control	Adjusted relative risk (95% CI)	Adjusted difference in risk (95% CI)
Presence of AD in the previous year based on parental report of a clinical diagnosis of AD				
3 years	81/469 (17%)	61/493 (12%)	1.31 (0.97 to 1.76)	4.1% (−0.4% to 8.6%)
4 years	50/462 (11%)	46/509 (9%)	1.20 (0.83 to 1.73)	1.9% (−1.9% to 5.7%)
5 years	49/462 (11%)	34/492 (7%)	1.41 (0.94 to 2.12)	3.1% (−0.5% to 6.6%)
Presence of AD based on completion by parents of UK Working Party Diagnostic Criteria for AD				
3 years	119/474 (25%)	109/495 (22%)	1.07 (0.87 to 1.33)	1.7% (−3.4% to 6.8%)
4 years	122/458 (27%)	134/511 (26%)	1.01 (0.82 to 1.24)	0.2% (−5.2% to 5.5%)
5 years	137/461 (30%)	132/495 (27%)	1.07 (0.88 to 1.30)	1.9% (−3.7% to 7.5%)
Moderate, severe, or very severe AD according to POEM				
3 years	30/464 (6%)	37/482 (8%)	0.85 (0.55 to 1.31)	−1.2% (−4.4% to 2.0%)
4 years	32/453 (7%)	45/505 (9%)	0.82 (0.54 to 1.23)	−1.6% (−4.9% to 1.7%)
5 years	42/458 (9%)	39/496 (8%)	1.12 (0.76 to 1.66)	1.0% (−2.4% to 4.5%)

Abbreviation: POEM, Patient-Oriented Eczema Measure.

Note: Adjusted relative risk/difference in risk estimated using a mixed effects logistic regression model using all available outcome data (including time points prior to 3 years) adjusting for randomization stratification variables and including a random effect for participants. The number of participants and observations included in each analysis model are shown in Table S1.

TABLE 3 Parental report of reactions to foods and clinical diagnosis of food allergy at 3, 4 and 5 years

	Emollient	Control	Adjusted relative risk (95% CI)	Adjusted difference in risk (95% CI)
Parental report of reaction to any food within the previous year				
3 years	81/430 (19%)	56/455 (12%)	1.37 (1.02 to 1.85)	5.0% (0.3% to 9.7%)
4 years	59/419 (14%)	43/472 (9%)	1.54 (1.08 to 2.20)	5.0% (0.9% to 9.2%)
5 years	52/432 (12%)	49/459 (11%)	1.07 (0.75 to 1.51)	0.8% (−3.4% to 4.9%)
Parental report of immediate reaction to milk, egg or nuts within the previous year[a]				
3 years	40/437 (9%)	26/468 (6%)	1.44 (0.92 to 2.27)	2.7% (−0.6% to 5.9%)
4 years	29/432 (7%)	21/485 (4%)	1.64 (0.97 to 2.76)	2.8% (−0.2% to 5.7%)
5 years	21/429 (5%)	21/453 (5%)	1.05 (0.60 to 1.84)	0.3% (−2.5% to 3.0%)
Parental report of a clinical diagnosis of food allergy within the previous year				
3 years	37/407 (9%)	20/422 (5%)	1.55 (0.96 to 2.49)	3.0% (−0.3% to 6.2%)
4 years	26/453 (6%)	17/498 (3%)	1.54 (0.89 to 2.66)	2.1% (−0.6% to 4.7%)
5 years	19/441 (4%)	15/474 (3%)	1.16 (0.64 to 2.11)	0.6% (−1.8% to 3.0%)

Note: Adjusted relative risk/difference in risk estimated using a mixed effects logistic regression model using all available outcome data (including time points prior to 3 years) adjusting for randomization stratification variables and including a random effect for participants. The number of participants and observations included in each analysis model are shown in Table S1.

[a]Immediate defined as reaction within 2 h of eating the food.

5 years with no difference between groups observed at 5 years (Table 4). Parental report of symptoms of allergic rhinitis were similar between groups at 3, 4 and 5 years, with approximately a quarter of parents in each group reporting such symptoms in the previous year (Table 4).

3.6 | Cumulative incidence outcomes

There were no differences between the two groups in the cumulative incidence of a parental report of a clinical diagnosis of AD, food allergy, asthma or allergic rhinitis by 5 years (Table 5). By 5 years, 188/608 (31%) parents in the emollient group and 178/631 (28%) parents in the control group had reported a clinical diagnosis of AD since their child was 12 months old (adjusted RR 1.10, 95% CI 0.93 to 1.30). Parental report of clinical diagnosis of food allergy by 5 years was reported in 92/609 (15%) parents in the emollient group compared with 87/632 (14%) parents in the control group (adjusted RR 1.11, 95% CI 0.84 to 1.45). Results from sensitivity analyses exploring the impact of a worse outcome in those with missing data were consistent with the main analyses (see Table S3). Subgroup analyses according to *FLG* genotype found no evidence of an interaction (see Table S4). Although safety data was not specifically recorded in the 3- to 5-year follow-up period, no safety concerns such as serious infections or slippages were spontaneously reported during that period.

TABLE 4 Parental reported wheezing and allergic rhinitis symptoms at 3, 4 and 5 years

	Emollient	Control	Adjusted relative risk (95% CI)	Adjusted difference in risk (95% CI)
Parental report of wheezing or whistling in the chest in previous year				
3 years	96/449 (21%)	134/472 (28%)	0.79 (0.64 to 0.98)	−6.0% (−11.4% to −0.5%)
4 years	81/456 (18%)	115/501 (23%)	0.84 (0.66 to 1.07)	−3.7% (−8.7% to 1.3%)
5 years	63/459 (14%)	72/490 (15%)	1.00 (0.74 to 1.35)	0.0% (−4.4% to 4.4%)
Parental report of allergic rhinitis symptoms in previous year				
3 years	120/455 (26%)	123/477 (26%)	1.02 (0.83 to 1.25)	0.5% (−5.2% to 6.2%)
4 years	111/453 (25%)	136/498 (27%)	0.91 (0.74 to 1.12)	−2.5% (−8.1% to 3.1%)
5 years	120/457 (26%)	116/485 (24%)	1.10 (0.89 to 1.35)	2.4% (−3.1% to 8.0%)

Note: Adjusted relative risk/difference in risk estimated using a mixed effects logistic regression model using all available outcome data (including time points prior to 3 years) adjusting for randomization stratification variables and including a random effect for participants. The number of participants and observations included in each analysis model are shown in Table S1.

4 | DISCUSSION

4.1 | Main findings

This study presents the first long-term follow-up data from an emollient for AD prevention trial documenting AD and other atopic outcomes to 5- years. Consistent with earlier findings from the BEEP trial, we found no evidence for an effect of daily emollient application during the first year of life on longer-term AD risk.

Our data also show no clear evidence for an effect of regular emollient application during infancy on risk of other atopic outcomes during the first 5 years of life. Some food allergy outcomes were *increased* in the emollient group, consistent with findings at age 2 years. Food allergy findings were however inconsistent and imprecise with no effect seen in cumulative incidence of parent-reported food allergy diagnosis by age 5 years. Similar to AD outcomes, we can be reasonably confident that daily emollient during infancy did not *reduce* food allergy risk. There was also no evidence of a protective effect of emollients for the development of parentally reported wheeze or doctor-diagnosed asthma or allergic rhinitis – perhaps now best considered as co-morbidities rather than sequential development of similar diseases.[31–33]

At 2 years, there was no evidence of a difference in the effect of daily emollient on risk of developing AD according to presence of mutations on the gene encoding for *FLG* and findings were similar at 5 years. However, confidence intervals for the interaction effect show a large amount of uncertainty as the trial was not powered to detect interactions.

Although data at 2 years in the BEEP study showed an increase in parental reported physician-diagnosed minor skin infections in the emollient group in the first year,[22] no new safety concerns were identified between 2 and 5 years.

4.2 | Interpretation in context with other studies

Our findings are consistent with another large clinical trial[34] and with the recent individual patient data (IPD) meta-analysis of emollient prevention studies.[35] The IPD included 10 trials of 5154 participants and showed that skincare interventions did not change the risk of AD by the age 1–3 years (RR 1.03, 95% CI 0.81 to 1.31; I2 = 41%; moderate certainty; 3075 participants, 7 trials). One single-centre study[36] has reported a 30% reduction in AD at 12 months following early initiation of daily specialized emollient use until 2 months of age. Other studies using more sophisticated emollients containing ceramides have not shown any benefit for AD prevention.[35] Not all emollients are the same in terms of their effects on the skin barrier.[37] It is still possible that some emollients could reduce or delay AD development as the role of epithelial barrier disruption in the development of allergic disorders is quite convincing.[38] Perhaps barrier enhancement would work in a low-risk rather than high-risk population or perhaps only when combined with enhanced skin care such as reduced bathing and soap avoidance, but the evidence for benefit so far has been disappointing. The alternative conclusion is that emollient application in early life does not work in terms of preventing AD and that the strongest influences on AD development in high-risk children are genetic and in utero programming. Although data on food allergy from BEEP is inconclusive, data from the Enquiring About Tolerance (EAT) trial showed a significant dose–response relationship between parent-reported moisturization frequency at 3 months of age and the subsequent development of food allergy raising the possibility that that regular application of moisturizers in early life could paradoxically promote food allergy development through transcutaneous sensitization.[39]

4.3 | Strengths and limitations of this study

Strengths include the long duration of follow-up (up to 5 years since birth) as well as the randomized study design. Follow-up rates of around 70% beyond 2 years are excellent for such a low-contact pragmatic trial, especially given that the lack of benefit for the primary outcome at 2 years had been shared with participants. It is possible that knowledge of the primary outcome results at 2 years could have influenced responses after that point, but it is unlikely

TABLE 5 Parental report of clinical diagnoses of AD, food allergy, asthma and allergic rhinitis by 5 years

	Emollient	Control	Adjusted relative risk (95% CI)	Adjusted difference in risk (95% CI)
Parental report of a clinical diagnosis of AD between 12 and 60 months[a]	188/608 (31%)	178/631 (28%)	1.10 (0.93 to 1.30)	2.8% (−2.3% to 7.8%)
Parental report of clinical diagnosis of food allergy by 5 years[a]	92/609 (15%)	87/632 (14%)	1.11 (0.84 to 1.45)	1.5% (−2.5% to 5.6%)
Parental report that child ever had clinical diagnosis of asthma or allergic rhinitis by 5 years[b]	63/431 (15%)	60/454 (13%)	1.06 (0.77 to 1.47)	0.9% (−4.0% to 5.8%)
Parental report that child ever had clinical diagnosis of asthma	38/431 (9%)	36/456 (8%)	1.08 (0.71 to 1.64)	0.7% (−3.2% to 4.6%)
Parental report that child ever had clinical diagnosis of allergic rhinitis	36/459 (8%)	35/485 (7%)	1.04 (0.67 to 1.63)	0.3% (−3.4% to 4.1%)

Note: Analysis used multiple imputation for missing outcomes and included all randomized participants (693 emollient and 701 control). See Supporting Information for further details of the multiple imputation model. Adjusted relative risk/difference in risk estimated in each imputed dataset for food allergy, asthma and allergic rhinitis outcomes using a mixed effects logistic regression model adjusting for randomization stratification variables (using fixed effect for of number of immediate family members with atopic disease and a random effect for the recruiting centre) and for the AD outcome, due to convergence problems with the mixed effects logistics regression models in some of the imputed datasets, using generalized estimating equations with the Binomial family and log/identity link respectively, with an exchangeable correlation matrix to account for randomization being stratified by centre and number of immediate family members with atopic disease (1, 2, or more than 2) included as a covariate. Estimates were combined using Rubin's rules.

[a]Outcome derived from responses to questionnaires at 12 (food allergy only), 18 (AD only), 24, 36, 48 and 60 months.

[b]Collected on 5 year questionnaire.

that a parent report of AD in their child after 2 years would vary according to their allocation status. Questionnaire completion in the control group was very slightly higher and it is unclear whether this was due to chance or some other factor. Non-responders to long-term follow-up differed slightly from responders as listed above, but sensitivity analyses assuming non-responders were more likely to have had the outcomes of interest did not change any of the conclusions. Unlike the 2-year primary outcome data for AD that included an objective assessment of the presence or absence of AD using the UK refinement of the Hanifin and Rajka criteria and the Eczema Area and Severity Index measure, follow-up data at 3, 4 and 5 years was based on parental report only, raising the possibility of response bias. Yet it is hard to comprehend why such a response bias should result in such a consistent null result. Furthermore, several alternative outcomes for AD were used including parental report of a clinical diagnosis and completion of a questionnaire-version of the UK diagnostic criteria which has previously been shown to have good validity compared to the face-to-face version.[40]

4.4 | Implications for research

Since application of simple emollients does not appear to prevent AD or associated atopic conditions in high-risk families, we suggest that the value of further emollient prevention studies needs to be carefully considered, with a priority given to novel approaches to infant skincare. Around 15 emollient trials are in progress and ensuring that all are transparently published and contribute to the living IPD meta-analysis is important. Although replicating a systematic review can sometimes be useful, lots more systematic reviews using the same aggregate data and an incomplete list of existing studies are unlikely to be helpful.[24,41] Longer-term data, such as the 5-year data presented in this paper, are useful as are more data on the possible increased risk of skin infections and food sensitization and allergy in other trials. Other approaches for protecting the skin barrier in early life such as softening domestic water and reducing soap exposure[42] are also needed.

4.5 | Implications for clinical practice

Evidence up to 5 years plus combined evidence from other emollient prevention studies do not support a preventative effect on AD or associated allergic diseases and cannot be recommended. Asking parents to apply emollient all over a baby's body daily for the first year of life is a significant undertaking, so producing evidence to show that it is not beneficial is helpful in reducing burden on families. Daily emollients for a whole year can also represent a significant socio-economic burden for families and their use risks over-medicalizing otherwise healthy children. The potential signals of possible adverse effects can also not be ignored. An increase in parental report of skin infections in the emollient group at 2 years in the BEEP study, was also noted in other studies including the IPD meta-analysis (RR 1.34, 95% CI 1.02 to 1.77; I2 = 0%; moderate certainty; 2728 participants, 6 trials). Although the reported skin infections were very diverse and none of the infections were serious, they can lead to morbidity, unnecessary antibiotic use and increased healthcare consultations. The food allergy data from BEEP at 2 years was inconclusive (adjusted RR 1.47, 95% CI 0.93 to 2.33) but data from observational studies suggest that frequency of emollient use in infancy is associated with

increased risk of food allergy.[39] Concerns regarding increased skin infections and food allergy are therefore both additional reasons why emollient use for AD prevention should not be recommended.

5 | CONCLUSION

This study presents follow-up of infants participating in the BEEP randomized controlled trial up to 5 years and, consistent with other previously published outcome data at 2 years, does not show any effect in preventing or delaying atopic dermatitis occurrence or its severity. There was also no benefit with regard to a potential prevention of other atopic diseases. Healthcare professionals including dermatologists, paediatricians, allergologists and general practitioners should be aware that intense moisturization from birth cannot be recommended for AD prevention or other atopic diseases. Research efforts need to explore other ways of enhancing the skin barrier in early life as a means to prevent AD and associated conditions.

AUTHOR CONTRIBUTIONS

HCW conceived of the trial and was the Chief Investigator. HCW, JRC, RJB, RHH, LEB, AAM, KST, SJB, MJR, SL, ELS, MJC, THS, CF, EJM, SDJ, NJ, and MP all contributed to the conception or design of the trial. JB, LAW, EJM, RHH, RS and ST supported the conduct of the trial, including acquisition of the data. RJB led on the food allergy outcomes and NJ, MK, HA and MRP contributed to this. AAM and LEB were responsible for the statistical analysis. THS was the health economist with STL. MJC provided expertise in emollients and the skin barrier. SJB was responsible for the genetic analysis. ELS, KST, MJR, SJB, SL, SDJ and CF all contributed clinical experience of eczema and/or eczema trials. The manuscript was drafted by HCW, LAW, RJB and LEB; all other authors critically reviewed and revised the manuscript. All authors have approved the final version.

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The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, or the Department of Health.

CONFLICT OF INTEREST

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request. Access to the data will be subject to review of a data sharing and use request (available from ctu@nottingham.ac.uk) by a committee including the CI and sponsor, and will only be granted upon receipt of a data sharing and use agreement. Any data shared will be pseudoanonymised which may impact on the reproducibility of published analyses. The study protocol, statistical analysis plan and health economics analysis plan are available on the trial website: https://www.nottingham.ac.uk/research/groups/cebd/projects/1eczema/beep-maintrial.aspx.

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REFERENCES

1. Odhiambo JA, Williams HC, Clayton TO, Robertson CF, Asher MI. Global variations in prevalence of eczema symptoms in children from ISAAC Phase Three. *J Allergy Clin Immunol*. 2009;124(6):1251-8 e23.
2. Abuabara K, Yu AM, Okhovat JP, Allen IE, Langan SM. The prevalence of atopic dermatitis beyond childhood: A systematic review and meta-analysis of longitudinal studies. *Allergy*. 2018;73(3):696-704.
3. Barbarot S, Auziere S, Gadkari A, et al. Epidemiology of atopic dermatitis in adults: Results from an international survey. *Allergy*. 2018;73(6):1284-1293.
4. Williams H, Stewart A, von Mutius E, Cookson W, Anderson HR. Is eczema really on the increase worldwide? *J Allergy Clin Immunol*. 2008;121(4):947-54.e15.
5. Brown SJ. Atopic eczema: how genetic studies can contribute to the understanding of this complex trait. *J Invest Dermatol*. 2022;142(4):1015-1019.
6. Williams HC. Atopic eczema-- we should look to the environment. *BMJ*. 1995;311(7015):1241-1242.
7. Ständer S. Atopic dermatitis. *N Engl J Med*. 2021;384(12):1136-1143.
8. Williams HC, Chalmers J. Prevention of atopic dermatitis. *Acta Derm Venereol*. 2020;100(12):adv00166.
9. Bawany F, Beck LA, Järvinen KM. Halting the march: primary prevention of atopic dermatitis and food allergies. *J Allergy Clin Immunol Pract*. 2020;8(3):860-875.
10. Foisy M, Boyle RJ, Chalmers JR, Simpson EL, Williams HC. Overview of reviews the prevention of eczema in infants and children: an overview of cochrane and non-cochrane reviews. *Evid Based Child Health*. 2011;6(5):1322-1339.
11. Garcia-Larsen V, Ierodiakonou D, Jarrold K, et al. Diet during pregnancy and infancy and risk of allergic or autoimmune disease: A systematic review and meta-analysis. *pLoS Med*. 2018;15(2):e1002507.
12. Paller AS, Spergel JM, Mina-Osorio P, Irvine AD. The atopic march and atopic multimorbidity: Many trajectories, many pathways. *J Allergy Clin Immunol*. 2019;143(1):46-55.
13. Brown SJ, Elias MS, Bradley M. Genetics in atopic dermatitis: historical perspective and future prospects. *Acta Derm Venereol*. 2020;100(12):adv00163.
14. Lowe AJ, Leung DYM, Tang MLK, Su JC, Allen KJ. The skin as a target for prevention of the atopic march. *Ann Allergy Asthma Immunol*. 2018;120(2):145-151.
15. Sugita K, Soyka MB, Wawrzyniak P, et al. Outside-in hypothesis revisited: The role of microbial, epithelial, and immune interactions. *Ann Allergy Asthma Immunol*. 2020;125(5):517-527.
16. Tsakok T, Marrs T, Mohsin M, et al. Does atopic dermatitis cause food allergy? A systematic review. *J Allergy Clin Immunol*. 2016;137(4):1071-1078.
17. 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(1):7-18.
18. Maiello N, Comberiati P, Giannetti A, Ricci G, Carello R, Galli E. New directions in understanding atopic march starting from atopic dermatitis. *Children (Basel)*. 2022;9(4):450.
19. Simpson EL, Chalmers JR, Hanifin JM, et al. Emollient enhancement of the skin barrier from birth offers effective atopic dermatitis prevention. *J Allergy Clin Immunol*. 2014;134(4):818-823.
20. Horimukai K, Morita K, Narita M, et al. Application of moisturizer to neonates prevents development of atopic dermatitis. *J Allergy Clin Immunol*. 2014;134(4):824-30 e6.
21. Chalmers JR, Haines RH, Mitchell EJ, et al. Effectiveness and cost-effectiveness of daily all-over-body application of emollient during

the first year of life for preventing atopic eczema in high-risk children (The BEEP trial): protocol for a randomised controlled trial. *Trials*. 2017;18(1):343.
22. Chalmers JR, Haines RH, Bradshaw LE, et al. Daily emollient during infancy for prevention of eczema: the BEEP randomised controlled trial. *Lancet*. 2020;395(10228):962-972.
23. Kelleher MM, Cro S, Cornelius V, et al. Skin care interventions in infants for preventing eczema and food allergy. *Cochrane Database Syst Rev*. 2021;2(2):Cd013534.
24. Kelleher MM, Cro S, Phillips R, Williams HC, Lowe AJ, Boyle RJ. Correspondence to"" Emollients in infancy to prevent atopic dermatitis: A systematic review and meta-analysi"". *Allergy*. 2022;77(6):1931-1933.
25. Williams HC, Burney PG, Pembroke AC, Hay RJ. The U.K. working part''s diagnostic criteria for atopic dermatitis. III. Independent hospital validation. *Br J Dermatol*. 1994;131(3):406-416.
26. BEEPTrial. The BEEP Study, Participant Newsletter-- Results Edition 2019 [Available from: https://www.nottingham.ac.uk/research/groups/cebd/documents/researchdocs/beep-parentsresultsnewsletterweb.pdf]
27. Spuls PI, Gerbens LAA, Simpson E, et al. Patient-oriented eczema measure (POEM), a core instrument to measure symptoms in clinical trials: a harmonising outcome measures for eczema (HOME) statement. *Br J Dermatol*. 2017;176(4):979-984.
28. Endre KMA, Landrø L, LeBlanc M, et al. Diagnosing atopic dermatitis in infancy using established diagnostic criteria: a cohort study. *Br J Dermatol*. 2022;186(1):50-58.
29. BEEPTrial. A randomised controlled trial to determine whether applicatoin of emollient from birth can prevent eczema in high risk children (BEEP Trial)-- Statistical Analysis Plan 2022. https://www.nottingham.ac.uk/research/groups/cebd/documents/researchdocs/0935-beep-sap-final-v2.0-20220106-signed.pdf
30. Norton EC, Miller MM, Kleinman LC. Computing adjusted risk ratios and risk differences in Stata. *Stata J*. 2013;13(3):492-509.
31. Maiello N, Giannetti A, Ricci G, et al. Atopic dermatitis and atopic march: which link? *Acta Biomed*. 2021;92(S7):e2021525.
32. Custovic A, Custovic D, Kljaić Bukvić B, Fontanella S, Haider S. Atopic phenotypes and their implication in the atopic march. *Expert Rev Clin Immunol*. 2020;16(9):873-881.
33. Williams H, Flohr C. How epidemiology has challenged 3 prevailing concepts about atopic dermatitis. *J Allergy Clin Immunol*. 2006;118(1):209-213.
34. Skjerven HO, Rehbinder EM, Vettukattil R, et al. Skin emollient and early complementary feeding to prevent infant atopic dermatitis (PreventADALL): a factorial, multicentre, cluster-randomised trial. *Lancet*. 2020;395(10228):951-961.
35. Kelleher MM, Cro S, Van Vogt E, 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(3):402-418.
36. Chaoimh CN, Lad D, Nico C, et al. Early initiation of short-term emollient use for the prevention of atopic dermatitis in high risk infants – the STOP AD randomised controlled trial. *Allergy*. 2022.
37. Danby SG, Andrew PV, Taylor RN, et al. Different types of emollient cream exhibit diverse physiological effects on the skin barrier in adults with atopic dermatitis. *Clin Exp Dermatol*. 2022;47:1154-1164.
38. Akdis CA. Does the epithelial barrier hypothesis explain the increase in allergy, autoimmunity and other chronic conditions? *Nat Rev Immunol*. 2021;21(11):739-751.
39. Perkin MR, Logan K, Marrs T, et al. Association of frequent moisturizer use in early infancy with the development of food allergy. *J Allergy Clin Immunol*. 2021;147(3):967-76.e1.
40. Fleming S, Bodner C, Devereux G, et al. An application of the United Kingdom Working Party diagnostic criteria for atopic dermatitis in Scottish infants. *J Invest Dermatol*. 2001;117(6):1526-1530.
41. Williams HC. Are dermatology systematic reviews spinning out of control? *Dermatology (Basel)*. 2021;237(4):493-495.
42. Jabbar-Lopez ZK, Ezzamouri B, Briley A, et al. Randomized controlled pilot trial with ion-exchange water softeners to prevent eczema (SOFTER trial). *Clin Exp Allergy*. 2022;52(3):405-415.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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